Chapter

1

Anatomical and Physiological Issues Affecting Anaesthesia in Neonates and Young Children

Pratheeban Nambyiah

Introduction

The neonatal period (first 28 days after birth, or to 44 weeks postconceptional age) is a time of transition from prenatal to postnatal life. It is characterised by rapid physiological change and developmental plasticity. It is also the time of maximum vulnerability in childhood. Whilst overall infant mortality in England and Wales is low (3.7 per 1,000 live births in 2019), neonatal mortality accounts for 2.8 deaths per 1,000 live births, and this is up from 2.5 in 2014 (driven by the small increase in babies born in extreme prematurity). Anaesthesia at this stage has the potential to cause adverse effects or to alter the neurodevelopmental outcome of the child. Understanding the physiological changes in this period is key to ensuring safe and effective care. Anaesthesia for the premature and ex-premature infant will be considered in more detail in Chapter 19.

The Development of the Respiratory System

There are five stages of lung development. During the embryonic stage, between three to eight weeks of gestation, the respiratory diverticulum arises as a protrusion of the foregut endoderm. It separates from what will become the oesophagus and forms the trachea and major bronchopulmonary segments.

In the pseudoglandular phase (5–16 weeks), the structure of the bronchial tree is laid down, and all lung elements are added except those involved in gas exchange; this includes the conducting airways, cartilaginous exoskeleton, pulmonary vasculature and diaphragm. The airways are lined with columnar epithelium.

In the canalicular phase (16–26 weeks), the bronchial tree enlarges, and respiratory bronchioles and alveolar ducts are formed. The surrounding mesenchyme (embryonic connective tissue) thins, and the capillary network which will supply the respiratory acini becomes established. The epithelium of the proximal airways differentiates into mucus-producing goblet cells, ciliated cells and basal cells. Distal regions, where the future acini will develop, are lined with cuboidal epithelium with a glycogen-laden cytoplasm. Towards the end of this phase, some terminal sacs develop, and respiration becomes possible. The acinar cuboidal epithelium differentiates into type 1 pneumocytes, which form part of the gas exchange surface, and type 2 pneumocytes, which contain the lamellar bodies that will store phospholipid surfactant for secretion.

The terminal saccular phase (from 26 weeks to birth) sees the continued development of terminal sacs and primitive alveoli. The epithelium thins, and capillaries become closely apposed to the walls of the terminal sacs. Fetal plasma cortisol levels rise in preparation for birth, stimulating alveolar cell differentiation, fluid resorption and surfactant release, which reduces surface tension to prevent airway collapse.

In the alveolar phase (from birth to eight years), the alveolar morphology matures, and there is an exponential rise in their number.

The Cardiovascular System in Utero

The heart is the first functional organ within the embryo, beginning its work in the fourth week, when the nutritional demands of the fetus can no longer be met by diffusion from the placenta. Initially, it beats as a primitive tube, but loops and folds into a recognisable four-chambered structure by week eight. However, the physiology of the emerging fetal circulation (Figure 1.1) is very different from that of the postnatal
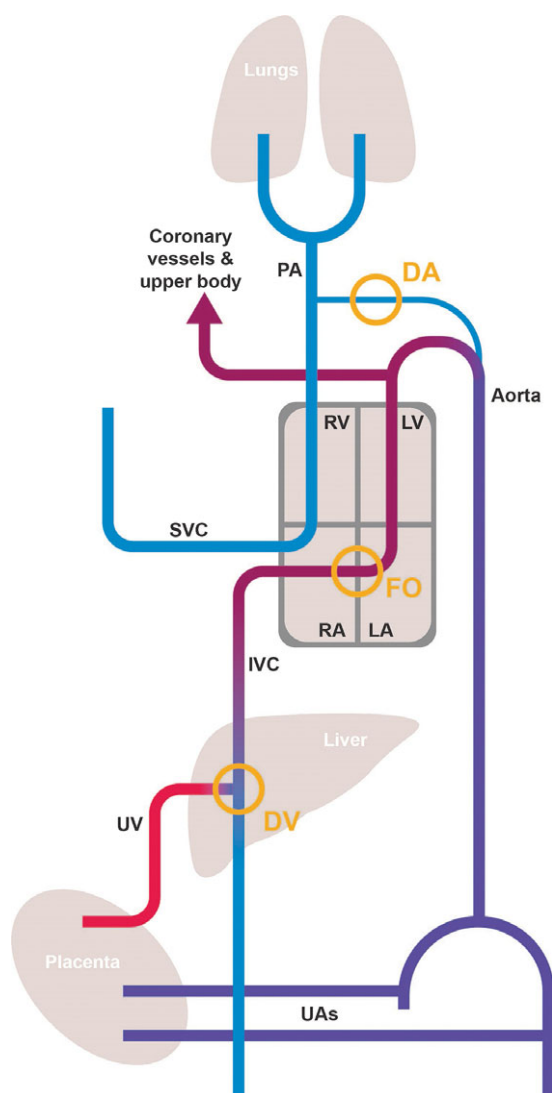
Figure 1.1 The fetal circulation. In utero supply is dependent on the presence of three shunts: the ductus venosus (DV), between the umbilical vein and inferior vena cava (IVC); the foramen ovale (FO) between the right and left atria; and the ductus arteriosus (DA) between the pulmonary artery and the descending aorta. See the text for full details. Vessels: PA = pulmonary artery; SVC = superior vena cava; UAs = umbilical arteries; UV = umbilical vein. Heart chambers: RA = right atrium; LA = left atrium; RV = right ventricle; LV = left ventricle.

circulation, largely due to the presence of three right-to-left shunts:

- The ductus venosus, between the umbilical vein and inferior vena cava (IVC)
- The foramen ovale between the right and left atria
- The ductus arteriosus between the pulmonary artery and the descending aorta

Taken together, the function of these is to direct oxygenated blood away from organs whose postnatal roles are largely performed by the placenta in prenatal life: the lungs and abdominal organs.

