Review Article

Cardiovascular and respiratory physiology in children

Address for correspondence:
Dr. Diganta Saikia,
D. Q.- 10, G- Lane, Assam Medical College Campus,
Dibrugarh - 786 002, Assam, India.
E-mail: drdigantasaikia@gmail.com

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Diganta Saikia, Bandana Mahanta

Department of Anaesthesiology and Critical Care Medicine, Tezpur Medical College and Hospital, Tezpur, Sonitpur, Assam, India

ABSTRACT

Children are at increased risk of perioperative respiratory and cardiovascular complications because of their unique respiratory and cardiovascular physiology compared to adults. Anaesthesia can exaggerate respiratory deterioration in young children because of their inability to control respiration and inherent susceptibility to rapid desaturation, airway obstruction, early respiratory fatigue and lung atelectasis. Premature infants (less than 60 weeks of postconceptional age) can be exposed to the danger of prolonged apnoea and consequent worsening of respiratory function. The transitional phase of circulation is vulnerable to revert to persistent foetal circulation in neonates. Myocardium and autonomic control of the heart is immature and different in neonates and infants compared to older children and adults and are predisposed to inadvertent life-threatening haemodynamic changes during the perioperative period. In this review article, we discuss respiratory and cardiovascular physiology in neonates, infants and younger children and their differences with older children and adults. We mainly focus on transitional physiology of both respiratory and cardiovascular system in newborns and infants and the deleterious changes that may occur during anaesthesia or perioperatively.

Key words: Cardiovascular physiology, children, foetal circulation, respiratory physiology

INTRODUCTION

Cardiovascular and respiratory systems undergo extensive changes during foetal through neonatal life and infancy until early childhood. Thus, respiratory and cardiovascular physiology is different in young children, especially in neonates and infants, from that of older children and adults. These unique differences make young children more vulnerable to anaesthesia related critical events and even cardiac arrest.[1,2] As majority cases of anaesthesia related mortality in children occur because of inadvertent respiratory (airway-related) and cardiocirculatory events,[1] knowledge of the main developmental changes of these two vital organ systems that occur over time since birth makes anaesthesia safer for young children. At the same time, an understanding of the differences of both cardiovascular and respiratory physiology between different groups of children and adults is essential to apply appropriate anaesthetic principles to improve perioperative outcome in paediatric patients.

RESPIRATORY PHYSIOLOGY IN CHILDREN

Respiratory physiology is different in young children, especially in neonates and infants, from that of older children and adults. Neonates and infants have immature respiratory control, inefficient respiratory muscles, different airway and lung mechanics and higher basal metabolic requirement of oxygen. Appreciation of these distinctive respiratory characteristics in young children is necessary to formulate suitable anaesthetic plans for safe conduct of anaesthesia as respiratory-related morbidity and mortality occurs even in healthy children [Table 1].[3]

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Table 1: Major characteristics of respiratory physiology in neonates and infants, and their anaesthetic implications

Physiologic characteristics	Anaesthetic implications
Immature control of respiration/Periodic breathing	Preterm infants of <60 weeks postconceptual age have higher risk of postoperative apnoea. Anaesthetics may impair ventilatory response to hypoxia and hypercarbia. Laryngeal stimulation/lung overinflation may produce apnoea.
Smaller, highly compliant airways	Increased airway resistance: Increased work of breathing, Prone to respiratory fatigue. Increased tendency to collapse: Susceptible to airway obstruction.
Higher metabolic oxygen demand/Small Functional Residual Capacity (FRC)	Vulnerable to rapid desaturation.
Unfavourable rib configuration	Greater chest wall compliance. Cannot increase lung capacity during inspiration. Increases workload on the diaphragm.
Inefficient respiratory muscles	Vulnerable to early respiratory fatigue.

