Chapter 1: Physiological Aspects

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INTRODUCTION

FOCUS POINTS

1. The posterior fontanelle closes around 6 months of age and the anterior fontanelle around 12 to 18 months. Therefore, a slow increase in intracranial volume prior to cranial suture fusion can be compensated by an increase in head circumference.
2. Signs of intracranial hypertension differ in adults compared to children. Typical signs of high intracranial pressure (ICP) include increased irritability, headaches, decreased feeding, and morning emesis.
3. $CMRO_2$ in children increases to 5.2 mL/100 g/min making them more susceptible to hypoxemia, contrary to neonates who have a lower $CMRO_2$ at 3.5 mL/100 g/min making them relatively tolerant to hypoxemia.
4. By the age of 5, children have the normal adult volume of cerebrospinal fluid (CSF) which is 150 mL.

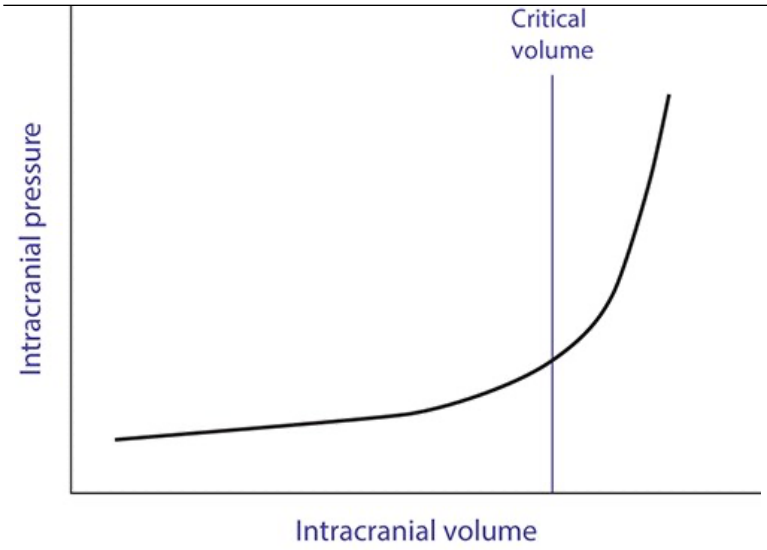
CENTRAL AND AUTONOMIC NERVOUS SYSTEM

The brain at birth is one-tenth of the body weight. Only one-fourth of neuronal cells that exist in adults are present in the newborn. By one year of age, the cells in the cortex and brain stem are developed completely. Myelinization and synaptogenesis are not complete until the age of 3. Primitive reflexes such as Moro reflex and grasp reflex disappear with myelination. At birth, the conus medullaris is at L3, and the dural sac ends at S1. By one year of age, the conus medullaris recedes to L1 and the dural sac shortens to S1. Unlike the central nervous system, the autonomic nervous system is developed at birth, though immature. The parasympathetic system is intact and fully functional in contrast to the sympathetic component which develops by 4 to 6 months of age.[1–3]

The intracranial space has three components: brain tissue (80%), CSF (10%), and blood (10%). The Monro–Kellie hypothesis states that the sum of all intracranial components is constant (Figure 1-1). Specifically, an increase in volume of one of the components that causes an increase in intracranial pressure will result in a compensatory reduction in the other components to offset the change. The exception to this doctrine are neonates and infants since cranial sutures are open at birth. The posterior fontanelle closes around 6 months of age and the anterior fontanelle around 12 to 18 months. Therefore, a slow increase in intracranial volume prior to cranial suture fusion can be compensated by an increase in head circumference. However, acute dramatic increases in ICP can still cause herniation. Children with closed fontanelles have a higher risk of herniation than adults, due to a lower intracranial compliance and smaller cranial volume.[4]

Figure 1-1

Monro–Kellie hypothesis. An increase in volume of one of the components that causes an increase in intracranial pressure will result in a compensatory reduction in the other components to offset the change. (Adapted with permission, from Butterworth IV JF, Mackey DC, Wasnick JD. eds. *Morgan & Mikhail's Clinical Anesthesiology*, 6e. 2018. https://accessmedicine.mhmedical.com. Copyright © McGraw Hill LLC. All rights reserved.)