Oxygenated blood from the placenta travels in the umbilical vein. Most passes through the ductus venosus to the IVC, with a small amount supplying the liver via the portal vein. In the IVC, there is now a mixture of oxygenated blood from the placenta and desaturated blood returning from abdominal organs. On entering the right atrium, most of this blood is directed through the foramen ovale into the left atrium, from where it passes into the left ventricle and is pumped into the ascending aorta to supply the coronary vessels and upper body. Deoxygenated blood from the head and upper limbs returns via the superior vena cava (SVC) to the right atrium; this blood is preferentially directed to the right ventricle (RV) and main pulmonary artery. Pulmonary arterioles are tightly constricted due to low levels of oxygen, nitric oxide and prostacyclin PGI_2, and pulmonary vascular resistance (PVR) is high. As a consequence, only about 15% of the RV output reaches the lungs. The rest is shunted across the ductus arteriosus to supply the descending aorta, returning to the placenta via the umbilical arteries.

Cardiorespiratory Adaptation for Birth

At birth, this circulation must transition to one capable of supporting independent life. In most infants, this remarkable process happens within the course of a few hours. Failure of the process can have serious consequences, and stressors early in postnatal life can cause a reversion to the fetal physiology.

Fetal lung fluid is essential to lung development. It distends the lung and provides a stimulus to growth. Inadequate fluid volume leads to lung hypoplasia. However, this fluid must be cleared to allow postnatal respiration. The secretory pulmonary epithelium becomes absorptive towards term. Glucocorticoids and thyroid hormones sensitise the epithelium to β-adrenergic agonists, which mediate increased sodium and water uptake. Catecholamine surges during labour facilitate this process, and there is a modest contribution from mechanical thoracic compression in vaginal birth.

Tactile stimulation and exposure to cold at delivery prompt the neonate's expiratory efforts,

mediated via an upregulation in central chemo-receptors and release from placental inhibition. The lungs become aerated, aided by mature surfactant activity and the resultant reduction in alveolar surface tension. Fluid is cleared by expulsion from the trachea. Crying increases end-expiratory airway pressure and helps avoid airways collapse, as well as displacing liquid from the airways into the interstitial space. The increased alveolar volume provides a greater surface area for this resorption. At the same time, there is a dramatic increase in pulmonary blood flow, which helps to drain the interstitial fluid into the micro-circulation. This early increase in flow is due to vasodilation of pulmonary arterioles and a rapid fall in PVR, mediated by lung aeration, oxygenation and release of vasoactive agents by the pulmonary endothelium, including nitric oxide and prostacyclin (prostaglandin PGI_2). PVR then continues to fall slowly in the first weeks after birth due to involution of smooth muscle in the arteriolar walls.

Pulmonary flow is also promoted by involution of the ductus arteriosus. Immediately after birth, there is a decline in the levels of prostaglandins which promote duct patency (PGE_1 and PGE_2, produced during intrauterine life by the placenta and by the duct itself) and therefore a reduction of the right to left shunt at the ductus arteriosus. The loss of the low-resistance placental circulation and the resulting increase in systemic vascular resistance (SVR) contribute to this reduction. Constriction of the duct leads to functional closure by day 2 in healthy term infants, and by day 4 in most preterm babies. The increase in pulmonary venous return and left atrial pressure then causes a functional closure of the 'flap valve' of the foramen ovale.

The ductus venosus closes functionally within hours of birth but can be used immediately after birth to provide access to the central circulation via an umbilical venous catheter. In healthy term babies, anatomical closure of the shunts usually occurs within days to weeks, although the foramen ovale may remain 'probe patent' into adult life.

Managing the Transition from Intrauterine to Extrauterine Life

The transition from intrauterine to extrauterine life may not be smooth, and it can be influenced by clinical interventions. Premature babies may produce inadequate levels of surfactant and are at risk of respiratory distress syndrome (RDS). Antenatal corticosteroids are given to mothers at risk of preterm birth to increase endogenous surfactant, and exogenous surfactant is administered to preterm infants. Surfactant function can be impaired by the presence of blood, meconium and bacteria and also by high glucose concentrations (e.g. in gestational diabetes); RDS may therefore complicate other diseases. For infants who do not breathe adequately at birth, the priority is to establish a patent airway, lung aeration and a functional residual capacity. Intermittent positive pressure ventilation (IPPV) with positive end expiratory pressure (PEEP) may be required, with FiO_2 titrated to oxygen saturation. There is growing recognition of the dangers of hyperoxaemia, and 100% oxygen is no longer recommended for initiation of resuscitation. It is associated with increased mortality in term infants and reduced cerebral perfusion in preterm infants.

Recent work has examined the effect of delayed cord clamping (DCC) on cardiovascular parameters and developmental outcomes. In utero, pulmonary venous return makes only a small contribution to left atrial filling, which is largely achieved by the right-to-left shunt across the foramen ovale. This in turn is dependent on flow from the umbilical vein. At birth, cord clamping leads to an immediate drop in left atrial volume, which only recovers once the lung is aerated, PVR drops and pulmonary venous return is established as the source of left atrial filling. DCC (by one to two minutes after birth) provides a transfer of 80–100 ml of blood to the newborn, which helps maintain left atrial volume. DCC is associated with increased birth weight, haemoglobin concentration and iron stores in term babies, and improved cardiovascular stability, decreased need for blood transfusion and lowered incidence of necrotising enterocolitis and intraventricular haemorrhage in preterm infants. There is also an association with improved motor and social neurodevelopmental outcomes, which may be linked to the alleviation of iron deficiency. No mortality benefit has yet been shown, although trials are under way.

