Pediatric Physiology: How Does it Differ from Adults?

7

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Introduction

Safe sedation of pediatric patients requires a thorough understanding of the physiological differences between infants, children, adolescents, and adults. Especially in small infants, there is much less margin for any errors in diagnosis and treatment of respiratory or cardiovascular depression during sedation procedures. This chapter will review developmental aspects of respiratory, cardiovascular, central nervous system, renal, hepatic, hematologic, and temperature homeostatic systems, highlighting the differences between children and adults and emphasizing their relevance to sedation procedures in children.

Respiratory Physiology

Many physiologic differences in respiratory physiology between children and adults can be understood by anatomical differences in the airway and lungs [1]. The major anatomical airway differences include the tongue, where the infant's tongue is relatively large compared to the adult, and more prone to airway obstruction. The larynx of the infant is more cephalad, lying at the C3–4 level, versus the adult position of C4–5. The infant epiglottis is narrow and omega-shaped, versus the flat, broad, U-shaped epiglottis of the adult. The cricoid ring is the narrowest portion of the infant and child up to about 4–6 years of age; thereafter the glottic opening itself is the narrowest portion of the airway. In terms of the intrathoracic airways, they are fully formed, including the terminal bronchioles, relatively early in gestation. However, alveolar number and development are incomplete at birth, with the full term infant having 20–50 million terminal airspaces, which are immature alveoli. Lung development occurs rapidly with nearly the adult number of 300 million or more alveoli reached by 3 years of age [2]. Early in postnatal life the lung volume of the neonate and young infant is disproportionately small in relation to body size, the functional residual capacity (FRC) is only about 25 mL/kg in contrast to 40–50 mL/kg in the older child and adolescent. In addition, metabolic rate and therefore oxygen requirement in mL/kg/min is 2–3 times higher in the neonate compared to the adult.

Lung and chest wall mechanics are very different in the neonate and young infant, compared to the older child and adult [2, 3]. The soft and compliant thoracic cage means that the outward recoil of the thorax is very low in the neonate, and this means that resting negative thoracic pressure in

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infants is low. Neonates depend on the diaphragm for the power to produce lung expansion to a much greater degree than the older child. In addition, since airway resistance is proportional to the inverse of the fourth power of the radius of the airway, the much smaller airways of infants and young children experience a significant increase in resistance when partially obstructed by edema, inflammation, bronchospasm, or secretions. The low FRC, small airways, and poor elastic recoil of the thorax in neonates makes the small airways vulnerable to airway closure, and thus hypoventilation and hypoxemia can occur quickly in the sedated infant who is not crying or taking deep breaths [4]. Figure 7.1 displays the difference in lung volumes between the neonate and adult [5], and Table 7.1 summarizes the developmental changes in respiratory physiology from birth through adulthood.

Fetal hemoglobin predominates in the neonate and young infant, and this causes another important difference in respiratory physiology from the older child and adult. The oxyhemoglobin dissociation curve is shifted to the left in neonates because of fetal hemoglobin, meaning that the partial pressure of oxygen necessary to produce an oxyhemoglobin saturation of 50% (the P_{50}) is only 19 mmHg, versus 27 mmHg with mature adult hemoglobin A [6] (Fig. 7.2). This is an adaptation to fetal life, where oxygen tensions are low, and with hemoglobin F loading the hemoglobin with oxygen molecules is facilitated; however unloading of oxygen to the tissues is more difficult with a left-shifted curve. Therefore in the neonate and young infant, a given oxygen tension will produce a higher oxygen saturation, but this extra reserve is required to provide additional oxygen to unload to the tissues. Adult hemoglobin A predominates by 6 months of age.

Pulse oximetry is the standard for monitoring of oxygenation during all sedation procedures. Pulse oximeter arterial saturation (SpO_2) is a very useful monitor, generally accurate to ±2% when compared to arterial blood oxygen saturation measured by co-oximetry. In a child without cardiac or pulmonary disease, normal SpO_2 is 96–100% on room air and unsedated. Sedative medications often cause a degree of hypoventilation, both in slowing respiratory rate, and decreasing tidal volumes and FRC. Upper airway obstruction is also common, which may interfere with oxygenation. These factors make it necessary to deliver supplemental oxygen to virtually all patients undergoing sedation procedures, either by nasal cannula or face-mask, to enable SpO_2 to remain in the normal 96–100% range. A decrease of 5% or less from baseline, as long as the patient is otherwise stable without significant respiratory depression or upper airway obstruction, is common and can usually be treated with increased supplemental oxygen. A decrease of 10% or more from baseline is cause for urgent intervention to detect and treat upper airway obstruction or hypoventilation, the two most common causes of arterial desaturation during sedation. Children with cyanotic congenital heart disease may have resting awake SpO_2 ranging from 70–95%, and it is important to understand the anatomy, pathophysiology, and normal baseline saturations before proceeding with sedation in these patients. The general guideline that a 5% decrease in SpO_2 from baseline is common and may be treated with additional supplemental oxygen, and that a 10% decrease is a cause for urgent intervention, applies to the congenital heart disease population as well. Other patients with chronic lung diseases, i.e., bronchopulmonary dysplasia (BPD) or cystic fibrosis, may also have decreased baseline SpO_2, often ranging from 85 to 95%.