INITIATION OF BREATHING

Lung remains collapsed and filled with liquids in prenatal life. The first gasp of breath generates high negative inspiratory pressure to initiate lung expansion by overcoming opposing forces, i.e. airway resistance, the inertia of fluid in the airway and the surface force of air-fluid interface in alveoli.[4] The active pressure gradient thus developed shifts the lung fluids into the interstitial tissue from where lymphatics and pulmonary circulation gradually remove it. Delayed clearance of lung fluids, which may occur in some children, may produce "transient tachypnoea of newborn" that may persist for 24 to 72 hours. Surfactant, secreted near term pregnancy, lowers the air-liquid interfacial tension and reduces the "opening pressure" necessary to aerate the alveoli and prevent alveolar collapse. Surfactant production is adequate in neonates born after 35 weeks of gestational age.[5] Premature neonates may require administration of exogenous surfactant to facilitate proper pulmonary ventilation.

REGULATION OF BREATHING

Respiratory control is immature at birth and takes several weeks to months to mature.[6] Neonate's ventilatory response to hypoxia and hypercarbia is impaired. During hypoxia, following a brief initial rise, preterm infants' respiratory rate decreases and often results in apnoea.[7] Term infants have a similar pattern of response to sustained hypoxia during the first week of life, after which they respond by a prolonged increase in ventilation.

High inspired concentration of oxygen depresses neonate's ventilation and may cause retinopathy and bronchopulmonary dysplasia, especially in preterm neonates due to their immature antioxidative system. Administration of low concentration oxygen stimulates neonate's respiration. Preterm infants respond poorly to hypercapnia unlike term infants, older children and adults who respond by increasing tidal volume and respiratory rate. Hypoxia depresses hypercapnic ventilatory responses in young infants. Anaesthetic medications may impair ventilatory response to hypoxia and hypercarbia in both term and preterm infants.

Infants have an irregular and periodical breathing pattern. Periodic breathing often occurs in both preterm and term neonates and is different from clinical apnoea. Life-threatening apnoeas are frequent, especially in preterm infants.[8] Prolonged apnoea persisting for more than 20 seconds may occur and is common in the first 12 hours postoperatively (usually within 2 hours) in infants less than 60 weeks of postconceptual age. In many cases, the risk persists even for more than twelve hours for which these high risk infants require diligent monitoring for at least twenty four hours in a tertiary care setting. If surgery can't be deferred in any such infants, prophylactic intravenous caffeine (10 mg/kg) or theophylline (8 mg/kg) can be used intraoperatively to reduce the risk of postoperative prolonged apnoea. In suitable surgical cases, utilizing regional anaesthesia technique without deep sedation should be better considered. When general anaesthesia is chosen, use of short acting anaesthetics (such as sevoflurane or desflurane) and opioids (fentanyl or sufentanyl) is logical. Some infants may require treatment with methylxanthines (theophylline or caffeine), continuous positive airway pressure (CPAP) or even mechanical ventilation.[9] Afferent laryngeal stimulation during laryngoscopy or over inflation of lungs (Herring–Breuer inflation reflex) also contributes to apnoea in neonates.

PHYSIOLOGY OF THE UPPER AND LOWER AIRWAY

Mastering oxygenation and ventilation in children is often challenging. The physiology of airway in young children, especially in neonates and infants, differ

from the physiology of airway in older children and adults. As the infants grow, these differences become less and less pronounced, and the management of airway becomes less troublesome.[10]

Children have a proportionately large head and a big occiput compared to their body size until around six years of age. Because of this large head and other anatomical differences, infants have larger anatomical dead space than older children and adults.[11] On placing supine neck gets flexed quickly in these young children and may lead to potential upper airway obstruction. Neck flexion and thereby airway obstruction can be avoided by keeping the child's head in a neutral or slightly extended position with the help of a small folded towel placed underneath his/her shoulders.

Neonates have a proportionally smaller oral cavity and a large tongue with a flat dorsal surface and limited lateral mobility. This further decreases the size of the oral cavity and may cause airflow obstruction during sleep or under sedation. However, the rapid growth of the mandible over next several months increases the volume of the oral cavity in older infants and children.

