

Anatomy and Physiology

CENTRAL NERVOUS SYSTEM

The central nervous system in the neonate differs from that in the older child: the myelination of nerve fibers is incomplete, and the cerebral cortex is less developed; its cellular elements continue to increase during the first years of life. Reflexes not seen in older children may be elicited. Neonatal spinal reflexes are more generalized and the threshold is lower. In the preterm, brainstem-evoked potentials are prolonged, and the normalization of these coincides with maturation of respiratory control mechanisms.

Anesthesia-induced developmental neurotoxicity has been demonstrated in some neonatal animal models, but the significance of this to humans remains uncertain and will be difficult to fully determine. Meanwhile, appropriate anesthesia and analgesia should be provided to all young children.

Sensitivity to Pain

Until quite recently, little was understood of the ability of infants and small children to appreciate pain. As a result, there was an unfortunate tendency to ignore the need for analgesia during painful procedures, even during and after surgical operations. It is now well established that neonates, including those born prematurely, may have increased sensitivity to pain and will react to it with tachycardia, hypertension, increased intracranial pressure, and a neuroendocrine response that exceeds that reported in adults. Infants demonstrate measurable behavioral responses to pain (e.g., crying, grimacing, restlessness); these responses have been used as a basis for pain scoring systems. Evidence suggests that infants who are subjected to painful procedures (e.g., circumcision) without adequate analgesia may experience an increased sensitivity to pain as older children. This has been attributed to the persistence of alterations in the infant's central processing of painful stimuli. Control of intraoperative and postoperative pain, by modifying stress responses, may possibly even improve survival in infants with critical illness. It is for these reasons that we provide optimal analgesia or anesthesia for all infants and children during and after *any* painful

procedure with the same care as we do for adults. As children grow from infancy into early childhood, their pain threshold remains reduced compared with that of older children or adults.

CRANIUM AND INTRACRANIAL PRESSURE

The skull is less rigid in infants than in adults. As a result, an increase in the volume of its contents—blood, cerebral spinal fluid (CSF), and brain tissue—can be accommodated to some extent by expansion of the fontanelles and separation of the suture lines. Palpation of the fontanelles can be used to assess intracranial pressure in infants. Intracranial pressure (ICP) increases with age ranging from 0–6 mmHg in infants to 13–15 mmHg in adolescents.

CEREBRAL BLOOD FLOW AND INTRAVENTRICULAR HEMORRHAGE

Autoregulation of cerebral blood flow (CBF) is impaired in sick neonates, rendering CBF pressure dependent. The threshold below which autoregulation of CBF is impaired is unknown, although some hold that this threshold (mean BP) is the gestational age in mmHg. Hypotension may lead to cerebral ischemia, and pressure fluctuations are transmitted to the capillary circulation. In the preterm infant, the cerebral vessels are very fragile, especially in the region of the germinal matrix overlying the caudate nucleus. Rupture of these vessels leads to intracerebral hemorrhage, which often extends into the ventricular system as an intraventricular hemorrhage (IVH).

Small preterm infants are very prone to IVH, which usually occurs during the first few days after birth and is a leading cause of mortality and morbidity; survivors have a high incidence of cerebral palsy, mental retardation, hydrocephalus, and psychiatric disorders. Potential predisposing factors to IVH include hypoxia, hypercarbia, hypernatremia, fluctuations in arterial or venous pressure, low hematocrit, overtransfusion, and rapid administration of hypertonic fluids (e.g., sodium bicarbonate, dextrose).

The anesthesiologist should avoid precipitating these factors in the small preterm infant: airway manipulations, including awake tracheal intubation, and suctioning have been shown to increase blood pressure and anterior fontanelle pressure to similar extents, similar to coughing as well. “Awake” intubation should be avoided whenever possible (even though a definite relationship between “awake” tracheal intubation and IVH has never been established). If the airway is known or appears to be difficult to secure or maintain by facemask, then an “awake” or preferably sedated tracheal intubation is a reasonable choice.

If an awake tracheal intubation is planned, topical analgesia to the mouth and palate (using weight-appropriate doses of local anesthetic [see p. 142]) may attenuate the infant's physiologic responses.

To further prevent blood pressure fluctuations during surgery or painful procedures, adequate anesthesia and analgesia should be provided. Rapid injections of undiluted hypertonic solutions, such as dextrose or sodium bicarbonate, should be avoided. Care should be taken to replace blood losses accurately. Severe anemia and/or coagulopathy should be corrected promptly. Periventricular leukomalacia is a major feature of persistent brain damage in small preterm infants and may follow IVH or may be a direct consequence of prematurity, hypoxia, ischemia, inflammation, and chronic persistent hypotension. Indomethacin therapy may reduce the incidence of severe IVH.

CEREBROSPINAL FLUID AND HYDROCEPHALUS

The CSF, which occupies the cerebral ventricles and the subarachnoid spaces surrounding the brain and spinal cord, is formed by choroid plexuses in the temporal horns of the lateral ventricles, the posterior portion of the third ventricle, and the roof of the fourth ventricle. Meningeal and ependymal vessels and blood vessels of the brain and spinal cord also contribute small volumes of CSF.

The choroid plexuses are cauliflower-like structures consisting of blood vessels covered by thin epithelium through which CSF continuously exudes. The rate of CSF formation is variable, increasing in the first two years to ~0.13 mL/min. Except for the active secretion of a few substances by the choroid plexus, CSF is similar in composition to interstitial fluid.

CSF flow is initiated by pulsations in the choroid plexus. From the lateral ventricles, CSF passes into the third ventricle via the foramen of Monro and along the aqueduct of Sylvius into the fourth ventricle, each ventricle contributing more fluid by secretion from its choroid plexus. CSF then flows through the two lateral foramina of Luschka and the midline foramen of Magendie into the cisterna magna and throughout the subarachnoid spaces. CSF is reabsorbed into the blood by hydrostatic filtration through the arachnoid villi, which project from the subarachnoid space into the venous sinuses. Hydrocephalus is an abnormal accumulation of CSF within the cranium that may be either obstructive or nonobstructive.

Obstructive hydrocephalus is caused by a blockage in the flow of CSF. It may be communicating (e.g., when the CSF pathway into the subarachnoid space is open, as after chronic arachnoiditis) or noncommunicating (e.g., when the fluid's pathway proximal to the subarachnoid space is obstructed, as in aqueductal stenosis or Arnold-Chiari malformation).

Nonobstructive hydrocephalus is caused by a reduction in the volume of brain substance, with secondary dilation of the ventricles; by overproduction of CSF (e.g., in choroid plexus papilloma); or by diminished reabsorption of CSF due to scarring.

EYES

Retinopathy of Prematurity

Retinopathy of prematurity (ROP), which is caused by retinal vessel proliferation and retinal detachment, is a leading cause of blindness. Improved survival of very-low-birth-weight infants increased the incidence of this condition. ROP is most common in neonates weighing less than 1500 g. The role of increased oxygen levels in the blood in the etiology of ROP has long been recognized. Limiting the inspired oxygen concentration reduces ROP but, if excessive, may increase both mortality and the incidence of necrotizing enterocolitis. The development of ROP is now considered to progress in stages. Preterm birth exposes the retina to oxygen levels in the blood that are greater than those during intrauterine development, which decreases local vascular growth factors, interrupting the orderly vascularization to the retinal periphery. In the second phase, the peripheral retina becomes metabolically active but with inadequate perfusion. Hypoxic ischemic damage ensues. Inspired oxygen levels in the blood accelerate this process and compound the situation by high levels of damaging “reactive oxygen species.”