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Maintaining cerebral perfusion pressure (CPP) helps prevent cerebral ischemia. CPP is dependent on mean arterial pressure (MAP), intracranial pressure (ICP), and central venous pressure (CVP). CPP is defined as MAP – ICP (or CVP if it is higher than ICP). Therefore, either an increase in ICP or a decrease in MAP can cause a decrease in CPP. Normal ICP in children and adults is less than 15 mm Hg. ICP in full-term infants is 2 to 6 mm Hg, and likely lower in premature neonates.[2] ICP can remain normal in the setting of significant intracranial pathology in infants with open fontanelles. Signs of intracranial hypertension differ in adults compared to children. Typical signs of high ICP include increased irritability, headaches, decreased feeding, and morning emesis.

Data is limited regarding normal neurophysiological values in the pediatric population. Most data is extrapolated from animal and adult data. Cerebral blood flow (CBF) varies with age (Table 1-1). CBF is coupled with cerebral metabolic rate of oxygen ($CMRO_2$). Normal $CMRO_2$ in adults is 3.5 mL/100 g/min. $CMRO_2$ in children increases to 5.2 mL/100 g/min making them more susceptible to hypoxemia, contrary to neonates who have a lower $CMRO_2$ at 3.5 mL/100 g/min making them relatively tolerant to hypoxemia.[5–8]

Table 1-1

CBF Variation with Age

Age	Cerebral Blood Flow (CBF)
Preterm neonate	~14–20 mL/100 g/min
Term neonate	~40 mL/100 g/min
Child	~90–100 mL/100 g/min, which is 25% of the cardiac output
Adult	~50 mL/100 g/min, which is 15% of the cardiac output

Cerebral autoregulation is able to keep CBF constant despite changes in CPP due to arteriolar contraction and relaxation in response to distending pressures.[5] In adults, CBF remains constant between MAP of 50 and 150 mm Hg. Beyond these limits of autoregulation, CBF is pressure dependent, which can lead to ischemia or hyperemia. Autoregulation numbers are not well known in children, although it has been shown that neonates and young children are especially vulnerable to cerebral ischemia and intraventricular hemorrhage. Attention should be given to proper blood pressure control.[9]

Cerebral spinal fluid is produced by the choroid plexus and absorbed by arachnoid villi. Adults and children synthesize about 500 mL/day, which is 0.3 to 0.4 mL/min. By the age of 5, children have the normal adult volume of CSF, which is 150 mL. Acetazolamide, furosemide, and corticosteroids all transiently decrease CSF production. Increase in ICP will cause an increase in the rate of reabsorption of CSF, unless in the setting of intracranial hemorrhage, inflammation, or obstruction in CSF flow.[1,2,4,10]

Cardiovascular System

1. In fetal circulation, both the right and left ventricles provide system blood flow, and various connections allow for mixing of oxygenated blood with deoxygenated blood.
2. The three fetal connections are ductus arteriosus, ductus venosus, and foramen ovale.
3. Fetal hemoglobin has higher affinity for oxygen than adult hemoglobin helping offload oxygen to the fetus.
4. Four physiological features aid in the adequate delivery of oxygen to fetal tissues despite higher affinity for oxygen.
5. The transition from fetal to neonatal physiology begins with the neonate's first breath and involves the closure of the patent foramen ovale, patent ductus arteriosus, and ductus venosum.
6. The circulatory system undergoes a change from parallel to one in series.
7. Cardiac hemodynamic changes include decreased afterload and volume load in the right ventricle and increased afterload and volume load of the left ventricle.
8. Persistence of a patent foramen ovale occurs in up to a quarter of adults.
9. The neonate and infant myocardium is immature and is sensitive to myocardial depressive effects of various agents and anesthetics.
10. Neonates and infants have a predominance of parasympathetic autonomic innervation until the sympathetic nervous system reaches maturity in early infancy.