Persistence of the fetal shunts into extrauterine life can be pathological or be vital to sustaining the circulation in some congenital cardiac lesions. Patent ductus arteriosus (PDA) may be seen in about 30% of preterm infants, rising to 50% in babies with birth weight <800 g. In utero ductal

patency is dependent on low fetal arterial oxygen tension and elevated prostaglandin levels. For a healthy infant at birth, reversal of this situation leads to constriction of the smooth muscle of the ductus and a subsequent ischaemic hypoxia, which causes irreversible remodelling of the ductus into the ligamentum arteriosum. Persistently low oxygen tension or elevated prostaglandins, as often seen in preterm infants with respiratory insufficiency, can cause failure of duct constriction. Even where there is some constriction, the hypoxic ischaemia required to cause remodelling does not always occur, meaning that preterm infants can reopen their ductus and revert to a transitional circulation during times of oxygen stress, (including intraoperative stress, as may occur during neonatal surgery). If PVR is sufficiently low, a haemodynamically significant PDA will cause left-to-right shunting and increased pulmonary flow, with worsening respiratory distress and heart failure.

If PVR fails to fall after birth or increases in early neonatal life, then shunting will be right to left. This causes central hypoxaemia when the shunt occurs at the foramen ovale, and systemic hypoxaemia if the shunt occurs at the ductus arteriosus (therefore implying that pulmonary arterial pressures are suprasystemic). This condition is termed persistent pulmonary hypertension of the newborn (PPHN). It may be idiopathic or occur in association with perinatal asphyxia, sepsis, meconium aspiration, or pulmonary hypoplasia (e.g. congenital diaphragmatic hernia). In this setting, continuing hypoxia and acidosis can exacerbate pulmonary vasoconstriction, creating a vicious cycle that can quickly lead to deterioration. Treatment requires management of the underlying pathology (or relief from the precipitating factor during an intraoperative crisis) by:

- Alleviation of elevated PVR with increased FiO_2 support
- Pulmonary vasodilator therapy
- Adequate sedation
- Increased systemic pressures to reduce the unfavourable gradient between the pulmonary and systemic circulations

An untreated left-to-right shunt with high pulmonary flows will eventually lead to pulmonary vascular remodelling and a secondary rise in PVR, with subsequent reversal in ductal flow (Eisenmenger's syndrome).

Initial management of a PDA may be medical, with COX inhibitors such as ibuprofen or indomethacin, which block prostaglandin synthesis and hence promote ductal constriction. These methods become less successful with increasing gestational age, in which case transcatheter closure or surgical ligation and division may be required.

Continued ductal patency may be essential in some cardiac conditions (see Chapter 31) to allow flow into either the systemic circulation (e.g. hypoplastic left-heart syndrome or critical coarctation) or to the pulmonary circulation (e.g. pulmonary atresia). In these cases, a prostaglandin infusion may be required to keep the duct open until surgical correction can be performed.

Ventricular remodelling occurs after birth. In utero, the right ventricle pumps 65% of the cardiac output. After birth, the left ventricle becomes dominant, and left-ventricular wall thickness increases to adapt to the rising SVR. In babies with transposition of the great arteries, the left ventricle pumps into the low-resistance pulmonary circulation. These children require an arterial switch procedure in the first weeks of life. If this is delayed, left-ventricular remodelling does not occur, and the left ventricle will be unable to respond to the demands of the systemic circulation.

Clinical Implications of Newborn Physiology and Anatomy

Respiratory

Oxygen consumption in neonates, at 6–8 ml kg^{-1} min^{-1}, is twice that of adults. Tidal volume is relatively fixed at around 7 ml kg^{-1}, but respiratory rate is raised (30–40 per minute), resulting in a high minute ventilation, which accelerates induction and emergence from anaesthesia.

Airway obstruction is a hazard for neonates and infants undergoing anaesthesia. The prominent occiput predisposes to neck flexion. The tongue is large, and together with the soft palate it can easily obstruct the airway by falling against the posterior pharyngeal wall. Loss of pharyngeal tone during anaesthesia exacerbates this situation. The long epiglottis, coupled with a relatively high and anterior larynx, means that a straight blade laryngoscope may offer better visualisation of the laryngeal inlet (although whether it is placed within the vallecula or used to lift the epiglottis

directly may be judged on a case-by-case basis by the practitioner). A shoulder roll can help by reducing the neck flexion caused by the large occiput. Traditionally, the infant larynx was held to be conical in shape, with the narrowest portion at the level of the cricoid cartilage. This led to the mantra that cuffed tracheal tubes (TT) were to be avoided in children under eight years old because of the risk of airway oedema and subsequent subglottic stenosis. Recent studies have questioned this view. Some endoscopic assessments of children undergoing anaesthesia suggest that the larynx may in fact be the narrowest portion. However, in vitro studies of autopsy specimens continue to show that the smallest fixed and non-distensible aperture in the upper airway is at cricoid level. Nevertheless, the new generation of high-volume, low-pressure cuffed tubes are widely and safely used now in children down to <3 kg. Uncuffed tubes are associated with leaks, which may lead to inaccurate monitoring of tidal volumes and capnography and potentially inadequate delivery of ventilation. In one large single-centre trial, cuffed tubes were associated with *lower* risks of perioperative laryngospasm and postoperative stridor, whilst another multi-centre trial failed to show a difference in postoperative stridor between cuffed and uncuffed tubes. A recent Cochrane review concluded that there was insufficient evidence to draw definitive conclusions about the advantages of one over the other. If cuffed tubes are used, cuff pressures should be monitored and care taken to avoid over-inflation (<20 cm H_2O).