The clinical factors associated with ROP include hyperoxia, hypoxia, hypercarbia, or hypocarbia, blood transfusion, recurrent apnea, sepsis, and other systemic illness. Occasionally, ROP occurs in infants who have never been given supplemental oxygen and even in infants with cyanotic congenital heart disease. A major multi-institutional study of tight control of oxygen administration failed to reduce the incidence of ROP. Nevertheless, the inspired oxygen concentration should be carefully controlled in all preterm infants to prevent unnecessary hyperoxia. Large fluctuations in inspired oxygen concentrations should be avoided. The safe level of PaO_2 is now considered to be 50–70 mmHg. Monitoring oxygen saturation at a preductal site (right hand or earlobe), maintaining the arterial oxygen saturation (SaO_2) at 90–95 %, and avoiding large fluctuations in oxygen levels are recommended. On occasion, it may still be necessary to err on the side of safety and administer greater inspired oxygen concentrations. Major surgical procedures do not appear to predispose infants to ROP.

RESPIRATORY SYSTEM

The respiratory system is of special interest to the anesthesiologist since this is the route of administration of inhaled anesthetic agents, and its functions may be significantly compromised before, during, and after anesthesia. Changes in the respiratory system occur continuously from infancy to about age 12 years as the child grows to maturity.

Anatomy

There are major anatomic differences in the airway between the neonate, the small infant, and the adult that are important for the safe conduct of anesthesia:

1. The head is relatively large and the neck is short, which may contribute to difficulty in laryngoscopy.
2. The tongue is relatively large and readily blocks the pharynx during and after anesthesia; therefore, an oropharyngeal airway or a jaw thrust is often needed. The large tongue may also hamper attempts to visualize the glottis at laryngoscopy.
3. The nasal passages are narrow and easily blocked by secretions or edema, which may cause serious problems. Neonates were previously described as “obligate nose breathers,” but whether this is always true has been questioned. It is certain that some neonates may not immediately convert to mouth breathing if the nasal passages are obstructed. Upper airway obstruction is more likely to occur when the neck is flexed. The anesthesiologist should extend the infant’s neck after extubation until the infant completely recovers from anesthesia. Insertion of a nasogastric tube (NGT) increases total airway resistance; if the nares are of unequal size, the NGT should be inserted into the smaller nostril where it will have the least adverse effect.
4. The larynx is situated more cephalad (C3–C4) and anteriorly, and its long axis is directed inferiorly and anteriorly. The high cervical level of the larynx in the infant means that elevating the head to the “sniffing position” during laryngoscopy will not assist in visualizing the glottis as it does in the adult. In the infant, if the head is elevated, the larynx also moves anteriorly (see p. 94).
5. The airway is narrowest at the level of the cricoid cartilage just below the vocal cords. This cartilage is the only solid circumferential component of the airway. The lining of the airway here is pseudostratified, ciliated epithelium that is loosely bound to the underlying tissue. Trauma to these tissues causes edema, and even a small amount of circumferential edema significantly

compromises the already small cross-sectional area of the infant's airway. The net effect is an increase in the resistance to airflow (which is turbulent [i.e., Reynold's number >2100]) resulting in stridor, where $R \propto 1/r^5$ and where R is the resistance and r is the radius of the airway. Insertion of an ETT similarly encroaches on this space, as the internal diameter of the ETT becomes the area for gas flow; hence, airway resistance increases. This is more significant in smaller children (<3 years). This is the reason that thinner-walled uncuffed tubes used to be advocated in pediatric cases. Today, the wall thickness of cuffed and uncuffed tubes is the same.

6. The epiglottis is relatively long and stiff. It is U shaped and projects posteriorly at an angle of approximately 45° above the glottis. Often, it must be lifted by the tip of a laryngoscope blade before the glottis can be seen. For this reason, a straight-blade laryngoscope is recommended for use in infants and children, although a properly used Macintosh blade may provide a similar view.
7. The trachea is short (approximately 5 cm in the neonate), so precise placement and firm fixation of the ETT are essential. The tracheal cartilages are soft and can easily be compressed by the fingers of an anesthesiologist holding a mask or collapsed (dynamic compression) by the infant's vigorous attempts to breathe against an obstructed airway.
8. The right main bronchus is larger than the left and is less acutely angled at its origin. For this reason, if the ETT is advanced too far, it almost invariably enters the right main bronchus. This most often occurs while taping the tube in place or with changes in position for surgery after tracheal intubation. Flexion of the head advances the tip of the tube. It is therefore essential to reassess the equality of bilateral breath sounds after repositioning for surgery (see Chaps. 4 and 8).
9. Because the ribs are almost horizontal, ventilation is mainly diaphragmatic. The abdominal viscera are bulky and can hinder diaphragmatic excursion, especially if the gastrointestinal tract is distended.

Table 2.1 lists the approximate airway dimensions in infants and children.

Physiology

Breathing movements begin in utero and are characteristically rapid, irregular, and episodic during late pregnancy. Normally, they are present 30% of the time in the third trimester, vary with the sleep state of the fetus, and are subject to diurnal variation. Fetal breathing movements may play a role in lung development and provide exercise for the muscles of respiration. Monitoring of these movements may provide information on fetal health: hypoxemia leads to a

Table 2.1 Approximate airway dimensions in infants and children

Age (year)	Tracheal length (cm) (vocal cords to carina)	Trachea (AP diameter (mm))	Diameter (mm)	
			Right bronchus	Left bronchus
<0.5	5.9	5.0	4.5	3.5
0.5–1	7.2	5.5	4.8	3.7
1–2	7.5	6.3	5.1	3.9
2–4	8.0	7.5	6.4	4.9
4–6	8.6	8.0	6.7	5.3
6–8	9.5	9.2	7.9	6.1
8–10	10	9.75	8.4	6.5
10–12	11.5	10.5	9.2	6.8
12–14	13.5	11.5	9.8	7.5
14–16	14.5	13.2	11.5	8.8

AP anteroposterior

decrease in fetal breathing, and severe hypoxemia leads to gasping movements. The fetal lungs are filled with fluid, which is moved by this respiratory muscle activity. After 26–28 weeks of gestation, production of surface-active substances (surfactants) is established in the type II pneumocytes. Surfactant is secreted into the lung and can be detected in amniotic fluid samples, providing a diagnostic index of lung maturity and hence neonatal prognosis.

Passage of the fetus through the birth canal compresses the thorax, forcing much of the fluid from the lungs through the nose and mouth. On delivery, this compression is relieved and some air is sucked into the lungs. Peripheral (cold, touch, temperature, etc.) and biochemical (respiratory and metabolic acidosis) stimuli have been thought to initiate the onset of regular, continuous breathing. Other factors may be important, such as an increase in the P_{aO_2} or removal of central biochemical inhibitors. The first few spontaneous breaths are characterized by increased transpulmonary pressures (more than 50 cm H_2O). They establish the functional residual capacity (FRC) of the neonate's lungs. Remaining lung fluid is removed over the first few days of life by the pulmonary lymphatics and blood vessels. Infants who are delivered by cesarean section are not subjected to the same thoracic squeeze and may have more residual fluid in the lungs. This may cause them to have transient respiratory distress (transient tachypnea of the newborn).

The stability of the alveolar matrix in the neonate depends on the presence of adequate amounts of surfactant, which may be deficient in the preterm infant. Lack of surfactant leads to collapse of alveoli, maldistribution of ventilation, impaired gas exchange, decreased lung compliance, and increased work of breathing (i.e., RDS). Not surprisingly, pneumothorax occurs more commonly during the neonatal period than at any other age.

Control of Respiration in the Neonate

Control of respiration, which involves biochemical and reflex mechanisms, is well developed in the healthy full-term neonate but exhibits several differences from adults. Respiration in the infant in relation to body mass is greater for any given arterial carbon dioxide tension (PaCO_2), reflecting a greater metabolic rate. The ventilatory response to hypercapnia is less in the neonate than in older infants and less still in the preterm neonate. Any increase in the work of breathing is not well sustained. The slope of the carbon dioxide response curve is decreased in infants displaying episodes of apnea, and hypoxemia decreases the response of the neonate to hypercapnia.