Neonates and young infants have long omega-shaped epiglottis horizontally positioned high in the pharynx very near to the soft palate than in older children and adults. Combined with the absence of paranasal sinuses, this causes less resistance to airflow in the nasal passages than in the oral route. Thus, neonates and infants prefer to breathe nasally rather than orally.[12] However, nasal passages in these young children are small and prone to be easily obstructed by thick secretions or oedema and may cause difficulty in breathing and increase in work of ventilation. Nasal passages should be cleared of secretions or blood before induction of anaesthesia and postoperatively. Nasogastric tube and nasally introduced tracheal tube may further damage the small nasal passages and should preferably be avoided. Keeping the mouth open during mask ventilation will help achieve optimum ventilation in these young children rather than ventilating through small nasal passages. Over months to years, the laryngeal structures descend and separate the epiglottis from the soft palate and allow infants to transit from obligatory nasal to oral breather.

The cricoid ring is ellipsoid, smaller in size with a mucosal layer and forms the narrowest part of the upper airway in newborns. As the cricoid is a complete cartilaginous ring, repeated or prolonged tracheal intubation may produce acquired subglottic laryngeal stenosis in young infants.[13]

Trachea in preterm and term infants is short and narrow and more compliant than in older children and adults because of the presence of immature cartilages. Endobronchial displacement or accidental extubation of the tracheal tube can occur from within the short trachea and hence require close monitoring throughout a procedure when the child's trachea is intubated. The trachea is also poorly supported by surrounding structures and thus is prone to dynamic collapse during forced inspiration or expiration.

Because of small diameters, airways produce higher resistance to airflow in both term and preterm neonates.[14] Further narrowing of the lower airway due to mucosal oedema at cricoid level or laryngeal stenosis or due to the presence of blood, secretions or placement of the inappropriately small tracheal tube may compromise airway patency and increase work of breathing in neonates and infants. One should carefully select a tracheal tube of an appropriate size for the age of the child before intubation and clear the airway of blood or secretions whenever warranted. However, airway resistance gradually decreases over the first year of life.[10]

The vagus nerve supplies the inferior surface of the epiglottis as well as the inlet of the larynx. Lifting of the epiglottis by the straight laryngoscope blade may activate vagal reflex and consequently produce bradycardia and hypotension in infants and young children. Vagal stimulation can be avoided by using a curved blade or by placing the tip of a straight blade in the vallecula, which is innervated by the ninth cranial nerve.[15]

PHYSIOLOGY OF THE LUNG AND THORAX

Neonates, especially premature ones, have fewer alveoli. These continue to grow and develop through childhood until adolescence and thereby increase the lung surface area for gaseous exchange in older children and adults. However, during the neonatal period and early infancy, these alveoli lack interalveolar communications and remain at risk of collapse and may produce atelectasis in dependent areas of the lung.

In young children, intercostal muscles are poorly developed and less effective as the accessory

muscles of respiration. Ribs are horizontally aligned from the vertebral column and cannot increase the cross-sectional area of the thorax during inspiration, unlike older children and adults. Thus, inspiration occurs almost entirely because of diaphragmatic descent and the diaphragm bears all the workload of breathing in neonates and infants. To reduce diaphragmatic workload and maintain minute ventilation, these children then breathe rapidly with smaller tidal volumes. However, the diaphragm has less type-1 muscle fibres and is prone to early fatigue. Thus, respiratory fatigue occurs early in neonates and infants and can result in respiratory failure.

Young infants have markedly low total lung (TLC) and functional residual capacity (FRC).[16] Closing volume is higher than the FRC because of the highly compliant thoracic wall and poorly compliant lung tissue, which tends to cause air trapping in alveoli because of early closure of the terminal airways. Infants modify respiratory mechanics to maintain small airway patency and thus increase FRC by controlling expiratory flow through the larynx (auto-PEEP) and with the help of activity of inspiratory muscles post inspiration.[17] General anaesthesia blunts these laryngeal braking mechanisms and results in reduced FRC and increased pulmonary shunt fraction. These combined with high metabolic oxygen demand (newborn 9.0 ml O2/kg/min, and a 1-year-old child 10.9 ml O2/kg/min per active mass unit) may cause a rapid fall of arterial oxygen tension in neonates and infants during induction of anaesthesia.