The trachea is short, and accidental endobronchial intubation is a common hazard, so the TT position should be checked by auscultation and/or endoscopy. A small TT, when placed out of sight under warm drapes, can soften and kink. The airways are narrow and easily blocked by blood, oedema or secretions. They are also more compliant in neonates and so can be compressed relatively easily. As per Poiseuille's law, airway resistance is inversely proportional to the fourth power of airway radius, so small reductions in airway size can have significant consequences for airflow. Children with laryngo-, tracheo- or bronchomalacia are at particular risk of conducting airways narrowing during expiration, when intrathoracic pressure rises. This risk is raised if expiratory efforts are increased due to airflow obstruction, thus increasing the work of breathing and intrathoracic pressure and reducing airways' diameter further.

The lower airways in infants are also more likely to collapse because of reduced tissue elasticity. Elastic recoil is a property of mature lungs and maintains the patency of small airways through radial attachments between alveoli. In infants, the process of alveolarisation is not yet complete, and these attachments are not mature.

The functional residual capacity (FRC) is the volume remaining in the lungs at the end of a normal expiration. It represents an equilibrium: the point at which the tendency of the lung to recoil inwards is balanced by the tendency of the chest wall to recoil outwards. The infant chest wall is highly compliant and less able to recoil outwards, meaning that FRC is reduced; it also wastes diaphragmatic energy on chest wall deformation. This means that there is a smaller oxygen store available, which, combined with the higher oxygen consumption, means that desaturation occurs quickly if the child becomes apnoeic. The poor elastic properties of both the lung and the chest wall means that closing volume in infants is greater than FRC, with dependent airways closing during expiration in normal tidal breathing. Infants exhibit several adaptations to mitigate this:

- A higher respiratory rate, which allows less time for exhalation down to the equilibrium point
- Laryngeal adduction during exhalation ('auto-PEEP'), which increases airflow resistance (at the expense of raised mean intrathoracic pressure)
- Diaphragmatic tone is maintained during expiration

Several factors combine to reduce the efficiency of neonatal respiration. The thoracic cavity is round rather than dorso-ventrally flattened, and the ribs are soft and horizontally aligned, so the 'bucket handle' action that increases thoracic volume in adults does not occur. The diaphragm is less efficient because of the compliant chest wall, and because it is more horizontally mounted. It also has fewer fatigue-resistant type 1 fibres, so increasing the neonate's susceptibility to respiratory failure.

Gastric insufflation is common after face mask ventilation and may result in diaphragmatic splinting. Decompression with a nasogastric tube will improve respiratory function and reduce the aspiration risk.

In anaesthetised infants, apparatus dead space and resistance should be kept to a minimum to reduce the work of breathing. In neonates, spontaneous ventilation under anaesthesia is best avoided except for very short cases, and pressure support should be employed to supplement efforts. Application of continuous positive airway pressure (CPAP) or PEEP increases lung volumes and maintains FRC, reduces the work of breathing, improves gas exchange and reduces atelectasis.

Lung-protective ventilation strategies should be employed where possible to reduce the risk of ventilator-induced lung injury, which is a risk factor for the development of bronchopulmonary dysplasia. Volutrauma, barotrauma and atelectrauma (injury caused by ventilating inadequately recruited lungs, such that there is shear stress from repeated alveolar collapse and distension) can combine to trigger biotrauma (lung injury caused by the release of inflammatory mediators). Oxygen toxicity via free radical formation is another cause of lung biotrauma. Unrestricted oxygen concentrations also promote atelectasis and decrease FRC, as oxygen is easily absorbed (whereas nitrogen is poorly absorbed). They also increase the rate of retinopathy of prematurity (ROP) in preterm infants. The clinically optimal saturation range for infants is unknown; neither is it known whether saturations on spontaneously breathing babies should be the same as ventilated, or whether infants ventilated on intensive care should be managed differently from those anaesthetised for surgery. The pragmatic practice in our institution is that FiO_2 for infants undergoing surgery should be titrated to maintain oxygen saturation in the normal range.

Control of carbon dioxide levels is also important in neonates, and particularly in preterm infants. Hypocapnia has been associated with an increased risk of bronchopulmonary dysplasia (BPD), development of periventricular leukomalacia and intraventricular haemorrhage. Mild hypercapnia appears to be safe, and a permissive hypercapnia strategy (target 6–8 kPa whilst maintaining a normal pH) may help reduce lung injury in mechanically ventilated infants.

Control of Ventilation

Control of ventilation is immature at birth. Brainstem rhythm-generating centres and peripheral and central chemoreceptors mature to oversee a transition from irregular fetal breathing efforts to continuous respiratory activity capable of maintaining homeostasis. The response to hypoxia is biphasic, with an initial increase in ventilation followed by hypoventilation or apnoea. Hypercapnia leads to an increased minute ventilation in term neonates and children, but this response is attenuated in preterm infants.

Apnoeic episodes are common in neonates, occurring predominantly during REM sleep. Laryngeal reflexes are potentiated and can stimulate prolonged apnoea. Paradoxical breathing (chest and abdominal movements out of synchrony) can be seen in REM sleep because of underdeveloped control of musculature. The risk of apnoeic episodes increases with prematurity, anaemia and exposure to opioids or other respiratory depressants and decreases with increasing age. Term infants are at low risk after 44 weeks postmenstrual age (PMA). For premature neonates, 60 weeks PMA is often taken as the timepoint at which control of ventilation is sufficiently mature to reduce the risk to acceptable levels. Most institutions would not routinely schedule day-case surgery for premature infants before this date. Apnoeas are mostly central, but obstructive and mixed episodes are seen and are more common in preterm infants.