The neonate is sensitive to changes in arterial oxygen tension (PaO_2). Administration of 100% oxygen decreases ventilation, indicating the existence of tonic chemoreceptor activity. The ventilatory response of the neonate to hypoxia is modified by many factors, including gestational and postnatal age, body temperature, and sleep state. Preterm and full-term infants younger than 1 week of age who are awake and normothermic usually demonstrate a biphasic response to hypoxemia—a brief period of hyperpnea followed by ventilatory depression. Hypothermic infants and very small preterm infants respond to hypoxemia with ventilatory depression without the initial hyperpnea. This depression of ventilation has been attributed to the central effects of hypoxia on the cortex and medulla. The peripheral chemoreceptors, although active in neonates, are unable to maintain a significant influence on this hypoxic response. Infants show a less sustained response to hypoxia during REM sleep. In neonates, hypoxia also depresses the ventilatory response to carbon dioxide. Hypoxia may induce periodic breathing in infants, and this may be abolished by oxygen administration. Full-term infants older than 2–3 weeks of age demonstrate hyperpnea in response to hypoxia, probably as a result of maturing of the chemoreceptor function.

Reflexes that arise from the lung and chest wall are probably more important in maintaining ventilation in the neonate, possibly compensating for inadequacies in other control mechanisms. They primarily determine the rate (f) and V_t but are also important for maintaining lung volume (i.e., terminating expiration). The Hering-Breuer inflation reflex, which is active in the neonate, is even more powerful in the preterm infant. This reflex disappears during rapid eye movement (REM) sleep and progressively fades during the early weeks of life. The paradoxical “head” reflex, a large inspiration triggered by small lung inflation, is active in the neonate. It may play a role in maintaining lung volumes in the neonate and may be present during anesthesia.

Periodic breathing (rapid ventilation alternating with periods of apnea lasting 5–10 s) occurs in many preterm and some full-term infants. It is associated with increased peripheral chemoreceptor activity. In the preterm infant, the PaCO_2 is greater than normal during these episodes of periodic breathing, but

the heart rate does not change significantly. In the full-term infant, hypocapnia may occur during periodic breathing, which seems to have no serious physiologic consequences and usually ceases by 44 to 46 weeks of postconceptional age. Periodic breathing generally only occurs about 3% of the time in full-term infants; a greater fraction of periodic breathing in a full-term infant is a warning sign of possible abnormal control of ventilation. Some preterm infants demonstrate far more serious and indeed life-threatening episodes of apnea. These commonly exceed 15 s and may be accompanied by bradycardia (possibly due to a chemoreceptor-mediated reflex) and hemoglobin oxygen desaturation. Brief apnea spells (<15 s) may also be accompanied by significant bradycardia (<80 beats/min). The pathogenesis of apnea in preterm infants is not fully understood. Apnea may reflect an immature central respiratory control system because it tends to resolve as the brain matures. However, a variety of pathophysiologic mechanisms are involved. Apneic episodes may result from a failure of central control mechanisms (central apnea); in such instances, there is no ventilatory effort. It may also result from airway obstruction (obstructive apnea), in which case ventilatory effort may be observed, but there is no gas exchange. Obstruction usually occurs in the infant's nasopharynx, pharynx, or hypopharynx. Mixed apnea (a combination of central and obstructive) commonly occurs, and one type may progress to another (i.e., obstructive apnea may progress to central apnea). Apnea may also result from failure of the ventilatory muscles. Many apneic episodes occur during REM sleep, when it is possible that fatigue of the ventilatory muscles is an important factor. Although neonatal apnea may be idiopathic, it may also be symptomatic of an underlying disease process, such as sepsis, intracranial bleeding, anemia, hypoglycemia, hypothermia, sensitivity to sedating medications, or patent ductus arteriosus.

Preterm infants must be carefully monitored to detect apneic episodes. Treatment is by tactile stimulation or, if this fails, by bag-mask resuscitation. The incidence of apneic episodes is decreased by therapy with aminophylline or caffeine (central stimulation) or by institution of continuous positive airway pressure (increased reflex activity of lung and chest wall reflexes and "splinting" of the airway). Preterm and former preterm infants up to 60-week postconceptional age, particularly those with anemia, are at risk for postoperative apnea even if apnea free at the time of anesthesia. These infants will benefit from appropriate postoperative monitoring in an ICU or similar close observation unit with apnea monitoring.

Muscles of Respiration

In the neonate, the muscles of respiration are subject to fatigue, a tendency that is determined by the types of muscle fiber present. In the diaphragm, 10% of the muscle fibers are type I (slow twitch, highly oxidative, fatigue resistant) in preterm

infants, which increases to 25 % in full-term infants and reaches a maximum of 55 % (the adult level) after 8 months postpartum. In the intercostals, 20, 46, and 65 % of the fibers are type I for the same age groups, with the maximum reached by 2 months postpartum. Thus, the preterm infant is prone to ventilatory muscle fatigue, a predisposition that progressively disappears with maturity. Ventilation is also affected by changes that occur during changing sleep states. The preterm infant spends 50–60 % of this time in REM sleep, during which time, intercostal muscle activity is inhibited, and paradoxical movement of the soft chest wall occurs. The reduced intercostal muscle activity is offset in part by an increase in diaphragmatic activity. Much of this activity is wasted when the ribs move paradoxically and may lead to diaphragmatic fatigue.

Respiratory Mechanics

The specific lung compliance (CL) increases slowly after birth as fluid is removed from the lung. Chest wall compliance in the infant (especially the preterm infant) is great, so that total compliance approximates CL. This highly compliant chest wall provides a relatively weak force to maintain the FRC and to oppose the action of the diaphragm. The FRC of the small infant is maintained by a rapid respiratory rate, the point of termination of expiration, the controlled expiration (“laryngeal braking”), and the tonic activity of the ventilatory muscles. This being so, it is not surprising that large decreases in FRC occur with apnea and during anesthesia when inhalation agents depress intercostal muscle function.

These large decreases in FRC are accompanied by airway closure and impaired oxygenation. Intercostal muscle inhibition during REM sleep or with inhaled anesthetic agents compounds the weakness of the chest wall and results in paradoxical movement. This paradoxical chest wall movement is markedly augmented by any airway obstruction. It may be inferred that infants generally require controlled ventilation during anesthesia and benefit from rapid respiratory rates or the use of positive end-expiratory pressure to maintain the lung volume and avoid airway closure and pharyngeal collapse during mask ventilation. As the child grows through infancy and childhood, the rib cage stiffens so that it becomes better able to oppose the action of the diaphragm and less reliant on intercostal muscle tone.

The transpulmonary pressures needed to optimally inflate the lungs are remarkably similar in healthy infants, children, and adults. During artificial ventilation, peak inspiratory pressures of 15–20 cm H₂O are normal.

The nasal air passages contribute up to 50 % of the total airway resistance in infants and slightly less in African-American infants. Insertion of an NGT increases this resistance by as much as 50 %. The nasal passages are usually of unequal size; if an NGT is inserted, it should be placed through the smaller

nostril, so as to have a lesser effect on total nasal airway resistance. The resistance of the neonate's peripheral airways is small but increases with age.

Lung Volumes

In the full-term infant, total lung capacity (TLC) is approximately 160 mL; the FRC is about half this volume. The tidal volume (V_t) is approximately 16 mL (6–7 mL/kg), and dead space volume (V_D) is about 5 mL (30% of the V_t). Relative to body size, all of these volumes are similar to adult values. Note, however, that any dead space in anesthesia or ventilator circuits is much more significant in relation to the small volumes of the infant (e.g., a 5-mL apparatus dead space would increase the total effective V_D by 100%).