INTRAUTERINE ANATOMY AND PHYSIOLOGY

Fetal Circulation and Anatomy

In utero, the placenta is responsible for respiratory gas exchange between the mother and the fetus. Deoxygenated blood travels through two umbilical arteries to the placenta for prenatal respiration. Blood is returned to the fetus via a single umbilical vein that carries oxygenated blood that is approximately 80% saturated, with about 30 mm Hg partial pressure of oxygen (Po_2). In comparison, the Po_2 in the umbilical arteries is approximately 16 mm Hg. Fifty percent of the blood flow bypasses the liver through the ductus venosus. The rest of the blood perfuses the left lobe of the liver. Blood flow to the right lobe is via the portal circulation. Blood from the right and left hepatic veins combines with blood from the ductus venosus and travels to the right atrium via the inferior vena cava (IVC).[11–14]

Much of the blood that enters the right atrium is shunted to the left atrium through the *patent foramen ovale* (PFO) bypassing the right ventricle with the directional help provided by the eustachian valve located at the junction of the IVC and right atrium. The blood continues into the left ventricle and is pumped to the upper body to perfuse the brain and heart through the aorta. Oxygen saturation of the blood ejected from the left ventricle is approximately 70% due to the direct passage of flow provided by the ductus venosus. The superior vena cava carries deoxygenated blood from the upper body to the right atrium and ventricle. The high pulmonary vascular resistance (PVR) favors almost all the right ventricular output to be shunted through the *ductus arteriosus*, a connection between the pulmonary artery and aorta, to bypass the lungs and enter systemic circulation. Studies report that total pulmonary blood flow is about 25% of combined ventricular output in utero at 30 weeks of gestational age but may be as little as 13% at 20 weeks of gestational age before decreasing to 21% at 38 weeks of gestational age.[15] The lower part of the body, including the kidneys and gut, is perfused with blood that has an oxygen saturation of only 55%.[11–14]

Oxygen Delivery in Utero

The four physiological features that aid in the adequate delivery of oxygen to fetal tissues despite low oxygen saturation are (1) the presence of fetal hemoglobin (HbF), (2) low levels of 2,3-diphosphoglycerate (2,3-DPG) as well as (3) low affinity of HbF for 2,3-DPG and (4) erythropoietic environment resulting in a higher baseline hematocrit of around 17 g/dL. The P_{50}, partial pressure of oxygen at which 50% saturation of hemoglobin occurs, is lower at 19 mm Hg as opposed to that of adult hemoglobin (HbA) that has a P_{50} of 26 mm Hg. The fetal hemoglobin thus has a higher affinity for oxygen, improving the oxygen uptake from mother's blood at the placenta. In turn, the increased affinity for oxygen is offset by the slightly lower fetal pH allowing for adequate oxygen delivery to tissues.[11,16]

Perinatal Transition of Circulation

The fetal physiology undergoes dramatic changes in the first few minutes after birth to ensure survival. The once parallel circulation now changes to that in series as the pulmonary vascular resistance (PVR) significantly drops due to increased oxygen tension. Aeration of the lungs stimulates the endothelium to secrete nitric oxide and PGI_2 which are potent vasodilators. With the increased blood flow through the lungs and clamping of the umbilical vessels causing increased systemic vascular resistance (SVR), left-sided heart pressures are increased. The foramen ovale functionally closes when the left atrial pressure surpasses right atrial pressure by exerting hydrostatic pressure on the septum primum but remains anatomically patent in most infants. Up to a quarter of adults and half of children younger than 5 years may have an anatomically patent foramen ovale.[17] The ductus arteriosus begins to close within the first hours of life due to loss of placental prostaglandins and increase oxygen tension in almost all term infants by day 4.[18] Fibrosis of the ductus arteriosus occurs within 3 weeks of birth, completing the transformation to the ligamentum arteriosum.[19,20]

Left ventricular cardiac output increases after birth due to the increased pulmonary venous return and a transient left to right shunt at the level of the ductus. There is an increase in ventricular preload, stroke volume, and heart rate to accommodate for the increased metabolic rate that is double that of an adult. The right ventricle observes a decrease in volume and pressure load due to the elimination of the umbilical vein return and decreased pulmonary vascular resistance. Flow through the ductus venosus stops after clamping of the umbilical cord and invaginates usually by week 2 of life. Hypoxia, acidosis, hypercarbia, and hypothermia have the possibility to revert neonates to a persistent fetal circulation.[11,12,15,20]