Monitoring of respiration also often includes end-tidal CO_2, which can easily be monitored using a special or modified nasal cannula. Although dilution of the exhaled gas with inspired oxygen, poor fit of nasal cannula, increased dead-space ventilation, or right to left intracardiac shunting often increases the gap between arterial blood $PaCO_2$, and end-tidal CO_2, it is a very sensitive monitor of airway obstruction, and an accurate method to measure respiratory rate. In addition, low cardiac output states or cardiac arrest are accompanied by a sudden decrease or absence of end-tidal CO_2.

Common conditions in pediatric patients which reduce respiratory reserve even further include BPD in former premature infants who suffered from respiratory distress syndrome (RDS) [7]. BPD is defined as a chronic condition of fibrosis and loss of alveoli in the lung following RDS with a requirement for supplemental oxygen beyond

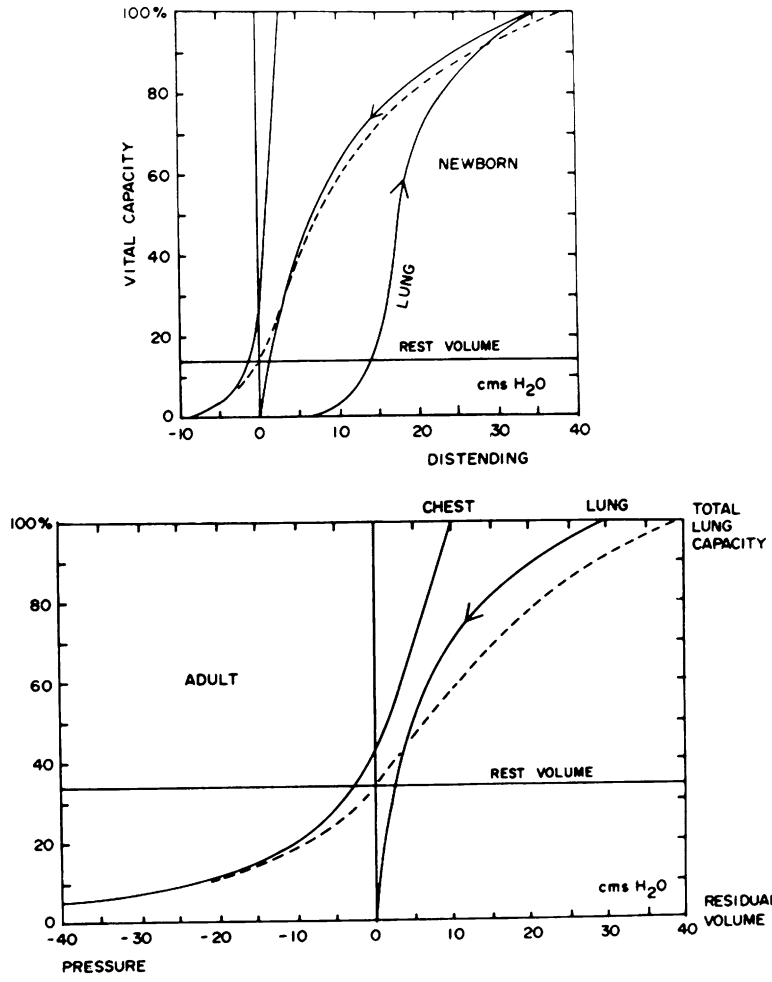

Fig. 7.1 Pressure–volume curves of the infant and adult respiratory systems. The rest volume is the volume at zero intrathoracic pressure, where the outward recoil of the chest wall is equal to the inward elastic recoil of the lungs. In the neonate, this volume is very low (10–15% of total lung capacity) compared to the adult, and is just above the FRC and often below the closing volume of the small airways. In the adult this value is much higher at 30–35% of the total lung capacity. During sedation, where quiet breathing or respiratory depression may occur, the neonate and small infant is much more prone to airway closure, resulting in intrapulmonary shunting and hypoxemia. (Reproduced with permission from Smith and Nelson [5])

30 days of life. These infants may present for sedation months or years later, and even though they have apparently recovered, pulmonary reserve is often considerably limited. Other common chronic conditions include asthma or reactive airways disease, affecting an estimated six million children in the United States [8]. Pre-sedation assessment must always include questioning about asthma and a thorough airway and pulmonary examination; elective sedation in the face of an asthma exacerbation is contraindicated. Children also have frequent upper respiratory infections, which predispose them to increased airway complications during a sedation procedure. Elective sedation procedures should be performed in children with upper respiratory tract infections only after a thorough risk-benefit assessment.