Anaesthetic agents affect both control of ventilation and ventilatory parameters. Inhaled volatiles depress ventilatory drive, tidal volume and minute ventilation, whilst also blunting the response to CO_2. Neuromuscular blocking agents and propofol decrease FRC.

Cardiovascular

Cardiac output is high in neonates (300 ml kg^{-1} min^{-1} vs 60–80 ml kg^{-1} min^{-1} in adults) to meet the increased metabolic demand and oxygen requirement. As in adults, the Frank–Starling mechanism regulates the relationship between myocyte stretch and contractility. However, the ability to increase stroke volume is limited, particularly in preterm infants. Studies show that fluid response in neonates is maintained only to around 1.3 times normal end diastolic volume. Beyond this, preload responsiveness is unlikely, and the risk of pulmonary oedema rises. In addition, immature myocytes do not generate the same contractile force as adult myocytes throughout the entire range of the length-tension curve. It is often

said therefore that cardiac output in infants is rate dependent, and whilst this may be an over-simplification, the immature myocardium has limited reserve to increase its output. The neonatal heart is also very sensitive to changes in afterload; increases in systemic or pulmonary vascular resistance can reduce cardiac output.

Neonates are sensitive to the negative inotropic effects of anaesthetic agents and less able to mount a compensatory response. Volatile agents depress contractility and diastolic function by impairing Ca^{2+} flux, and this effect appears to be more pronounced in infants than adults.

Innervation of the heart is functionally immature at birth, and sympathetic tone dominates, resulting in high contractility and high resting heart rate. Parasympathetic tone increases with age, but vagally mediated cardiac reflexes are well developed in infancy and can predispose to bradycardia when stimulated in certain situations. Examples include CO_2 insufflation to create a pneumoperitoneum in laparoscopic surgery and the oculocardiac reflex during ophthalmic surgery. Atropine protects against vagally mediated reflexes and was once given routinely as a premedication, but this practice is now uncommon.

Haematology

At birth, fetal haemoglobin (HbF) forms 70–80% of total haemoglobin. HbF has a higher affinity for oxygen than adult haemoglobin (HbA), ensuring that oxygen is transferred from mother to fetus in the placental circulation. Figure 1.2 displays the oxyhaemoglobin dissociation curves for HbA and HbF and is annotated with generally accepted values. Note that the P_{50} (the value at which haemoglobin is 50% saturated) for HbA is 3.5 kPa but around 2.5 kPa for HbF, indicating the higher affinity of the latter for oxygen. This higher affinity comes at the cost of oxygen dissociation. In the relatively hypoxic environment of the fetal organs, oxygen dissociates readily from HbF and is available for tissue extraction. However, in postnatal life, tissue oxygen extraction occurs between the arterial PaO_2 of 13.3 kPa and the venous PaO_2 of 5.3 kPa. Under these conditions, the amount of oxygen available for the tissues is significantly
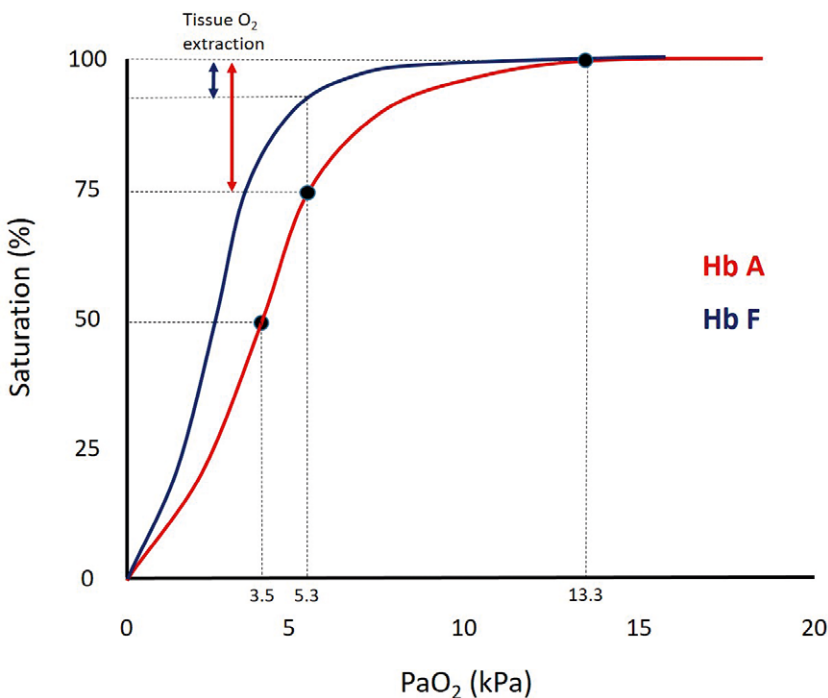

Figure 1.2 Oxygen-haemoglobin dissociation curves for HbA and HbF haemoglobin molecules, annotated with generally accepted values. Note the P50 values for HbA and HbF are 3.5 and 2.5 respectively, indicating the higher affinity of HbF for oxygen. Tissue oxygen extraction occurs between the arterial value of 13.3 kPa and the venous value of 5.3 kPa. Arrows indicate the difference in tissue oxygen delivery between the two haemoglobin molecules.

greater from the HbA carrier compared to HbF. A high Hb concentration during the neonatal period partially compensates for this – 180–200 g L^{-1} at birth, falling to around 150 g L^{-1} in the first week of life. HbA then quickly becomes the dominant component, reaching over 90% of total haemoglobin in the first weeks of life. At this infant age, tissue oxygen delivery is even more efficient than in adults because of a high cardiac output coupled with increased levels of 2,3-diphosphoglycerate (2,3 DPG), which shift the oxyhaemoglobin dissociation curve further rightwards.