In contrast to the static lung volumes, alveolar ventilation (V_A) is proportionally much greater in the neonate (~100–150 mL/kg/min) than in the adult (~60 mL/kg/min). This high V_A in the infant results in a V_A :FRC ratio of 5:1, compared with 1.5:1 in the adult. Consequently, the FRC is a much less effective “buffer” in the infant, so that changes in the concentration of inspired gases (including anesthetic gases) are more rapidly reflected in alveolar and arterial values.

The closing volume (CV) is relatively greater in infants and young children than in young adults; it may exceed the FRC to encroach on the V_t during normal respirations. Airway closure during normal respirations may explain the reduced normal values for PaO_2 in infants and neonates (Table 2.2). A decrease in FRC, which usually occurs during general anesthesia and persists into the postoperative period, further increases the significance of the large CV and increases the alveolar-arterial oxygen tension gradient ($A-a\text{DO}_2$). The younger the infant or child, the greater the decrease in FRC. The intraoperative decrease in FRC may be partially reversed by continuous positive airway pressure.

The total surface area of the air-tissue interface of the alveoli is small in the infant (2.8 m²). When this area is related to the high metabolic rate for oxygen, it is apparent that the ratio between surface area and rate of oxygen consumption is smaller in the infant than the adult. As a result, the infant has a reduced reserve capability for gas exchange. This developmental fact assumes greater significance in the presence of congenital pulmonary hypoplasia or lung damage (e.g., from meconium aspiration). In such cases, the remaining healthy lung tissue may be inadequate to sustain life.

Table 2.2 Arterial oxygen tension in healthy infants and children

Age	Normal arterial oxygen (mmHg) in room air
0–1 week	70
1–10 months	85
4–8 years	90
12–16 years	96

Work of Breathing

The muscles of respiration generate the force necessary to overcome the resistance to airflow and the elastic recoil of the lungs and chest wall. These two factors dictate an optimal rate of ventilation and a V_I that delivers a given V_A while expending minimal muscular energy for each child. Because the time constant of the infant's lung is relatively small, efficient alveolar ventilation can be achieved at high respiratory rates. In the neonate, a respiratory rate of 37 breaths/min has been calculated to be most efficient, a rate that is close to the rate in healthy neonates. Full-term infants are similar to adults in that they require 1% of their metabolic energy to maintain ventilation; the oxygen cost of breathing is 0.5 mL / 0.5 L of ventilation. The preterm infant has a greater oxygen cost of breathing (0.9 mL/0.5 L), which is greatly increased if the lungs are diseased, as in respiratory distress syndrome (RDS) or bronchopulmonary dysplasia.

Ventilation-Perfusion Relationships in the Neonatal Lung

Ventilation ($\dot{V}$) and perfusion ($\dot{Q}$) are imperfectly matched in the neonatal lung. This may be in part a result of gas trapping in the lungs. $\dot{V}/\dot{Q}$ mismatch is evident in the alveolar-arterial nitrogen difference ($A-aDN_2$), which is 25 mmHg immediately after birth and declines to about 10 mmHg within the first week. The normal PaO_2 in an infant breathing room air is about 50 mmHg just after birth and increases to 70 mmHg by 24 h of age. The large $A-aDO_2$ in infants is mainly caused by persisting anatomic shunts (see p. 26) and the relatively large CV.

Lung Surfactant

Surfactants in the alveolar lining layer stabilize the alveoli, preventing their collapse on expiration. Reducing the surface tension at the air-liquid interface in the alveoli also reduces the force required for their re-expansion. The principal surfactant in the lung is lecithin, which is produced by type II pneumocytes. The quantity of lecithin in the fetal lung increases progressively, beginning at 22 weeks of gestation and increasing sharply at 35–36 weeks as the lung matures. The lecithin production of the lung can be assessed by determining the lecithin/sphingomyelin (L/S) ratio in amniotic fluid, and this is used as a measure of lung maturity and predictor of RDS. The L/S ratio is usually less than 1 until 32 weeks' gestation, reaching 2 by 35 weeks, and 4–6 by full term.

Preterm infants with inadequate pulmonary lecithin production suffer from RDS. The biochemical pathways for surfactant production may also be depressed by hypoxia, hyperoxia, acidosis, or hypothermia; therefore, early correction of

these abnormalities in the sick neonate is vitally important. Inhaled anesthetic agents seem to have little effect on surfactant production. Maturation of biochemical processes in the lungs of the fetus in utero may be accelerated by the administration of corticosteroids to the mother. The use of exogenous surfactant therapy to treat RDS is now standard practice, reducing severity of the disease, air leaks, pneumothorax, and mortality. The optimal preparation, dose, and mode of delivery remain controversial.

Lung Growth and Development

The lungs continue to develop during the first two decades of life. The number of alveoli increases rapidly over the first 6 years, almost reaching adult levels, but growth continues into adolescence. In young children, the small size of the peripheral airways may predispose to obstructive lung diseases such as bronchiolitis.

Pulmonary Function Testing in Children

Children older than 6 years of age may cooperate sufficiently to enable standard tests of pulmonary function to be performed, and these may be an important part of the preoperative assessment. However, they should be interpreted within the context of their cooperation. Maximum expiratory and inspiratory flow-volume curves may be useful in determining the site and nature of airway obstruction; for example, they can differentiate between intrathoracic and extrathoracic obstruction. Such studies may be most useful in the preoperative assessment of children with a mediastinal mass. Spirometric studies may provide useful information as to the degree of reversible airway obstruction present in those with a disease such as asthma and may assist in preoperative planning. They also may indicate the extent of restrictive disease such as accompanies scoliosis, thereby predicting the likelihood of postoperative pulmonary insufficiency. There is renewed interest in forced oscillometry as a method to study lung functions in children as this does not require patient cooperation.

Respiratory System Changes with Anesthesia

The following is a summary of some of the major changes that occur in the respiratory system during and after anesthesia.

1. Inhaled anesthetic agents decrease tidal volume, and respiratory rate increases during spontaneous ventilation. This is thought to occur because of the

combined effects of anesthetic drugs on the central chemical control of respiration and on the muscles of respiration. Intercostal muscle activity is inhibited by inhaled anesthetic agents; consequently, diaphragmatic breathing predominates, and the chest wall may move paradoxically, even if the airway is only partially obstructed. Surgical stimulation tends to increase ventilation back toward normal levels. The effect of intravenous agents on ventilation in children is variable and not fully documented.

2. The FRC is reduced during inhaled anesthetic agents with or without neuromuscular blockade. This reduction is greatest in the youngest children and is caused by elevation of the diaphragm and loss of chest wall stability. As the FRC decreases, airway closure may occur during tidal ventilation, resulting in impaired oxygenation. It is for this reason that 5-cm PEEP is commonly advocated during anesthesia in infants and toddlers.
3. The ratio of physiologic dead space to tidal volume ($V_D:V_T$) remains constant in children breathing spontaneously but may increase in those whose ventilation is controlled. During controlled ventilation, major alterations in gas distribution within the lungs occur as a result of changes in the action of the diaphragm. This effect tends to markedly unbalance the $\dot{V}/\dot{Q}$ matching within the lungs. Apparatus dead space may assume considerable significance given the small physiologic V_D and rapid rate of ventilation.
4. Compliance is little changed, and airway resistance is generally reduced by the bronchodilator action of inhaled anesthetic agents. Insertion of an ETT increases total flow resistance (see p. 14), especially in children less than 3 years of age.
5. The efficiency of gas exchange may be impaired by the effects of anesthetic drugs on the physiologic process that normally controls the regional distribution of inspired gases and blood flow throughout the lung (hypoxic pulmonary vasoconstriction).
6. Laryngospasm occurs more frequently in children compared with adults, especially those with an active or recent upper respiratory infection (URI), particularly during induction of anesthesia and after extubation (see p. 91). Laryngeal closure results from apposition of the vocal cords and supraglottic structures. The reason for the increased incidence of laryngospasm in children is unknown.