All of the factors reviewed earlier make the small infant in particular vulnerable to rapid onset of hypoxemia and hypercarbia if sedated too deeply, and the practitioner must be vigilant especially when sedating infants. Supplemental

Table 7.1 Age dependent respiratory variables

Variable	Units	Neonate	6 months	12 months	3 years	5 years	9 years	12 years	Adult
Approx. weight	kg	3	7	10	15	19	30	50	70
Respiratory rate	Breaths/min	50 ± 10	30 ± 5	24 ± 6	24 ± 6	23 ± 5	20 ± 5	18 ± 5	12 ± 3
Tidal volume	mL	21	45	78	112	170	230	480	575
	mL/kg	6–8	6–8	6–8	6–8	7–8	7–8	7–8	6–7
Minute ventilation	mL/min	1,050	1,350	1,780	2,460	4,000		6,200	6,400
	mL/kg/min	350	193	178	164	210		124	91
Alveolar ventilation	mL/min	665		1,245	1760	1,800		3,000	3,100
	mL/kg/min	222		125	117	95		60	44
Dead space/tidal volume ratio		0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Oxygen consumption	mL/kg/min	6–8							3–4
Vital capacity	mL	120			870	1,160		3,100	4,000
	mL/kg	40			58	61		62	57
Functional residual capacity	mL	80			490	680		1,970	3,000
	mL/kg	27			33	36		39	43
Total lung capacity	mL	160			1,100	1,500		4,000	6,000
	mL/kg	53			73	79		80	86
Closing volume as a % of vital capacity	%					20		8	4
No. of alveoli	Saccules × 10^6	30	112	129	257	280			300
Specific compliance	C_L/FRC:mL/cm H_2O/L	0.04	0.038			0.06			0.05
Specific conductance of small airways	Ml/sec/cm H_2O/g	0.02		3.1	1.7	1.2		8.2	13.4
Hematocrit	%	55 ± 7	37 ± 3	35 ± 2.5	40 ± 3	40 ± 2	40 ± 2	42 ± 2	43–48
Arterial pH	pH units	7.30–7.40		7.35–7.45					7.35–7.45
$PaCO_2$	mmHg	30–35		30–40					30–40
PaO_2	mmHg	60–90		80–100					80–100

Source: Adapted and reproduced with permission from O'Rourke and Crone [2]

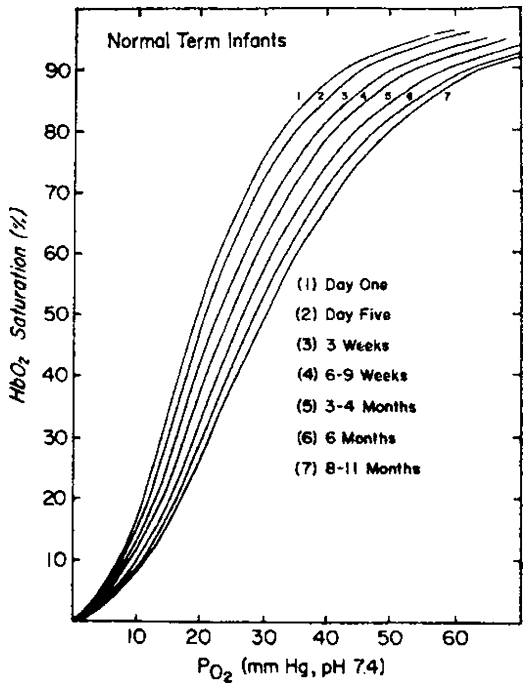

Fig. 7.2 Comparison of oxyhemoglobin dissociation curves from blood of infants at different ages. At birth the P50 is 19 mmHg, and by 8 months of age has shifted to the right and is 27 mmHg, a result of the change from predominately fetal hemoglobin F to adult hemoglobin A. (Reproduced with permission from Delivoria-Papadopoulos et al. [6])

oxygen should be used in almost every setting in which infants and children are sedated; the only exceptions being in premature neonates where retinopathy of prematurity may be a risk, and in relatively uncommon congenital heart defects in neonates with a single functional ventricle, such as hypoplastic left heart syndrome.

Cardiovascular Physiology

Development from Neonate to Older Infant and Child

At birth the neonatal heart must suddenly change from a parallel circulation to a series circulation, and the left ventricle in particular must adapt immediately to dramatically increased preload from blood returning from the lungs, and increased afterload as the placental circulation is removed. The very high oxygen consumption of the newborn necessitates a high cardiac output for the first few months of life. However, animal models have demonstrated that the fetal and newborn myocardium develops less tension in response to increasing preload (sarcomere length), and that cardiac output increases less to the same degree of volume loading [9, 10]. Resting tension, however, is greater in the newborn compared to the mature heart. This information suggests that the newborn heart is operating near the top of its Frank–Starling curve, and that there is less reserve in response to both increased afterload and preload. The newborn myocardium also has only a limited ability to increase its inotropic state in response to exogenous catecholamines, and is much more dependent on heart rate to maintain cardiac output than the mature heart. One reason for this is the high levels of circulating endogenous catecholamines that appear after birth, necessary to make the transition to extrauterine life [11]. As these levels decrease in the weeks after birth, contractile reserve increases.

The neonatal myocardium is less compliant than the mature myocardium, with increased resting tension as noted previously, and a significant greater increase in ventricular pressure with volume loading [12]. This implies that diastolic function of the neonatal heart is also impaired compared to the mature heart [13]. The myofibrils of the newborn heart also appear to have a greater sensitivity to calcium, developing a greater tension than adult myofibrils when exposed to the same free calcium (Ca^{++}) concentration in vitro [14]. Table 7.2 summarizes the major physiological differences between the neonatal and mature heart [15]. With increased metabolic needs, including oxygen consumption and glucose for metabolic substrate, cardiac output indexed to weight in the neonate is double that of the adult [16] (Fig. 7.3).