Many infants requiring intensive care will receive a blood transfusion at some point. The British Committee for Standards in Haematology (BCSH) transfusion guidelines for neonates suggests the thresholds given in Table 1.1. These are based on a number of studies and a 2011 Cochrane analysis on the risks and benefits of a liberal versus restrictive transfusion strategy. However, the safe lower limits for neonatal haemoglobin levels remain unknown, and clinical judgement must be exercised, particularly in the perioperative setting, when strict adherence to these guidelines may be inappropriate. As a guide, 4 ml kg^{-1} of packed red blood cells (PRBC) raises the haemoglobin (Hb) level by approximately 10 g L^{-1}. Neonates should receive cytomegalovirus (CMV) negative PRBC.

Thrombocytopenia is a common finding in unwell neonates. There is no clear correlation between the severity of thrombocytopenia and major bleeding, and prophylactic platelet transfusions are rarely indicated. Suggested platelet thresholds for transfusion are:

- $<20 \times 10^9$ L^{-1} in the absence of bleeding
- $<50 \times 10^9$ L^{-1} if actively bleeding or requiring surgery
- $<100 \times 10^9$ L^{-1} if major bleeding or planned surgery in critical areas (e.g. eye or neurosurgery)

The typical dose is 10–20 ml kg^{-1}.

Tests of coagulation in neonates are difficult to interpret because of age-related differences in normal values, and because laboratory reference ranges vary. Vitamin K-dependent clotting factors are low in neonates and preterm infants, and vitamin K prophylaxis is given to reduce the risk of haemorrhagic disease of the newborn.

Fresh frozen plasma or a solvent/detergent–treated pooled human plasma product (e.g. Octaplas®) are indicated for vitamin K deficiency with bleeding, disseminated intravascular coagulation (DIC) with bleeding or coagulation factor deficiencies where no specific factor concentrate is available. The usual dose is 15 ml kg^{-1}. There are significant adverse reactions associated with these products, so the expected benefit of transfusion must be balanced against the associated risk.

Cryoprecipitate is indicated for fibrinogen deficiency, at a dose of 5–10 ml kg^{-1}. In practice, these products are also used in the management of acute or intraoperative bleeding where surgical control is not possible, and in this setting their use should be guided by laboratory assays. Thromboelastography measures the global viscoelastic properties of blood clot formation and may be a better guide to rational blood product use in the acute setting than conventional tests of coagulation.

Renal, Hepatic and Metabolic

Renal development begins at 5 weeks gestation, with nephrogenesis commencing at around 9 weeks and being complete by 36 weeks. A functional renin-angiotensin system is present from early in gestation and is crucial for normal renal development. Fetal urine output contributes the majority of the amniotic fluid, which in turn is important for lung development. Renal abnormalities at this stage are associated with pulmonary hypoplasia. Preterm babies have fewer nephrons at birth and more abnormal glomeruli and often display impaired renal function in infancy. In adulthood, there are associations with chronic kidney disease and hypertension.

Table 1.1 BCSH-recommended haemoglobin threshold levels for neonatal top-up transfusions

Postnatal age	Suggested transfusion threshold Hb (g L^{-1})		
	Ventilated	On oxygen or CPAP	Off oxygen
<24 hr	120	120	100
1–7 days	120	100	100
8–14 days	100	95	<75–85 depending on clinical situation
Day 15 onwards		85	

At birth, antidiuretic hormone (ADH) levels are high and the glomerular filtration rate (GFR) is low, so urine output is low, and sodium and water are conserved. A brisk diuresis then occurs as ADH levels fall. Term infants lose around 10% of their extracellular fluid, with a corresponding loss of sodium. By day 3 in term neonates, distal tubular function becomes more responsive to aldosterone, and sodium conservation increases. An immature urinary concentrating ability means that babies produce large amounts of dilute urine that is isotonic with plasma. They are prone to dehydration if fasted, and renal failure is common in sick infants. Preterm infants have impaired ability to both conserve and excrete sodium, and sodium disturbances are common.

The liver in newborn infants contains only 20% of the adult complement of hepatocytes. Drug-handling systems are immature (see Chapter 2), and in general drug effects are pronounced and prolonged. Dose adjustments must be made for common perioperative drugs, including paracetamol and opioids.

Glucose is the primary energy substrate for the fetus and neonate. Until birth, the fetus is dependent on placental transfer to meet glucose and other metabolic requirements. Glycogenesis and lipogenesis occur in preparation for postnatal life. At birth, a cortisol and catecholamine surge leads to glycogenolysis and hepatic gluconeogenesis to meet neonatal energy requirements whilst enteral feeds are established. As glycogen is depleted, lipolysis yields glycerol and free fatty acids. The former is used for further gluconeogenesis, and the latter as a metabolic substrate either directly or after conversion into ketone bodies. Newborn infants have high metabolic rates but relatively small hepatic stores of substrate and immature gluconeogenic enzyme systems. They are therefore highly susceptible to hypoglycaemia if nutrition is interrupted. Asymptomatic hypoglycaemia may have neurodevelopmental sequalae. The normal range for blood glucose concentrations in neonates is undefined, but the World Health Organisation (WHO) suggests <2.6 mmol l^{-1} as the operational threshold of hypoglycaemia.