CARDIOVASCULAR SYSTEM

The Fetal Circulation

The fetal cardiovascular system perfuses the low-resistance placental circulation, directing 36–42 % of the combined ventricular output to this organ; only 5–10 % goes to the lungs. The high pulmonary vascular resistance limits flow to the fetal

lungs resulting in blood bypassing the lungs via the foramen ovale and the ductus arteriosus. Most of the blood returning from the placenta bypasses the liver via the ductus venosus. The pattern of flow from the inferior vena cava into the right atrium (RA) ensures that about one third of the oxygenated placental blood (partial pressure of oxygen (pO_2), 28–30 mmHg) is directed through the foramen ovale into the left atrium. This blood, which combines with the limited venous return from the lungs, is pumped by the left ventricle into the ascending aorta and thence to the coronary, cerebral, and forelimb circulations. Blood returning via the superior vena cava (pO_2 , 12–14 mmHg) passes through the RA into the right ventricle, from which most of the output flows through the ductus arteriosus into the descending aorta. Thus, blood supplied to the heart and upper body has a greater oxygen content (saturation, 65%; pO_2 , 26–28 mmHg) than that supplied to the abdominal organs, lower limbs, and placenta (saturation, 55–60%; pO_2 , 20–22 mmHg). In utero, the right ventricle pumps about 66% of the combined ventricular output, and the left ventricle pumps the remaining 34%.

Circulatory Changes at Birth

At birth, pulmonary ventilation is normally established quickly, and blood flow to the lungs is greatly increased while placental flow ceases. When the lungs expand and fill with gas, pulmonary vascular resistance (PVR) decreases markedly as a result of mechanical effects on the vessels and relaxation of pulmonary vasomotor tone when the pO_2 increases, and the partial pressure of CO_2 decreases in alveolar gas. PVR decreases by 80% from prenatal levels within a few minutes after normal initiation of respirations. As PVR decreases, blood flow to the lungs and then via the pulmonary veins into the left atrium increases, increasing left atrial pressure above that in the RA and closing the atrial septum over the foramen ovale.

Simultaneously, as flow to the placenta ceases because of clamping or umbilical artery constriction, a large, low-resistance vascular bed is excluded from the systemic circulation. This activity results in a large increase in systemic vascular resistance (SVR) and a decrease in inferior vena cava blood flow and RA pressure. The increase in SVR and the simultaneous decrease in PVR increase the aortic pressure above that in the pulmonary artery. Blood flow through the ductus arteriosus reverses (i.e., becomes left to right), and the ductus fills with oxygenated blood. This increased local pO_2 (to levels greater than 50–60 mmHg) causes the muscular wall of the ductus arteriosus to constrict secondary to a prostaglandin-mediated response. Shunts may persist through the ductus for some hours after birth, producing audible murmurs. Normally, however, flow through the ductus is insignificant by 15 h. Permanent closure of the ductus is usually complete within 5–7 days but may not be complete until 3 weeks.

The ductus venosus, which communicates between the umbilical veins, the portal vein, and the inferior vena cava, also remains patent for several days after birth. This channel provides a shunt past the hepatic circulation and therefore may delay the clearance of drugs metabolized in the liver (e.g., opioid analgesics).

The Transitional Circulation

During the early neonatal period, reversion to the fetal circulatory pattern is possible under some circumstances. If hypoxia occurs, the PVR increases, the foramen ovale opens, and the ductus arteriosus may also reopen; a significant proportion of blood then again bypasses the (now high-resistance) pulmonary circulation, causing a rapid decline in arterial oxygenation. Impaired tissue oxygenation then results in acidosis, which causes a further increase in PVR, establishing a vicious cycle of hypoxemia → acidosis → impaired pulmonary blood flow → hypoxemia. Reversion to a fetal pattern of circulation may complicate any condition that causes hypoxemia or acidemia (e.g., RDS or congenital diaphragmatic hernia).

The Neonatal Cardiovascular System

In healthy neonates, the wall thickness of the right ventricle exceeds that of the left. This preponderance is evident in the ECG, which shows an axis of up to $+180^\circ$ during the first week of life. After birth, the left ventricle enlarges disproportionately. By 3–6 months, the adult ratio of ventricular size is established (axis approximately $+90^\circ$). During the immediate neonatal period, the heart rate is between 100 and 170 beats/min, and the rhythm is regular. As the child grows, the heart rate gradually decreases (Table 2.3). Sinus arrhythmia is common in children. All other irregular rhythms must be considered abnormal.

Systolic blood pressure is approximately 60 mmHg in the full-term neonate, and the diastolic pressure is 35 mmHg. These pressures vary considerably and may be 10–15 mmHg more if clamping of the umbilical cord is delayed or the cord is “stripped,” causing an increase in circulating blood volume. In either case, they decrease to normal values within 4 h. Preterm infants have reduced arterial pressures, as low as 45/25 mmHg in a 750-g infant (Table 2.4).

The myocardium of the neonate contains less contractile tissue and more supporting tissue than the adult heart. Consequently, the neonate's ventricles are less compliant when relaxed and generate less tension during contraction. Because the reduced compliance of the relaxed ventricle tends to limit the size of the stroke volume, the cardiac output of the neonate is rate dependent. Bradycardia is invariably accompanied by reduced cardiac output. The less compliant ventricle of the neonate is also dependent on an adequate filling pressure,

Table 2.3 Normal heart rate

Age	Heart rate (beats/min)	
	Average	Range
Neonate	120	100–170
1–11 months	120	80–160
2 years	110	80–130
4 years	100	80–120
6 years	100	75–115
8 years	90	70–110
10 year	90	70–110
14 years		
Boys	80	60–100
Girls	85	65–105
16 years		
Boys	75	55–95
Girls	80	60–100

Table 2.4 Normal blood pressure^a

Age	Blood pressure (mmHg)		
	Systolic	Diastolic	Mean
<i>Neonate</i>			
Preterm (750 g)	44	24	33
Preterm (1000 g)	49	26	34.5
Full term	60	35	45
3–10 days	70–75	57	
6 months	95		
4 years	98		
6 years	110	60	
8 years	112	60	
12 years	115	65	
16 years	120	65	

^aReported normal blood pressure values for infants and children must be considered in light of their methods of determination. These values should serve as a guide only (see Monitoring During Anesthesia, p. 113)

so that hypovolemia is followed by a decrease in cardiac output. Thus, cardiac output is both rate dependent and volume dependent. Reduced compliance and contractility of the ventricles also predisposes the infant heart to failure with increased volume load. In the infant, failure of one ventricle rapidly compromises the function of the other and biventricular failure results.

The reduced contractility of the neonatal heart is also thought to be secondary to the immaturity of the myofibrils and to the less developed sarcoplasmic reticulum. It is postulated that the cyclic calcium flux within the neonatal

myocardium is more dependent on exchange across the cell membrane (sarcolemma) and less a function of the sarcoplasmic reticulum, thus a greater dependency upon ionized calcium levels. As the infant grows, the myocardial sarcoplasmic reticulum expands and progressively assumes a dominant role in intracellular calcium regulation, which is typical of the adult heart. The greater role of the sarcolemma in calcium regulation within the myocyte may explain the greater sensitivity of the neonate to myocardial depression because of inhalational anesthetics (calcium channel-blocking activity). It may also explain the severe cardiac depressant effects of calcium channel-blocking drugs or the rapid administration of citrated blood products such as fresh-frozen plasma or platelets in the neonate.

The autonomic innervation of the heart is incomplete in the neonate, and there is a relative lack of sympathetic elements. This may further compromise the ability of the less contractile neonatal myocardium to respond to stress. The differences in the neonate's myocardium are all particularly marked in the pre-term infant.

In the neonate, shunts hamper the precise measurement of cardiac output, which averages 2–3 times that of the adult on a milliliter per kilogram body weight basis and is appropriate for the metabolic rate. The total systemic vascular resistance is reduced, reflecting the great proportion of vessel-rich tissue in the neonate (18%—twice that in the adult) and resulting in a reduced systemic arterial pressure despite the large cardiac output.