Innervation of the Heart

Clinical observations in newborn infants have led to the hypothesis that the sympathetic innervation and control of the cardiovascular system is

Table 7.2 Summary of major differences between neonatal and mature hearts

	Neonatal	Mature
Physiology		
Contractility	Limited	Normal
Heart rate dependence	High	Low
Contractile reserve	Low	High
Afterload tolerance	Low	Higher
Preload tolerance	Limited	Better
Ventricular interdependence	Significant	Less
Ca^{++} cycling		
Predominant site of Ca^{++} flux	Sarcolemma	Sarcoplasmic reticulum
Dependence on normal iCa^{++}	High	Lower
Circulating catecholamines	High	Lower
Adrenergic receptors	Downregulated, insensitive β2, a1 predominant	Normal ß1 predominant
Innervation	Parasympathetic predominates; sympathetic incomplete	Complete
Cytoskeleton		
	High collagen and water content	Lower collagen/H_2O
Cellular elements		
	Incomplete SR, disorganized myofibrils	Mature SR, organized myofibrils

SR sarcoplasmic reticulum
Source: Reproduced with permission from Andropoulos and Ogletree [15]

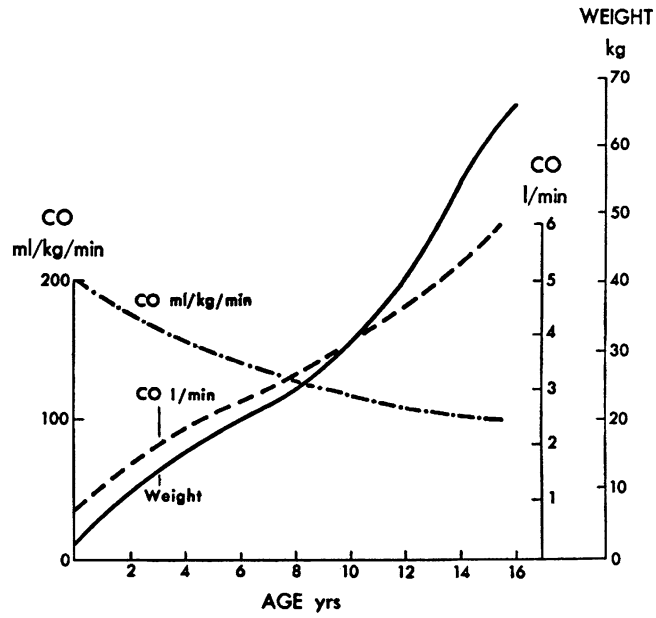

Fig. 7.3 The relationship between body weight, age, and cardiac output. Note that cardiac output in mL/min, when indexed to body weight, decreases by 50% from birth to adolescence. (Reproduced with permission from Rudolph [16])

incomplete in the newborn infant compared to older children and adults, and that the parasympathetic innervation is intact [17]. Examples of this include the frequency of bradycardia in the newborn in response to a number of stimuli, including vagal, and vagotonic agents, and the relative lack of sensitivity in the newborn to sympathomimetic agents. Histologic studies in animal models have demonstrated incomplete sympathetic innervation in the neonatal heart when compared to the adult, but no differences in the number or density of parasympathetic nerves [18, 19].

Autonomic cardiovascular control of cardiac activity can be evaluated by measuring heart rate variability in response to both respiration, and to beat-to-beat variability in systolic blood pressure [20]. The sympathetic and parasympathetic input into sinoatrial node activity contribute to heart rate variability changes with greater heart rate variability resulting from greater parasympathetic input into sinoatrial node activity [21]. Studies using these methodologies for normal infants during sleep suggest that the parasympathetic predominance gradually diminishes until approximately 6 months of age, coinciding with greater sympathetic innervation of the heart similar to adult levels [22].

Development from Child to Adult

Beyond the transition period from fetal to newborn life and into the first few months of postnatal life, there is not much human or animal information concerning the exact nature and extent of cardiac development at the cellular level. Most studies compare newborn or fetal to adult animals [23]. Cardiac chamber development is assumed to be influenced by blood flow [24]. Increases in myocardial mass with normal growth, as well as in ventricular outflow obstruction, are mainly due to hypertrophy of myocytes. Late gestational increases in blood cortisol are responsible for this growth pattern, and there is concern that antenatal glucocorticoids to induce lung maturity may inhibit cardiac myocyte proliferation. In the human infant, it is assumed that the cellular elements of the cardiac myocyte, i.e., adrenergic receptors, intracellular receptors and signaling, calcium cycling and regulation, and interaction of the contractile proteins, is similar to the adult by approximately 6 months of age. Similarly, cardiac depression by volatile agents is greater in the newborn changing to adult levels by approximately 6 months of age [25].

Normal Heart Rate and Blood Pressure Ranges at Different Ages

Heart rate must be monitored continuously by 3 or 5 lead ECG during all phases of a sedation procedure, because of the frequent effects of sedative and analgesic drugs on heart rate, and the added importance of maintaining acceptable heart rates to maintain cardiac output, especially in young infants. An understanding of the patient's baseline heart rates is important, and generally a decrease or increase of 20% or less is well tolerated and will maintain adequate cardiac output [26]. Maintaining normal sinus rhythm is obviously important, and any non-sinus rhythm needs to be diagnosed, its effect on blood pressure and cardiac output assessed, and treated if necessary. The most common arrhythmias are sinus bradycardia caused by decreased central nervous system sympathetic outflow from many sedatives, or sinus tachycardia caused by sympathomimetic effects of drugs. Slow junctional rhythms or supraventricular tachycardias are also seen during sedation procedures. It is important to understand the patient's baseline cardiac status, and rhythm, as many patients with preexisting arrhythmias will continue to experience them with sedation and no ill effects.