Postnatal Cardiovascular System

The neonate's immature heart has several limitations compared to that of older children and adults. Decreases in preload and heart rate are not well tolerated in neonates. The reduced number of sarcomeres and a poorly developed calcium transport system limit the heart's contractile reserve increasing its dependence on extracellular calcium for contractility. The immature myocardium, however, exhibits better tolerance to ischemia with rapid recovery of function in contrast to the adult myocardium possibly due to preference for carbohydrates and lactates as energy sources. The cardiac stroke volume is relatively fixed and cardiac output is tied to the heart rate due to a minimally compliant left ventricle, but more recent echocardiographic studies in human neonates and fetuses have demonstrated the heart's capability to increase stroke volume.[21–26]

Sympathetic system development lags behind the parasympathetic system and its activation through hypoxia, surgical stimulation, or even direct laryngoscopy can trigger bradycardia and hypotension in the neonate. The infant's vasculature is also less responsive to hypovolemia than that of older children and adults. Intravascular depletion in neonates and infants may present as hypotension without tachycardia. However, these physiological limitations usually resolve beyond infancy, if not as early as 6 months of age for a term neonate.[12,13,27–40]

Respiratory System

1. Terminal bronchioles are developed by 16 weeks of gestation, while alveolar formation begins at 36 weeks of gestation.
2. While alveoli development is completed by 18 months of age, the lungs continue to develop throughout childhood.
3. Compared to older children, the neonate lungs and chest wall both have high compliance (low elastic forces), which promotes atelectasis during inspiration.
4. Mechanisms that maintain functional residual capacity (FRC) in neonates and infants are absent under general anesthesia.

5. Apnea is common in premature and anemic patients up to 60 weeks of postmenstrual age.
6. The cricoid cartilage is the narrowest point of a child's airway.
7. Small changes in the airway diameter can lead to significant airway obstruction in children.
8. Pulmonary vascular resistance reaches adult levels by 6 months of age.

Fetal Lungs

Fetal lungs start to form in the first few weeks of life when the fetus is just 3 mm in length. The bronchial tree develops down to the terminal bronchioles by 16 weeks of gestation and the remaining distal structures develop throughout the rest of the gestation. At approximately 24 to 25 weeks of gestation during the terminal sac period, the pulmonary capillaries are formed and contact the immature alveolar epithelium. Starting at 30 weeks' gestational age, the cuboidal alveolar epithelium flattens and begins to produce pulmonary surfactant which provides alveolar stability to maintain lung inflation after birth. There is sufficient surfactant present at 34 weeks of gestation and glucocorticoid administration to the mother can hasten fetal surfactant production. A term newborn has only one-tenth of the alveoli of an adult which continue to multiply and develop significantly from birth to around 18 months of age. While in utero, the lungs remain poorly perfused and are filled with fluid that is intermittently released to form one-third of the amniotic fluid.[12,13]

Postnatal Respiratory System

The respiratory system functions primarily to maintain oxygen and carbon dioxide equilibrium in the body. With the clamping of the umbilical cord at birth, the lungs replace the placenta as the organ of gas exchange. Other components of the respiratory system include the brainstem respiratory centers; central and peripheral chemoreceptors; the phrenic, intercostal, hypoglossal, and vagal nerves; the thorax, upper and lower airways, alveoli, and lung parenchyma, as well as the pulmonary vascular system.[12,13]

The neonates' and infants' higher metabolic rates, high ventilatory requirements, and lower surface area for gas exchange of the neonate also contribute to rapid desaturations. Compared to older children, the neonate lungs and chest wall both have high compliance (low elastic forces), which promotes atelectasis during inspiration. Lung elastic fibers are poorly developed initially, but develop in the postnatal period. In neonates, there is little outward recoil of the chest wall due to the horizontal orientation of the cartilaginous rib cage poorly and developed chest wall muscles. However, FRC, the volume left in the lungs after passive exhalation, is maintained by different mechanisms than in adults. In older children and adults, the volume is maintained by the elastic forces of passive recoil of the chest balanced by the recoil of the lungs. Inspiration results largely due to the flattening of the diaphragm which is more prone to fatigue secondary to a higher proportion of type I fibers. Awake infants maintain higher end-expiratory lung volumes, therefore maintaining FRC by stiffening the chest wall with tonic contractions of the intercostal muscles and diaphragm all through the breathing cycle. In addition, they terminate their expiratory phase before lung volumes reach FRC by (1) diaphragmatic breaking and (2) glottic closure, effectively producing PEEP. However, all these mechanisms are lost while under anesthesia, resulting in atelectasis and desaturation. FRC may be only 15% of total lung capacity in young infants undergoing general anesthesia with muscle relaxation. In addition, the term neonate has only one-tenth the number terminal saccules as that of a grown child.[12,13,41–44]