The Pulmonary Circulation

The changes in the pulmonary circulation that occur at birth continue with a slower progressive decrease in PVR over the first 3 months of life. This is associated with a parallel regression in the thickness of the medial muscle layer of the pulmonary arterioles. During the neonatal period, PVR is still high, and the muscular pulmonary vessels are highly reactive. Hypoxia, acidosis, and stress (e.g., from endotracheal suctioning) may all increase PVR. If the increase in the PVR is sustained by such stimuli, right-sided intracardiac pressures may exceed those on the left, and right-to-left shunting may ensue via the ductus arteriosus or foramen ovale. Right ventricular failure, rapidly progressing to biventricular failure, may occur.

In some circumstances, the normal regression of the muscular layer of the pulmonary vessels and the associated decrease in PVR may not occur. Continued hypoxemia, caused, for example, by continued high-altitude or excessive pulmonary blood flow as a result of left-to-right shunts (ventricular septal defect, patent ductus arteriosus, etc.) may lead to persistence of a high PVR into childhood

and beyond. Initially, this high PVR is reversible (e.g., with pulmonary vasodilators) and correction of the underlying defect. Later, this high PVR results in structural changes in the pulmonary vascular bed that are irreversible, causing pulmonary vascular obstructive disease.

Nitric oxide has been identified as an endothelium-derived relaxing factor that is normally produced continually in the lung to regulate pulmonary vascular tone. This has led to the use of nitric oxide inhalation to treat increased pulmonary vascular resistance.

Blood Volume

The blood volume varies considerably during the immediate postnatal period (the primary variable being the amount of blood drained from the placenta before the cord is clamped) and during the first year of life. Delay in clamping or stripping the cord at delivery may increase the blood volume by more than 20 %, resulting in transient respiratory distress. Conversely, fetal hypoxia during labor may vasoconstrict the cord, shift blood to the placental circulation, and cause hypovolemia in the already asphyxiated neonate.

The Response to Hypovolemia

The response to hypovolemia and restoration of the blood volume are of great importance to the anesthesiologist because surgery in the neonate may be accompanied by significant blood loss. Withdrawal of blood during exchange transfusion causes a progressive parallel decrease in systolic blood pressure and cardiac output. Reinfusion of an equal volume of blood restores these parameters to their original values. The changes in arterial blood pressure are proportional to the degree of hypovolemia. The capacity of the neonate to adapt the intravascular volume to the available blood volume is very limited, perhaps due to less efficient control of capacitance vessels. The baroreflexes of the infant, especially the preterm infant, are inactive during anesthesia, further compromising the response to hypovolemia.

In summary, the infant's systolic arterial blood pressure is closely related to the circulating blood volume. Blood pressure is an excellent guide to the adequacy of blood replacement during anesthesia, a fact that is amply confirmed by extensive clinical experience. The hypovolemic infant is unable to maintain an adequate cardiac output; hence, accurate early volume replacement is essential.

Table 2.5 shows approximate normal values for blood volume in infants and children. Values may be greater however, particularly in preterm infants.

The Response to Hypoxia

Because of the high rate of metabolism for oxygen ($\dot{V}O_2$), hypoxemia can develop rapidly in the neonate. The first observed response is usually bradycardia in contrast to the tachycardia observed in the adult. The anesthesiologist should treat any episode of unexplained bradycardia by immediately ventilating the lungs with 100 % oxygen. During hypoxemia, pulmonary vasoconstriction occurs, and the pulmonary artery pressure increases more than in adults. The foramen ovale and the ductus arteriosus may reopen resulting in a large right-to-left shunt, further decreasing SAO_2 . Changes in cardiac output and SVR in infants also differ from those in older children and adults. During hypoxemia, the principal response in adults is systemic vasodilation, which, together with an increased cardiac output, helps to maintain oxygen transport to the tissues. The fetus and some neonates respond to hypoxemia with systemic vasoconstriction. During fetal life, this directs more blood to the placenta, but after birth, this response may reduce cardiac output, further limiting oxygen transport and forcing the heart to work harder. In the infant, the early and pronounced bradycardia in response to hypoxia may be caused by myocardial hypoxia and acidosis.

Neonates exposed to hypoxemia experience pulmonary and systemic vasoconstriction, bradycardia, and decreased cardiac output. Rapid intervention is necessary to prevent this state from proceeding to cardiac arrest.

Oxygen Transport

Blood volume in the neonatal period is approximately 80 mL/kg in the term infant and about 20 % greater in the preterm infant (Table 2.5). The hematocrit (Hct) may be as great as 60 % and the hemoglobin (Hb) 18–19 g/dL. The values for blood volume, Hct, and Hb vary from infant to infant, depending on the time of clamping of the umbilical cord. These values change little during the first week of life, after which the Hb level starts to decrease. This change occurs more rapidly in the preterm infant.

Most (70–90 %) of the Hb present at birth in a full-term infant is fetal hemoglobin (HbF). The affinity of HbF for oxygen is greater than that of adult hemoglobin (HbA), primarily because of a lack of effect of 2,3-DPG on the HbF– O_2 interaction. HbF combines with more oxygen but releases it less readily in the

Table 2.5 Normal blood volume of children

Age	Blood volume (mL/kg)
Neonate	80–85
6 weeks to 2 years	75
2 years to puberty	70

tissues than does HbA. The pO_2 at 50% hemoglobin saturation (P_{50}) for HbF is approximately 20 mmHg, in contrast to 26–27 mmHg for HbA. Adequate oxygen transport to the tissues of the neonate therefore demands a greater Hb concentration. Less than 12 g/dL constitutes anemia, and greater levels are very desirable in hypoxic states. However, there are many risks associated with transfusion. Current thought is that correction of anemia by blood transfusion may be indicated to maintain the Hct greater than 40% in cases of severe cardiopulmonary disease, 30% in moderate cardiopulmonary disease or major surgery, and 25% in symptomatic anemia (apnea, tachycardia, lethargy, poor growth).

Transfusion with HbA-containing erythrocytes may improve oxygen transport to the tissues in the sick preterm infant. However, this treatment has also been reported to increase the risk of ROP. During the first weeks of life, the Hct and Hb levels decline steadily, in part because of a progressive increase in blood volume but also a result of suppression of erythropoiesis caused by improved tissue oxygenation (see Table 4.10). This physiologic anemia of infancy reaches a nadir at 2–3 months of age, with Hb levels of 9–11 g/dL. At this time, the HbF content of the blood has been largely replaced by HbA. Thus, oxygen delivery at the tissues is improved. Provided that nutrition is adequate, the Hb level now increases gradually over several weeks to 12–13 g/dL, which is maintained during early childhood.

The preterm infant demonstrates an earlier and greater decrease in Hb concentration, reaching 7–8 g/dL in infants weighing less than 1500 g at birth. This is the result of a short erythrocyte life span, rapid growth, and decreased erythropoietin production. The early “physiologic” anemia of the preterm infant is often followed by a continuing “late” anemia, which is secondary to nutritional deficiencies. In the infant in the neonatal intensive care unit, this anemia is accentuated by repeated blood sampling. Iron therapy is not effective in correcting this anemia and may cause other problems (e.g., hemolysis, infection). Anemia of the preterm infant may lead to tachycardia, tachypnea, poor feeding and growth, diminished activity, and apnea. In severe states, congestive heart failure may occur.

METABOLISM: FLUID AND ELECTROLYTE BALANCE

Glucose Homeostasis

The term neonate has stores of glycogen that are located mainly in the liver and myocardium. These are used during the first few hours of life until gluconeogenesis becomes established. Small-for-gestational-age and preterm infants may have inadequate glycogen stores and may fail to establish adequate gluconeogenesis. Hence, they are very dependent upon IV infusions to prevent hypoglycemia.