CARDIOVASCULAR PHYSIOLOGY IN CHILDREN

Cardiovascular anatomy and physiology change in newborns rapidly over a few days to several weeks following birth and attain adult level later in infancy. As the newborns grow, circulatory pathway alters, myocardium gradually matures and autonomic control of the heart changes over time. These significant developments make neonates and infants cardiovascular physiology different from those of older children and adults. Appreciation of these differences is necessary to formulate a safe anaesthetic technique that helps to reduce perioperative morbidity and mortality in children [Table 2].

FOETAL CIRCULATION AND ITS TRANSITION TO ADULT TYPE

The transition from foetal to neonatal and then to adult circulation is complex as profound changes occur both in circulatory anatomy and physiology. A smooth and successful transition is necessary for the newborn to become independent from the mother (placenta) for life-sustaining oxygen and other nutrients in the extrauterine environment. The delayed or difficult transition of foetal circulation or return of the neonatal circulation to persistent foetal circulation, during the transitional phase, has several anaesthetic implications.

FOETAL CIRCULATION

During prenatal life, pulmonary vascular resistance is very high as lung remains collapsed and filled with liquids. Life-sustaining oxygen is transferred to the foetus from the mother's blood across the placenta through the single umbilical vein. Approximately half of this umbilical venous blood bypasses the liver and enters the inferior vena cava via ductus venosus. On entering the right atrium, this oxygenated stream of blood is directed preferentially into the left atrium through the foramen ovale which then passes into the left ventricle.[18] The left ventricle ejects this blood into the aorta and then distributes it to the brain, the myocardium and the upper part of the body. The other half of the oxygenated blood carried through the umbilical vein enters the liver to supply it oxygen and nutrients and passes into the inferior vena cava through the portal vein where it joins the deoxygenated blood

Table 2: Major characteristics of cardiovascular physiology in neonates and infants, and their anaesthetic implications

Physiologic characteristics	Anaesthetic implications
Persistent foetal circulation	Decreased peripheral tissue oxygen delivery.
	Prolonged inhalational induction/rapid iv induction with consequent cardio circulatory depression.
Vulnerable transitional circulation	Susceptible to revert to persistent foetal circulation, perioperatively.
Stiff myocardium/Less myocardial tension during contraction	Near static stroke volume/rate-dependent cardiac output.
Less functional cardiac reserve	Cannot tolerate increased pre- or after load, myocardial depression, hypovolaemia and arrhythmia.
Predominant parasympathetic control of heart	Prone to bradycardia in response to noxious and autonomic stimuli.
High basal endogenous catecholamines	Exogenous catecholamines are less effective.
Higher Foetal Haemoglobin in newborn	Prone to perioperative hypoxia

coming from the lower half of the body. Thus, two streams of blood flow through the inferior vena cava of which the oxygenated one is directed to the left atrium and then to the left ventricle, while the other, the deoxygenated stream goes directly to the right ventricle from the right atrium.[19] Deoxygenated blood drained from the upper part of the body enters the right atrium via the superior vena cava and passes preferentially into the right ventricle across the tricuspid valve. Most of the blood ejected from the right ventricle into the pulmonary artery bypasses the lungs and enters the descending aorta through the ductus arteriosus while a little, 8-10% of total cardiac output circulates through high vascular resistance pulmonary circulation.[20] A part of the blood in the descending aorta supplies the lower half of the body while the other travels to the placenta via two umbilical arteries for reoxygenation. The foetal circulation thus runs in parallel. The left ventricle provides well-oxygenated placental blood preferentially to the brain, the myocardium and the upper half of the body while the right ventricle supplies the blood with lower oxygen tension to the lower half of the body and the placenta.