Some practical suggestions are given here for the management of glucose and fluid requirements in the term neonate. These may not be applicable in all circumstances; premature infants, those with hypoxic ischaemic encephalopathy, those in renal or cardiac failure or those suffering from critical illness may need further advice from neonatal intensive care unit (NICU) or specialist teams. Fluids should be restricted until the postnatal diuresis has occurred. Excessive fluids may impair cardiorespiratory adaptation and promote PDA, particularly in premature infants. Sodium is usually withheld in the first days of life but is added to maintenance fluids after the postnatal diuresis. Table 1.2 reflects standard practice for maintenance fluids in our NICU.

A balanced crystalloid solution containing glucose (e.g. Plasma-Lyte 148 with 5% glucose) may be preferable to hypotonic solutions for perioperative care. Blood sugar should be measured routinely during surgery, and guidelines in our institution are to maintain this between 2.6–8.3 mmol L^{-1}. Intraoperative fluid boluses should be from a glucose-free balanced salt solution such as Hartmann's solution.

Table 1.2 Standard fluid maintenance volumes for the term neonate

Age	Fluid regime
Day 1	60 ml kg^{-1} day^{-1} 10% glucose
Day 2	90 ml kg^{-1} day^{-1} 10% glucose + 0.45% NaCl ± 10 mmol potassium
Day 3	120 ml kg^{-1} day^{-1} 10% glucose + 0.45% NaCl ± 10 mmol potassium
Day 4+	150 ml kg^{-1} day^{-1} 10% glucose + 0.45% NaCl ± 10 mmol potassium

Endocrine

Glucocorticoids, thyroid hormones and catecholamines play a vital role in fetal organ maturation. Cortisol is produced in the fetal adrenal glands and provided by placental transfer of maternal cortisol. Before birth, cortisol activates the hypothalamic–pituitary–adrenal (HPA) axis, induces liver enzyme activity and promotes organ maturation in the lung, digestive system and kidneys. It also plays a role in the onset of parturition. Exogenous corticosteroids are given to women at risk of preterm delivery, and these also coordinate the maturation response. Exposure to cortisol alters the lung parenchyma; collagen and elastin fibres increase, and the alveolar septae thin in readiness for gas exchange. Surfactant production is upregulated. Thyroid maturation is driven

by a cortisol rise before delivery, leading to increased circulating tri-iodothyronine (T3), which acts synergistically with cortisol to promote maturation in many tissues. The process of lung fluid resorption at birth is dependent on cortisol, T3 and adrenaline. Thyroid hormones play a role in cardiac growth, differentiation and contractility, and, together with catecholamines, prime the cardiovascular response to birth.

Thermoregulation

Thermoregulation in the neonate is limited and easily overwhelmed by environmental conditions. Thermal energy arises from two major sources: metabolically active tissues (primarily brain) and non-shivering thermogenesis. The latter describes metabolism of brown fat, a specialised store located within the thorax and abdomen, where adenosine triphosphate (ATP) synthesis within mitochondria is uncoupled from respiration. This process is inhibited by volatile anaesthetic agents, and there is a great potential for heat loss due to a high body surface area to weight ratio, increased thermal conductance and increased evaporative heat loss through thin skin. Premature infants are at particular risk and should have minimal handling and exposure to minimise heat loss. Where possible, surgery should be performed on the NICU to mitigate these risks.

Pain

Neonates, including premature neonates, show well-developed responses to painful stimuli. These responses are not always recognised in clinical practice, resulting in under-treatment of neonatal pain, which can have both short- and longer-term consequences. The former includes potentially deleterious physiological instability such as changes in heart rate and respiration. The latter may include altered pain thresholds and neurocognitive development in later life. In fact, the neonatal period is a time of great neuronal plasticity, and both pain stimuli and administration of exogenous analgesia may have effects on neuronal development.

Long-Term Effects of Early Exposure to General Anaesthesia

It is increasingly apparent that general anaesthetics have wider effects on the nervous system beyond altering consciousness, and that these effects persist beyond the period of clinical anaesthesia. In fact, it seems unlikely from first principles that anaesthetics *should* have only benign and reversible actions on consciousness. They are thought to act promiscuously on receptor targets such as γ-Aminobutyric acid (GABA), N-methyl-D-aspartate (NMDA) and a variety of other protein channels and are typically given at large concentrations to overcome their lack of selectivity. These targets are widespread and have important roles in neural development and plasticity. It is unsurprising, therefore, that interruption of consciousness at particular timepoints in brain age may be accompanied by other effects on the neuronal architecture, network or function. This has led to a call for anaesthetics to be seen not just as drugs which temporarily interrupt consciousness but as modulators of neural plasticity.

Although there is potential to harness these effects for good, (e.g. modulation of glutamatergic signalling by ketamine is being investigated in the treatment of severe depression), there is also significant public health concern about long-lasting and potentially toxic developmental effects of general anaesthetics. In 1999, ketamine, an NMDA receptor antagonist and widely used general anaesthetic, was shown to induce apoptotic neurodegeneration in the developing rat brain. Further work followed, showing that almost all clinically relevant general anaesthetic agents, including volatile gases, ketamine, nitrous oxide, midazolam and propofol, are associated with this phenomenon. Furthermore, rat pups exposed to commonly used anaesthetic agents also developed persistent impairments in learning and memory. These findings have now been broadly replicated in multiple different organisms, including non-human primates.