Table 2.6 Factors associated with hypoglycemia in neonates

Prematurity
Perinatal stress
Sepsis
Small for gestational age
Polycythemia
Hypoxia
Excess insulin
Infant of diabetic mother
Beckwith-Wiedemann syndrome

Hypoglycemia is common in the stressed neonate (Table 2.6). Blood glucose levels should be measured frequently in sick neonates, and if they decrease to less than 45 mg/dL or 2.2 mmol/L, they should be corrected by a slow continuous infusion of 10 % dextrose at 5–8 mg/kg/min (or 0.05–0.08 mL/kg/min). Symptoms of hypoglycemia (jitteriness, convulsions, apnea) should be treated immediately by slow injection of 10 % dextrose (1–2 mL/kg). Neurologic damage occurs in up to 50 % of infants with symptomatic hypoglycemia. Infants of diabetic mothers and those with Beckwith-Wiedemann syndrome must be treated with particular care because a bolus dose of intravenous glucose may precipitate hyperinsulinemia and serious rebound hypoglycemia. In these infants, a slow infusion of glucose as outlined above is recommended. Older infants and young children rarely become hypoglycemic even during an excessively long preoperative fasting period. Current pediatric practice minimizes preoperative fasting (see p. 77).

Hyperglycemia is a common iatrogenic problem of small infants receiving intravenous therapy, probably as a result of inadequate insulin release and continued hepatic glucose production. The effects of hyperglycemia can be serious. Osmotically induced cerebral fluid shifts may lead to cerebral hemorrhage, and glycosuria may cause diuresis resulting in water and electrolyte depletion. Hyperglycemia (glucose values >200 mg/dL) may also increase the extent of neurologic damage during a cerebral hypoxic-ischemic event. It is essential that glucose therapy be carefully controlled to avoid hyperglycemia. We recommend the use of a continuous infusion pump for maintenance glucose containing fluids with other intraoperative losses replaced with balanced salt solutions “piggy backed” to the maintenance fluids.

Calcium Homeostasis

Calcium is actively transported across the placenta to meet the needs of the fetus. This transport accelerates near term and may cause a decline in maternal calcium levels. After birth, the infant must depend on its own calcium reserves. However, parathyroid function is not fully established, and vitamin D stores may be inadequate. As a result, hypocalcemia must be anticipated—especially in the preterm infant—after birth trauma, neonatal asphyxia, any severe neonatal illness, or blood transfusion (especially fresh frozen plasma or platelets). Correction of metabolic acidosis in the neonate by administration of sodium bicarbonate may precipitate a significant decrease in ionized calcium levels. Continuing hypocalcemia may be a sign of parathyroid dysfunction and is typically present in DiGeorge syndrome (see p. 422, 543).

Symptoms of hypocalcemia include twitching, increased muscle tone, and seizures (hypocalcemia is not always easily distinguished from hypoglycemia). The Chvostek sign may be present, but confirmation depends on laboratory test results (total serum calcium, less than 7 mg/dL or 1.75 mmol/L; ionized calcium, less than 4 mg/dL or 1.0 mmol/L) or on the response to therapy. The infant prone to hypocalcemia is treated with continuous calcium chloride infusion at a rate of 5 mg/kg/h. Symptomatic hypocalcemia requires a slow infusion of either 10% calcium chloride (10–30 mg/kg) or 10% calcium gluconate (30–90 mg/kg), with continuous ECG monitoring. Note that calcium-containing solutions may cause severe skin damage, leading to sloughing if they leak into adjacent tissues. They should preferably be given through a central line.

Magnesium Homeostasis

Magnesium and calcium metabolism are closely related: an imbalance in one may affect the other. Magnesium levels affect parathyroid hormone secretion, and the renal excretion of calcium and that of magnesium are interrelated. Chronic hypomagnesemia is commonly accompanied by hypocalcemia secondary to the effect on parathyroid function.

Hypomagnesemia is more common in preterm infants, small-for-gestational-age infants, infants of diabetic mothers, and infants with intestinal disease. It may also complicate massive blood transfusion. Hypomagnesemia results in abnormal muscle activity, tremors, seizures, and cardiac arrhythmias and may alter sensitivity to muscle relaxant drugs.

Hypermagnesemia may complicate renal failure, or, in the neonate, it may be a consequence of the administration of magnesium sulfate to the mother. It may result in depression of the central nervous and respiratory systems, hyporeflexia, and hypotension.

Bilirubin Homeostasis

In the full-term neonate, unconjugated hyperbilirubinemia during the first week of life (physiologic jaundice) occurs secondary to an increased bilirubin load, limited hepatic cell uptake of bilirubin, and deficient hepatic conjugation to the water-soluble glucuronide. Serum bilirubin levels seldom exceed 7 mg/dL or 103 $\mu\text{mol/L}$. In preterm infants, greater levels (10–15 mg/dL or 170–255 $\mu\text{mol/L}$) are commonly reached. These persist for a longer period, owing to a greater bilirubin load and delayed maturation of the hepatic conjugation pathway. The preterm infant may sustain neurologic damage (kernicterus) at reduced serum bilirubin levels (6–9 mg/dL) than does the full-term infant (20 mg/dL). This predisposition is a result of the preterm infant's less effective blood-brain barrier and may be exacerbated by hypoxia, acidosis, infection, hypothermia, or a low level of serum albumin and hence decreased binding sites. The preterm infant must be carefully monitored for increased serum bilirubin levels, and specific treatment should be administered as required. Treatment includes phototherapy and possibly exchange transfusion. Some drugs (e.g., diazepam, sulfonamides, furosemide) displace protein-bound bilirubin (i.e., “acidic” binding sites for albumin) and therefore increase the danger of neurologic damage. There are no reports of anesthetic drugs (except benzodiazepines) producing adverse changes in bilirubin levels, but hypoxia, acidosis, hypothermia, and hypoalbuminemia may all increase the danger.

COMPOSITION AND REGULATION OF BODY FLUIDS**Body Water**

The amount of total body water in neonates and infants is relatively greater than in adults. Its distribution also differs, the proportion of extracellular fluid (ECF) being greater in neonates and young children. In the preterm infant, the ECF exceeds the intracellular fluid (ICF), whereas in the older child and adult, the ECF is only half the volume of the ICF (Table 2.7). Normal levels of serum electrolytes in the neonate are listed in Table 2.8.

Table 2.7 Extracellular and intracellular fluid compartments

Fluid	Preterm neonate	Full-term neonate	Infant (7–8 months)	Adult
ECF	50	35–40	30	20
ICF	30	35–40	35	45

Data are % body weight

Table 2.8 Normal blood chemistry values

Parameter	Preterm neonate	Full-term neonate	2 years to adult
Serum chloride (mEq/L)	100–117	90–114	98–106
Serum potassium (mEq/L)	4.6–6.7	4.3–7.6	3.5–5.6
Serum sodium (mEq/L)	133–146	136–148	142
Blood glucose (mEq/L)	40–60	40–80	70–110
Total protein (g/dL)	3.9–4.7	4.6–7.7	5.5–7.8
PaCO ₂ (mmHg)	30–35	33–35	35–40

Neonatal Renal Function and Water Balance

In the neonate, renal function is limited by immaturity of tubular function and an increased renal vascular resistance, which results in reduced renal blood flow and glomerular filtration rate (GFR). GFR rapidly increases after birth as renal blood flow increases. The preterm infant has an even lower GFR, which increases less rapidly over the first weeks of life than it does in the full-term infant. The GFR of the neonate increases with fluid loading but only to a limited capacity. Consequently, the neonate cannot readily handle an excessive water load and may be unable to excrete excess electrolytes (especially sodium) or other substances that depend on glomerular filtration for their elimination. The GFR is further decreased by hypoxia, hypothermia, congestive cardiac failure, or mechanical ventilation; adult values are usually achieved by approximately 1 year of age.