Blood pressure must be measured at least every 5 min during sedation procedures, and often more frequently, i.e., every 1–3 min, during the induction phase, or after a bolus of medication to deepen the level of sedation. Blood pressure is not equivalent to cardiac output, but perfusion to vital organs, especially myocardium and brain, needs to be preserved during sedation procedures and thus blood pressure should be maintained within acceptable limits, usually ±20% of the baseline blood pressure, again taking into account the patient's baseline state, and pathophysiology of any disease states. Blood pressure is usually measured with an automated oscillometric blood pressure device, and the cuff must be the proper size for the patient, according to the manufacturer's instructions. A cuff that is too small for the patient will read out a blood pressure that is falsely elevated, and a cuff that is too large will display a pressure that is spuriously low. Under normal circumstances, a cuff on the right or left upper arm is standard, although a properly-sized blood pressure cuff on the lower leg will also provide accurate measurements. The measured systolic pressure and mean pressure are very accurate

with the oscillometric devices, with the diastolic pressure being subject to increased measurement errors. Since the systolic blood pressure is most commonly used to determine high or low measurements, Table 7.3 includes this parameter for normal values. Systolic blood pressures more than 20% below baseline values, if accompanied by acceptable heart rate, oxygen saturation, and end-tidal CO_2, should be investigated and treatment such as fluid administration to increase cardiac preload and stroke volume, or decreasing the depth of sedation, should be instituted. If heart rate, SpO_2, or end-tidal CO_2 have also changed, very urgent diagnosis and treatment must be instituted, as this heralds a low cardiac output state, and possible impending cardiac arrest. Discontinuing sedation, administering fluid boluses and a vagolytic agent such as atropine or sympathomimetic agent such as ephedrine or epinephrine may be indicated. Elevated blood pressures may of course be due to inadequate sedation or analgesia, but often can be due to the drugs themselves, especially ketamine. In the latter case, the dose of ketamine should be reduced, or if sedation and analgesia judged to be inadequate, additional drugs other than ketamine should be used. Table 7.3 displays normal heart rate and systolic blood pressure for different ages.

Central Nervous System Physiology

Brain growth and development are very rapid during infancy, with the brain weight at birth about 20% of adult weight, but by 2 years of age the brain has attained 75% of adult weight [27]. The brain in the infant and young child receives a correspondingly higher percentage of the cardiac output than in the older child and adult. In addition, rapid proliferation and migration of neurons to their cortical and subcortical zones is taking place in early infancy, as is myelination and synaptogenesis [28] (Fig. 7.4). The neurotransmitters gamma-aminobutryic acid, and glutamate, and their corresponding receptors, play a crucial role in synaptogenesis, and also in the natural death of some neurons during the rapid proliferation phase (apoptosis). Most sedative agents, including benzodiazepines, barbiturates, chloral hydrate, propofol (GABA), and ketamine (NMDA) interact with these receptors giving rise to the concerns that sedative agents may increase apoptosis and potentially have adverse long-term neurodevelopmental effects [29]. Because of the relatively larger brain size and blood volume/flow, the dose per kilogram requirement for sedative agents is usually higher in the young infant to produce the desired effects than it is in the older child and adult. The exception to this is the neonate, where

Table 7.3 Normal heart rates and systolic blood pressure as a function of age

Age	Range of normal heart rates (beats per minute)	Range of normal systolic blood pressures, measured by oscillometric blood pressure device (mmHg)
Neonate (<30 days)	120–160	60–75
1–6 months	110–140	65–85
6–12 months	100–140	70–90
1–2 years	90–130	75–95
3–5 years	80–120	80–100
6–8 years	75–115	85–105
9–12 years	70–110	90–115
13–16 years	60–110	95–120
>16 years	60–100	100–125