TRANSITIONAL CIRCULATION

The transition of foetal circulation (parallel circulation) to postnatal type (one in series) begins at birth following lung inflation (first cry) and removal of the placental circulation (clamping of the umbilical cord). Lung inflation reduces the high pulmonary vascular resistance while removal of low resistance placental circulation increases the systemic vascular resistance. These changes augment pulmonary blood flow and increase the return of blood to the left atrium. Consequently, left atrial pressure rises. Ductus venosus narrows and decreases blood return to the right atrium via inferior vena cava, causing a fall in the right atrial pressure. Thus, a reversal of pressure gradient occurs between the left and the right atrium and produces functional closure of the foramen ovale over next few breaths.[21] Ductus arteriosus constricts because of the rise of oxygen tension and a decrease in circulating prostaglandin level following removal of the placenta. Blood flow across it reverses due to changes in systemic and pulmonary arterial pressure gradients. In term newborns, ductus arteriosus functionally closes within 24-48 hours. However, a small amount of left to right shunting of blood may persist through the narrow ductus arteriosus for few days to several weeks of life until when it permanently closes by 4-8 weeks.[22] Passive closure of ductus venosus and umbilical arteries occur over several days.

Healthy newborns adapt this transitional circulation successfully and produce equal left and right ventricular output. Premature infants and infants with underlying congenital heart disease and diaphragmatic hernia may have altered transitional physiology.[23]

Transitional circulation is vulnerable. Inadvertent rise of pulmonary vascular resistance during the perioperative period may reopen ductus arteriosus and foramen ovale in neonates and young infants and may bring back transitional circulation to persistent foetal circulation.[24] The same may render the foetal circulation to persist in infants who have not attained transitional circulation yet because of delayed or complicated transitional physiology. Hypoxia, hypothermia, hypercarbia and acidosis in neonates are potent pulmonary vasoconstrictors and may cause a rise in pulmonary vascular resistance resulting in the reversal of transitional circulation to persistent foetal circulation.[23] Right to left ductal shunting can be detected by measuring preductal and postductal oxygen saturation by simultaneous use of two pulse oxymeters, one in the right upper limb (preductal) and the other in a lower limb (postductal). Preductal arterial saturation of at least more than 3% above the postductal saturation implies right to left ductal shunting.

Persistent foetal circulation causes decreased pulmonary blood flow and right to left shunting of blood resulting in reduced oxygen delivery to peripheral tissues and hypoxia. Right to left shunting of blood in children slows the uptake of volatile anaesthetics and consequently prolongs inhalational induction of anaesthesia while induction with intravenous agents may result in unintended rapid unconsciousness, apnoea and life-threatening haemodynamic changes.

ADULT CIRCULATION

Transitional circulation persists for days to weeks in newborns with a healthy heart. Mature (adult) circulation begins following further fall in pulmonary vascular resistance and permanent anatomic closure of the ductus arteriosus usually in 4-8 weeks.[25]

MYOCARDIAL PERFORMANCE

Newborns hearts function with near maximal myocardial contractility because of ß- stimulation by large numbers of endogenous catecholamines and thyroid hormones released during late gestation and at birth.[26,27] This is necessary to produce sizeable

cardiac output to compensate for higher metabolic oxygen demand for the first several months of life. However, even though resting myocardial tension in neonates and infants is more significant than in older children and adults, newborn myocardium develops less stress during cardiac contraction. Also, the presence of a disorderly arranged higher amount of non-contractile proteins in cardiac myocytes make neonatal myocardium less compliant or stiff. For these reasons, stroke volume in neonates and infants remains near static and shows less ability to increase cardiac output with an increase in preload.[28] Thus, newborns and young infants are dependent on the heart rate to increase cardiac output. A decrease in cardiac output to the extent of 20-30% may occur if the heart rate is allowed to drop to ≤120 beats per minute from the normal range of 140-160 beats per minute in neonates.[29] As the newborns' hearts operate near the flat portion of the Frank-Starling curve, because of near maximal basal ß-stimulation and lower myocardial compliance, they have a less functional cardiac reserve in response to increased pre- and afterload.[24] Thus, newborns and young infants poorly tolerate volume loading or a rise in systemic vascular resistance. Depression of myocardial contractility caused by anaesthetic agents or exposure to other perioperative events like hypoxia, hypercarbia, acidosis and electrolyte imbalance may cause sudden and severe circulatory depression. Similarly, these children poorly tolerate hypovolaemia and arrhythmia. On the other hand, administration of exogenous catecholamines has significantly lesser effects on both myocardial contractility and relaxation in neonates and young infants in comparison to older children and adults. However, functional cardiac reserve increases with advancing age, as myocytes mature and basal circulating catecholamine level decreases, with increase in inotropic response to β-adrenergic stimulation.[30,31] Thus, as the infant grows, the heart gains capacity to better respond to stress.