The limited tubular function impairs the infant's ability to modify the glomerular filtrate for conservation or excretion. For this reason, sodium losses may be large, especially in the preterm infant, and must be balanced by intake. These losses are further increased if the GFR is increased by a high fluid intake, hence, the tendency of the neonate to hyponatremia. Glucose reabsorption is limited in the preterm infant, and glycosuria may occur. In the child with marked hyperglycemia, the resultant osmotic diuresis may lead to severe dehydration. The ability of the tubule to excrete acid is reduced in the preterm infant, thus impairing renal compensation during acidosis. The capacity to excrete H^{++} increases with gestational age. The renal threshold for bicarbonate excretion is less in infants than adults, and this leads to reduced serum bicarbonate levels. The limitations of renal function summarized above necessitate careful fluid and electrolyte replacement therapy planned to match losses. Renal vascular resistance decreases and renal function matures rapidly over the first few weeks after birth in the full-term infant. Preterm infants show less rapid changes in renal function.

Fluid loss and hence the required fluid replacement are related to insensible fluid losses, urine output, and metabolic rate. Insensible fluid losses are

relatively great during infancy, major factors being the increased alveolar ventilation and the thin skin of low-birth-weight infants. Fluid losses are markedly increased by the use of radiant heat and/or phototherapy. Because of the infant's proportionally greater water turnover and the limited ability to concentrate urine and conserve water, dehydration develops rapidly when intake is restricted or losses occur.

Maintenance Requirements

Although maintenance requirements are directly related to the metabolic rate and caloric expenditure and are more accurately expressed in milliliters per square meter of surface area, it is most convenient to relate them to body weight. Fluid requirements for full-term neonates are reduced (40–60 mL/kg per 24 h) during the first few days of life as excess fluid present at birth is being excreted. By 1 week of age, the requirements are increased. Table 2.9 shows the volumes of fluid required during the period of great metabolic activity in infants weighing 4–20 kg.

Intraoperative fluid management in the neonate must include replacement of fluid deficits, third-space losses, blood loss, and maintenance fluid therapy. Fluid deficits and losses are generally replaced with a balanced salt solution such as lactated Ringer's solution, whereas maintenance therapy is replaced with an infusion of 5% glucose and one half to one fourth normal saline, containing 20 mEq of K⁺ per liter. If high-concentration glucose solutions (D-10 or D-20) are infusing preoperatively, these solutions should be continued either at the

Table 2.9 Daily maintenance requirements for fluid, electrolytes, and carbohydrates in relation to weight

Weight	H ₂ O (mL/kg)	Na ⁺ (mEq/kg)	K ⁺ (mEq/kg)	Carbohydrate (g/kg)
<i>Neonate^a</i>				
1000 g	≤200	3.0	2.0–2.5	≤10
1000–1499 g	≤180	2.5	2.0–2.5	
1500–2500 g	≤160	2.0	1.5–2.0	≤8
2500 g	≤150	1.5–2.0	2.0	≤5
4–10 kg	100–120	2.0–2.5	2.0–2.5	5–6
10–20 kg	80–100	1.6–2.0	1.6–2.0	4–5
20–40 kg	60–80	1.2–1.6	1.2–1.6	3–4
Adult	30–40	50 mEq total	50 mEq total	100–150 g total

^aAdjust according to postnatal age, exposure to phototherapy, reduced insensible losses with assisted ventilation, etc.

(From The Hospital for Sick Children: Residents' Handbook of Pediatrics, 6th ed. Toronto, Canada, 1979, with permission)

same or at a somewhat reduced rate throughout surgery. In critically-ill neonates, balanced salt solutions should be replaced with colloid solutions or plasma early, as hypoproteinemia is common.

PHYSIOLOGY OF TEMPERATURE HOMEOSTASIS

Because of their large surface area relative to body weight and their lack of heat-insulating subcutaneous fat, infants lose heat rapidly via four routes in order of importance: radiation (39%) > convection (34%) > evaporation (24%) > conduction (3%). Evaporative heat is lost into the respiratory tract and through the skin, the latter being related to increased skin permeability and is thus a particularly important factor in preterm infants. When heat loss occurs, heat production within the body must increase to maintain a normal core temperature. In adults and older children, this heat production is principally a function of involuntary muscular activity (shivering) accompanied by increased oxygen consumption, both of which can be prevented by the administration of a neuromuscular blocking drug. Infants rely primarily on non-shivering thermogenesis to generate heat. This mechanism, which also results in increased oxygen consumption, occurs mainly in the brown adipose tissue, which makes up 2–6% of the full-term infant's body weight (less in the preterm infant) and is located around the scapulae, in the mediastinum, and surrounding the kidneys and adrenal glands. The cells of this "brown fat" have many mitochondria and fat vacuoles, and the tissue has a rich blood and autonomic nerve supply. Increased metabolic activity in brown fat is initiated by norepinephrine released at the sympathetic nerve endings. Hydrolysis of triglycerides to fatty acids and glycerol occurs with associated increased $\dot{V}O_2$ and heat production. Brown fat deposits decline during the first weeks of extrauterine life.

Exposure to a cool environment together with a decrease in central temperature normally triggers thermoregulatory vasoconstriction in unanesthetized infants and children. This vasoconstriction tends to limit further heat loss from the body surface. It is now recognized that the mechanisms for controlling body temperature are well developed in the full-term neonate. However, a decrease in core temperature results when compensatory increases in heat production cannot match heat losses. On exposure to a cool environment, increased metabolic activity is initiated in the brown fat so as to maintain the core temperature. This is accompanied by a progressive increase in oxygen consumption as the temperature gradient between the skin and the environment increases. Oxygen consumption is minimal when this gradient is less than 2 °C (i.e., neutral thermal environment). Exposure to a cool environment also leads to increased glucose use and acid metabolite formation.

Table 2.10 Neutral thermal environment temperatures (°C)

Age	Weight			
	1200 g	1200–1500 g	1500–2500 g	>2500 g
0–6 h	34–35.4	33.9–34.4	32.8–33.8	32.0–33.8
6–12 h	34–35.4	33.5–34.4	32.2–33.8	31.4–33.8
12–24 h	34–35.4	33.3–34.3	31.8–33.8	31.0–33.7
24–36 h	34–35	33.1–34.2	31.6–33.6	30.7–33.5
36–48 h	34–35	33.0–34.1	31.4–33.5	30.5–33.3
48–72 h	34–35	33.0–34.0	31.2–33.4	30.1–33.2
72–96 h	34–35	33.0–34.0	31.1–33.2	29.8–32.8
4–12 days	–	33–34 ^a	31–33.2	29.5–31.4
2–3 weeks	–	32.2–34 ^a	30.5–33.0	–
3–4 weeks	–	31.6–33.6 ^a	30.0–32.7	–

^a1500 g

The physiologic responses to cooling lead to increased oxygen and glucose use and result in acidosis, all of which may compromise the sick infant. The infant with chronic hypoxemia (e.g., cyanotic congenital heart disease) is unable to compensate if exposed to a cool ambient temperature and cools rapidly. To eliminate the need for compensatory responses, sick neonates should be maintained in a neutral thermal environment (i.e., in an ambient temperature that minimizes oxygen consumption [Table 2.10]).

During anesthesia, the normal thermoregulatory response of the infant to cold stress is lost, and oxygen consumption is unchanged in response to a cool environment. In addition, normal thermoregulatory skin vasoconstriction is inhibited. There is also a redistribution of body heat away from the central core to the periphery. Therefore, anesthetized infants and children have increased heat loss and a decrease in body temperature. Measures to minimize heat loss and avoid cold stress (warmed OR, warmed preparation and irrigation solutions, convective forced air warmers) are important during anesthesia (see p. 121).

Suggested Reading

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