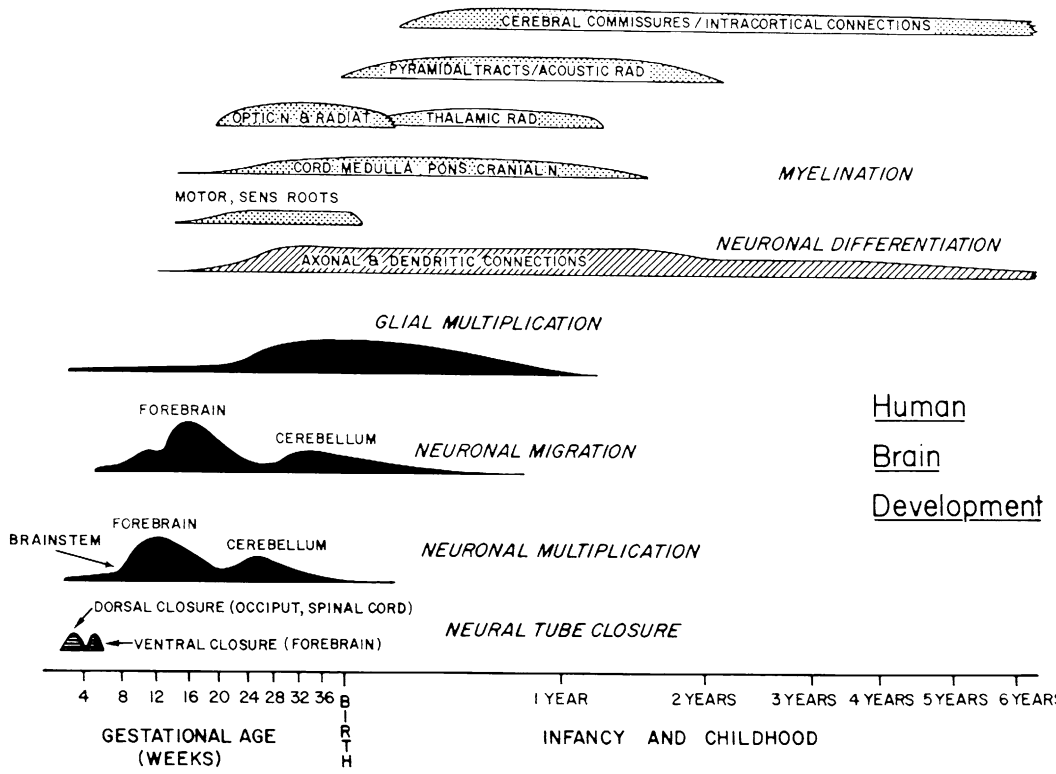

Fig. 7.4 Brain growth and development from conception to age 6 years. Note the very rapid brain growth and complexity of development from birth to age two years, when the majority of postnatal brain development occurs. This period of rapid development gives rise to the recent concerns that sedative agents interacting with gamma-aminobutryic acid and *n*-methyl-d-aspartate receptors could have long-term effects on the developing brain. See text for details. (Reproduced with permission from Kandt et al. [27])

the tight junctions of the basement membranes of the intracerebral capillaries are not fully formed, meaning the blood–brain barrier is not as fully intact, allowing passage of higher drug concentrations into neurons, causing an exaggerated effect of most drugs in this very young age group.

Cerebral autoregulation is normally intact in the full term neonate and older patient, albeit at lower blood pressures than in the adult patient. Responsiveness of the cerebral circulation to carbon dioxide tension is also intact, with significant hypercarbia causing maximal cerebral vasodilation.

Maturation of the EEG during infancy and childhood has important implications for any technology proposing to measure depth of sedation using EEG parameters. All current depth of sedation monitors using processed EEG parameters are based on the adult EEG and application of these monitors in infants and young children especially is unreliable. Infants and younger children have markedly different EEG profiles for both frequency and amplitude of EEG waveforms emanating from different regions of the brain. Older children, i.e., 8–10 years of age or older, have EEG characteristics much more similar to the adult and thus these monitors can be more reliable [30].

Developmental changes in motor, language, and behavior milestones are crucial to understand

Table 7.4 Age-specific anxieties of pediatric patients

Age	Specific type of perioperative anxiety
0–6 months	Maximum stress for parent Minimum stress for infants – not old enough to be frightened of strangers
6 months–4 years	Maximum fear of separation Not able to understand processes and explanations Significant postoperative emotional upset and behavior regression Begins to have magical thinking Cognitive development and increased temper tantrums
4–8 years	Begins to understand processes and explanations Fear of separation remains Concerned about body integrity
8 years-adolescence	Tolerates separation well Understands processes and explanations May interpret everything literally May fear waking up during surgery or not waking up at all
Adolescence	Independent Issues regarding self-esteem and body image Developing sexual characteristics and fear loss of dignity Fear of unknown

Source: Reproduced with permission from Ghazal et al. [31]

when sedating pediatric patients. Table 7.4 presents some of the important milestones in these areas [31]. In approaching the infant patient, with normal children of age 6–12 months, they will not experience stranger anxiety and thus will go with practitioners for sedation procedures with little to no protest. Extensive study and clinical experience demonstrate that infants from the premature neonate onward experience pain in the same manner as older children, and so will react accordingly to painful procedures such as IV catheter insertion. In the infant up to age 6 months, 24% sucrose, 0.2 mL placed on a pacifier and given 5–10 min before a painful procedure, will alleviate pain from venipuncture and heelsticks [32]. The mechanism of action is proposed to be endorphin release. Infants from age 6–12 months, toddlers, and preschool children up to age 5 can be expected to be quite fearful and resistant when separated from parents or familiar caregivers, and the process of separation must be planned to ameliorate this psychological discomfort as much as possible with distraction, familiar toys or objects, or having the parent present during initiation of sedation, if appropriate. School aged children of 5 of 6 years or older generally can accept simple explanations of medical procedures and will often separate from parents more easily. The patient aged 8–12 years is often the easiest to approach for sedation procedures and often has a very concrete understanding of explanations and instructions. The adolescent often has great concern about body image, and respecting this is very important. The child of any age who has been hospitalized frequently or has had prior painful or stressful experiences may be very upset at the prospect of separation from parents and sedation procedures.