Neonates and infants have a blunted response to blood carbon dioxide and oxygen concentrations. Lung inflation may result in apnea, known as the Hering-Breuer reflex. A vagal-mediated airway reflex physiologically is meant to allow for exhalation in the presence of lung hyperinflation but may lead to paradoxical apnea. Apnea is common in premature and anemic patients up to 60 weeks of postmenstrual age.[45,46] Also, breathing is independent of pulmonary arterial carbon dioxide partial pressure and hypoxia paradoxically depresses breathing.[47,48]

Compared to older children, infants have a proportionally larger head and tongue, and anterior and cephalad larynx, narrower nasal passages, and a longer omega-shaped epiglottis. The anatomic features of the neonates and infants up to 5 months of age make them obligate nasal breathers. Also, small changes in the infant airway diameter from swelling or secretions can result in significant airway obstruction.[12,13] The cricoid cartilage has been demonstrated to be the narrowest point of the airway in children less than 10 to 12 years of age, as opposed to the rima glottidis in adults.[49–56]

Regulation of Pulmonary Blood Flow

Pulmonary vascular resistance begins to decrease after birth, reaching adult levels by 6 months of age.[56] However, the neonate and infant pulmonary vasculature remains sensitive and certain conditions may increase the pulmonary vascular tone. In the neonate, these changes may result in the persistence of fetal circulation, shunting, and hypoxia even while 100% oxygen is delivered. Pulmonary disease, hypoxemia, hypercarbia, sepsis, acidosis, hypothermia, and coughing on the endotracheal tube can all increase the pulmonary vascular resistance.[57] Nitric oxide (NO), prostaglandins, histamine, and β-adrenergic catecholamines have vasodilatory effects on the pulmonary vasculature. Increases in right-sided pressures can consequently lead to right ventricular diastolic dysfunction and hypoxia from right to left shunting through the PFO.[58]

FOCUS POINTS

1. Nephrons complete formation by 36 weeks' gestation; however, the renal system is not fully mature at birth.
2. At term, GFR is only 25% of adult levels. GFR reaches adult levels at about 2 years of age.
3. All tubular transporters reliant on the sodium gradient are decreased and immature at birth. The combination of these factors decreases the newborn's ability to concentrate or dilute urine compared to adults.
4. Serum creatinine reflects maternal creatinine level at birth and then starts to decrease initially. As the child grows, creatinine clearance slowly increases and reaches adult levels at about 2 years of age due to the rapid increase in muscle mass and growth.

Renal System

Nephrons complete formation by 36 weeks' gestation; however, the renal system is not fully mature at birth. Urine output begins at 10 weeks of gestation, which helps maintain amniotic fluid balance.[59,60] The placenta helps maintain the fetus' electrolyte and fluid balance. The kidneys assume responsibility after birth. Glomerular filtration rate (GFR) and renal blood flow (RBF) are decreased in the neonate. Both increase with gestational age as renal vascular resistance decreases.[61] At term, GFR is only 25% of adult levels.[62] GFR reaches adult levels at about 2 years of age.[63,64] Similarly, tubular function also continues to increase during the first 2 years of life. All tubular transporters reliant on the sodium gradient are decreased and immature at birth. The combination of these factors decrease the newborn's ability to concentrate or dilute urine compared to adults.[65] Diluting capacity starts to mature around the fourth week of life.[66] Serum creatinine reflects maternal creatinine level at birth and then starts to decrease initially. As the child grows, creatinine clearance slowly increases and reaches adult levels at about 2 years of age due to the rapid increase in muscle mass and growth.[67]

Compared to adults, infants have lower serum bicarbonate levels and $Paco_2$. They have a greater production of endogenous acid due to calcium deposition into bone.[68] Normal bicarbonate absorption through the gastrointestinal tract helps neutralize the acid. When this process is disrupted due to gastroenteritis, starvation, or illness, infants can become extremely acidotic since they are unable to compensate for the acid load.[68] The renin–angiotensin system is present at early gestation. Serum renin activity is increased at birth and remains elevated. Renin activity decreases to adult levels by 6 to 9 years of age.[69]

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