The most consistent and robust findings of neuropathology and behavioural impairment have generally come under the following conditions:

- Exposure at particular species-specific developmental windows (for both rodents and non-human primates, this has typically been in postnatal days 1–7)
- Prolonged exposure rather than short episodes (typically for several hours)
- Exposure to combinations of multiple anaesthetic agents rather than to monotherapy

In 2016, the FDA placed an advisory warning on the administration of anaesthesia to children

under the age of three or to pregnant women in their third trimester. This has raised concerns amongst both practitioners and patient groups and led to much debate. In most situations where general anaesthesia is contemplated, there are simply no alternatives. Regional and neuraxial techniques block pain pathways without affecting consciousness but can rarely be used as a sole technique in young children. The only drugs in clinical use that have not been consistently shown to cause neurodegeneration in animal models are dexmedetomidine and opioids; neither are generally sufficient to provide anaesthesia on their own. Safely delaying surgery to an older age is rarely an option. Finally, suboptimal anaesthesia and pain may in themselves lead to altered neurodevelopmental trajectories.

Some studies of human children suggest an association between exposure to anaesthesia at a young age and diagnosis of neurodevelopmental disorders, whilst others have failed to demonstrate a correlation. These contradictory findings are not surprising; the challenges encountered in this field are well recognised and have been comprehensively discussed in the literature. Most studies have used retrospective cohorts drawn from historical databases and have found it difficult to separate the effects of anaesthesia from surgery or comorbidity. They encounter use of historical drugs and techniques, heterogeneous dose-exposure relationships and surgical interventions and are hampered by multiple population-specific confounders. The absence of a recognised human phenotype associated with anaesthesia-induced neurotoxicity means that there is no consistency in the use of outcome measures. To date, there have been three large trials with prospective neurodevelopmental testing: the Pediatric Anesthesia and NeuroDevelopment Assessment (PANDA) study, the General Anaesthesia Spinal (GAS) trial and the Mayo Anaesthesia Safety in Kids (MASK) study. These are reassuring to the extent that they suggest that a single short exposure to general anaesthesia in infancy does not lead to measurable differences in the studied primary outcome of global cognitive function in later childhood. However, paediatric anaesthetists should remain cautious. There *were* measurable differences in some parent-reported secondary outcome measures. The MASK study also found that multiple exposures are associated with impaired neurodevelopmental outcomes. Across these three studies, there are no significant associations across the same neurodevelopmental domain, raising questions about why this lack of consistency arises. Finally, neurodevelopmental outcome measures may have poor predictive validity, such that it is difficult to establish the significance of a finding at a particular point in time for a child's future development. The author's preferred position is that there is currently no compelling evidence to prompt immediate changes in clinical practice (beyond the pragmatic consideration of minimising exposure where possible).

Adverse Outcome Pathways (AOPs) are a structured approach to integrating the available information and aiding evidence synthesis. An AOP seeks to build a chain that links the key events, from the initial molecular stressor to the phenotypic change in the organism, with intervening steps at cellular, tissue and organ levels. Such pathways offer a framework for future integrated research in this area and may help to reconcile the pathology seen in basic science models with the uncertain clinical implications in the paediatric-population.

Key Points

- Early neonatal life is a time of rapid development, adaptation and plasticity.
- The physiological adaptation to postnatal life is complex, and failures in this process underlie many common neonatal presentations.
- Respiratory complications are common in the perioperative period and are mitigated by meticulous preparation, supported ventilation, titrated oxygen concentrations and constant vigilance. Apnoeas in preterm infants are to be expected, and risks are increased with anaemia and with exposure to opioids and other respiratory depressants.
- Cardiovascular reserve is limited, volume-loading has a limited ability to improve stroke volume and anaesthetic agents have a negative inotropic effect.
- BCSH transfusion guidelines for neonates assist the rational management of transfusion requirements, but clinical judgement must always be exercised.

- Organ development is immature, and homeostatic function is impaired. Disorders of fluid, electrolyte and glucose handling are common. Thermoregulation is limited.
- Neonates feel pain, and failure to treat pain is both cruel and may have longer-term developmental implications.

- Anaesthetics do not just impair consciousness. They are implicated in the modulation of neural plasticity, and animal evidence suggests they may affect neurodevelopmental trajectories. However, as yet there is no compelling evidence in children to change current best practice.

Further Reading

Baum VC, Palmisano BW. The immature heart and anesthesia. *Anesthesiology* 1997; 87(6):1529–48. doi:10.1097/00000542-199712000-00032

Ikonomidou C, Bosch F, Miksa M, et al. Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. *Science* 1999; 283(5398):70–4. doi:10.1126/science.283.5398.70

Murphy PJ. The fetal circulation. *Continuing Education in Anaesthesia Critical Care and Pain* 2005; 5(4): 107–12. doi:10.1093/bjaceaccp/mki030

Neumann RP, Ungern-Sternberg BS von. The neonatal lung: physiology and ventilation. *Pediatric Anesthesia* 2014; 24(1):10–21. doi:https://doi.org/10.1111/pan.12280

Riviere D, McKinlay CJD, Bloomfield FH. Adaptation for life after birth: a review of neonatal physiology. *Anaesthesia and Intensive Care Medicine* 2017; 18(2):59–67. doi:10.1016/j.mpaic.2016.11.008

Walkden G, Pickering A, Gill H. Assessing long-term neurodevelopmental outcome following general anesthesia in early childhood: challenges and opportunities. *Anesthesia and Analgesia* 2019; 128(4):681–94. doi:10.1213/ANE.0000000000004052

Waspe J, Chico T, Hansen T. Applying the adverse outcome pathway concept to questions in anaesthetic neurotoxicity. *British Journal of Anaesthesia* 2021; 126(3):1097–102.