Hematologic System Development

The neonate has a normal hemoglobin of 15–20 g/dL, and hematocrit of 45–60%, most all consisting of hemoglobin F, as noted earlier. Over the first 6 months of life, predominate hemoglobin species changes to adult hemoglobin A, and there is a decline to a physiologic nadir of about 11–12 g/dL of hemoglobin by 2–6 months of age. These values are maintained until about age 2 years, at which time they gradually increase in boys and girls to 12–14 g/dL by about age 12. With the onset of menstruation, hemoglobin remains at this level in girls until adulthood. In boys, hemoglobin levels continue to increase gradually to adult levels of 15–18 g/dL by age 18 [33].

The concept of a physiologic nadir of hemoglobin at 2–6 months of age is important, because this is an age when oxygen consumption is still twice that of the adult, yet oxygen carrying capacity is low, with the result that there is even less oxygen reserve in these young infants.

The blood volume of the neonate is approximately 90 mL/kg body weight, and this decreases to about 85 mL/kg by 6 months, 80 mL/kg at 1 year, and 75 mL/kg until age 2 years, after which the blood volume assumes the adult value of approximately 70 mL/kg.

Renal Physiology, and Fluid and Electrolytes

At birth the neonate has an expansion of total body water and the extracellular water space, combined with renal function that is decreased, with glomerular filtration rate only 15–30% of adult values. Renal function matures fairly rapidly, achieving levels of 50% of the adult by 2 weeks of life, and then gradually increasing to adult levels by 12 months of age [3]. Total body water also decreases to adult levels by about 12 months of age. However, fluid requirements remain high throughout the first 3–4 years of life, because of the increased body surface to weight ratio present in young children, which results in increased insensible fluid loss. Table 7.5 displays the approximate daily and hourly maintenance fluid and requirements for normal children at various weights and ages [3]. In children with normal renal function, intravenous fluids of one-quarter normal saline (38 meq NaCl/L) and 20 meq/L KCL will provide maintenance of sodium and potassium, and 5% dextrose for maintenance of glucose requirements. In actual practice, healthy infants and children over age 6 months will do well with a standard intravenous solution such as Lactated Ringer's solution during sedation procedures. This solution, which does not contain dextrose but has a sodium concentration of 130 meq/L and osmolarity similar to plasma, will allow a fluid bolus to be administered without producing hyperglycemia.

In general, modern nil per os (NPO) guidelines allowing clear liquid intake until 2 h before a sedation procedure will prevent significant fluid deficits, but frequently there are situations where the patient has been NPO for long periods of time. If NPO for greater than 6 h, many practitioners would calculate the fluid deficit accumulated during those 6 h, administer half the deficit during the first hour of the procedure, and one-quarter of the deficit in each of the next 3 h [31]. These fasting guidelines were published in 1999, approved by the American Society of Anesthesiologists (ASA) and represent a recommendation based on the review of clinical studies between 1966 and 1996, over 1,100 citations. They were intended for healthy patients undergoing elective surgery [34] (Table 7.6). The guidelines were not intended nor considered for sedation purposes, although they have been so adopted by many. A revised 2010 version of the Practice Guidelines for Preoperative Fasting is expected soon [35].

Glucose requirement is predictably high in the neonate and young infant, being 5–7 mg/kg/min in the neonate, which is 2–3 times that of the adult. The neonate and young infant less than 3–6 months of age is also prone to hypoglycemia

Table 7.5 Maintenance intravenous fluid requirements

Weight	Maintenance fluid, mL/kg/24 h	Maintenance fluid, mL/kg/h
<10 kg	100	4.16
10–20 kg	50	2.08
Each 10 kg increment above 20 kg	20	0.83

Table 7.6 American Society of Anesthesiologists' summary of fasting recommendations to reduce the risk of pulmonary aspiration[a]

Ingested material	Minimum fasting period[b] (hours)
Clear liquids[c]	2
Breast milk	4
Infant formula	6
Nonhuman milk[d]	6
Light meal[e]	6

Source: Reprinted with permission from American Association of Anesthesiologists Task Force on Preoperative Fasting [34]

[a]These recommendations apply to healthy patients who are undergoing elective procedures. They are not intended for women in labor. Following the Guidelines does not guarantee complete gastric emptying

[b]Fasting times apply to all ages

[c]Examples: water, fruit juice without pulp, carbonated beverages, clear tea, and black coffee

[d]Since nonhuman milk is similar to solids in gastric emptying time, the amount ingested must be considered when determining an appropriate fasting period

[e]A light meal typically consists of toast and clear liquids. Meals that include fried or fatty foods or meat may prolong gastric emptying time. Both the amount and type of foods ingested must be considered when determining an appropriate fasting period

because of a paucity of glycogen stores, compared to the older child and adult, thus it is especially important in this age group to encourage ingestion of clear glucose containing fluids until 2 h before a sedation procedure. And, young infants should have infusion of dextrose containing intravenous fluids during and after the sedation procedure, until they are recovered and can ingest dextrose containing fluids again.