AUTONOMIC REGULATION OF THE CARDIOVASCULAR SYSTEM

Parasympathetic innervation is predominant in the foetus in utero and mature at birth. Sympathetic control of the heart appears after the child is born and is not complete until later in infancy. Thus, predominant parasympathetic response with bradycardia is frequent in newborns and young infants in response to several noxious and autonomic stimuli such as hypoxia and direct laryngoscopy as well as to the administration of vagotonic agents used during anaesthesia. Bradycardia may result in severely reduced cardiac output and hypotension and hence insufficient tissue oxygen delivery. The parasympathetic predominance in infants gradually diminishes over the first six months of life when sympathetic innervations mature and take control of the cardiovascular system. Because of fluctuations in autonomic tone, older children may exhibit clinically insignificant variations in heart rate, conduction abnormalities and different kinds of arrhythmias.[32]

OXYGEN CARRIAGE

At birth, newborn blood contains more foetal haemoglobin (HbF) than adult haemoglobin (HBA). HbF has a higher affinity for oxygen than HbA. Thus, newborns are prone to hypoxia as oxygen delivery at tissue level is reduced in spite of a higher haemoglobin level. However, during the neonatal period level of 2, 3- diphosphoglycerate rises and oxygen dissociation curve shifts to the right. These changes decrease the affinity of HbF for oxygen and improve tissue oxygen delivery in infants.

Production of foetal haemoglobin declines gradually over the next few months and is entirely replaced by adult haemoglobin at about six months of age.[21] However, because of the low circulating level of haematopoetin during early infancy, HbA is synthesised slower than HbF is lost from the circulation. Increased HbF loss, decreased synthesis of HbA combined with a relative increase in circulating blood volume cause a decrease in total haemoglobin level and produce physiological anaemia in term infants at around 9-12 weeks of age. The fall in haemoglobin level is more in premature infants and is directly related to their gestational age. They also have their lowest haemoglobin level earlier (between 4-8 weeks life) than term infants. However, the affinity of oxygen for haemoglobin decreases as infants grow and results in increased oxygen unloading at the tissue level. Thus, in terms of tissue oxygen delivery, a reduced level of haemoglobin in infants and young children is equivalent to a higher level of haemoglobin in adults.[28]

CONCLUSION

Young children have different respiratory and cardiovascular physiology compared to older children and adults and are at increased risk of perioperative respiratory and cardiocirculatory complications. Neonates and infants, especially premature neonates,

have immature respiratory control, inefficient inspiratory muscles, different airway and lung mechanics and higher basal metabolic requirement of oxygen. Undetected apnoea or airway obstruction, respiratory fatigue or lung atelectasis under anaesthesia may produce rapid respiratory deterioration in these children perioperatively. Hypoxia, hypercapnia, acidosis or electrolyte disturbances increase pulmonary vascular resistance and may cause transitional circulation to revert to persistent foetal circulation in newborns. Young children have less cardiac reserves and rate dependent cardiac output. They poorly tolerate depression of myocardial contractility and changes in systemic vascular resistance or circulatory volume during anaesthesia. Predominant parasympathetic control of the heart frequently produces bradycardia and its deleterious effects in newborns and young infants in response to several noxious and autonomic stimuli. Newborns are prone to hypoxia because of higher HbF level in their blood, which causes less oxygen delivery at tissue level despite having a higher haemoglobin level. Anaesthetists therefore need to appreciate these unique characteristics of respiratory and cardiovascular physiology in young children, especially in neonates and infants, and formulate a safe and effective anaesthetic plan to reduce perioperative morbidity and mortality in children.

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Conflicts of interest

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