Hepatic/Gastrointestinal Physiology

Liver function, both synthetic and metabolic, is immature at birth, with only about 30% of the functional capacity of the adult [3]. Hepatic function also matures relatively rapidly, with normal function achieved by about 3 months of life. This means that drugs which depend on hepatic metabolism for clearance, especially the cytochrome P450 system, will often have prolonged effects in the very young infant once therapeutic plasma levels are reached. In addition, coagulation factor levels are low in the neonate because of this hepatic immaturity, so that normal partial thromboplastin time, which measures coagulation function in the extrinsic coagulation system and depends on proteins synthesized in the liver, is elevated at birth to as high as 60 s. Despite this, the protein factors that inhibit coagulation are also reduced in concentration, and neonates and young infants are not more prone to clinical bleeding than older patients.

As with other systems, the brush border of the neonatal small bowel is not mature, and is more prone to insults such as infections and ischemia, particularly in the premature infant, which predisposes them to necrotizing enterocolitis. The risk of this disease diminishes greatly toward term, but the ability of the full term neonate's intestine to absorb high osmolar loads is limited. With normal intake such as breast milk or infant formulas, however, gastric emptying is rapid. This normal gastric emptying has given rise to the standard recommendation in most institutions that in patients of all ages, who do not have bowel obstruction or other condition known to delay gastric emptying, ingestion of solid food, milk, or formula until 6 h prior to a sedation procedure is acceptable. Breast milk ingestion until 4 h before sedation, and clear liquids until 2 h before, have also been shown to result in complete gastric emptying.

Temperature Regulation

Maintenance of temperature homeostasis during sedation procedures is an important goal, and the young child in particular is prone to hypothermia during prolonged sedation. Heat loss (or gain) into or from the environment is via four basic routes [36, 37]: (1) radiation: from difference in temperature between the patient and the surrounding environment, e.g., a cold room; (2) conduction: heat transfer between two surfaces in direct contact, i.e., a cold irrigating solution; (3) convection: transfer of heat to moving molecules such as air or liquid, i.e., a cold drafty MRI scanning room; (4) evaporation: loss of heat from vaporization of water from the skin or mucosal surface.

Under normal circumstances, the older infant, child, or adult will sense temperature of the blood in the anterior hypothalamus, the thermostat for the body, and use various mechanisms to keep body temperature within 0.5 of 37°C [36]. In response to mild hypothermia, the CNS via α-adrenergic sympathetic activation will cause cutaneous blood vessels to constrict, especially in the extremities, reducing blood flow and thus conserving heat by shunting warmed blood flow to deeper structures not vulnerable to radiation heat loss. With moderate hypothermia shivering occurs, which through muscle aerobic metabolism will generate additional heat and help return body temperature toward normal. With hyperthermia, initially blood flow to the extremities will remain at normal levels, but with further warming vasodilation will occur, and heat loss from radiation, convection, and conduction all increase. The next response is sweating, with the evaporation of sweat resulting in significant heat loss.

Commonly used sedative agents, including propofol and dexmedetomidine, affect the thermoregulatory thresholds [36]. In general, the higher the dose of these agents, the wider the

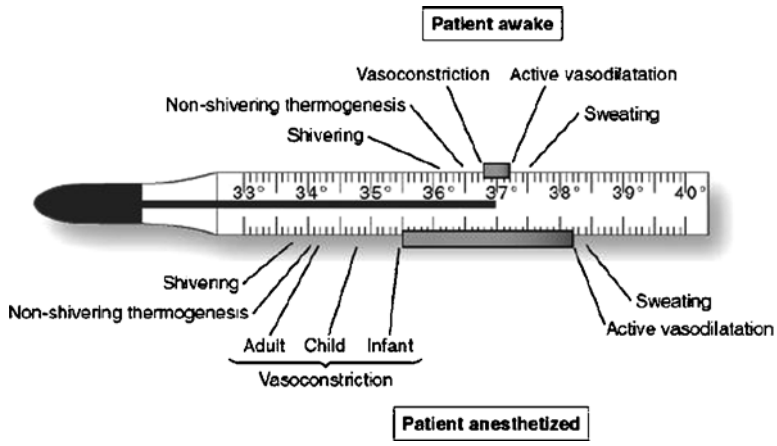

Fig. 7.5 Illustration of the thermoregulatory thresholds and gains for awake and anesthetized (sedated) infants, children, and adults in relation to the central (core) temperature. The distance between the edge of the thermometer and each effector response represents the maximal intensity of each response. The slopes of the lines (positive values for awake and negative values for anesthetized) between the thermometer and the response represent the gains of the responses. The threshold is defined as the corresponding core temperature that triggers a response. The sensitivity of the thermoregulatory system describes the range between the first cold response (vasoconstriction) and the first warm response (sweating), which is known as the interthreshold range. Sedation with agents such as propofol and dexmedetomidine produces the same dose-dependent changes in thermoregulation as general anesthesia. (Reproduced with permission from Luginbuehl and Bissonnette [37])

range of "normal" temperatures tolerated by the hypothalamus before the compensatory mechanisms described earlier occurs, meaning that temperatures will need to decrease by 1.5–2.5°C before vasoconstriction and shivering will begin, rather than 0.5°C in the awake patient (Fig. 7.5).

Adverse effects of significant hypothermia include enhanced effects of intravenous sedative medication and a lower dose requirement for sedation, as well as slowed metabolism and organ function, resulting in delayed metabolism of drugs by kidney and liver. This can result in prolonged awakening from sedation. Significant hypothermia accompanied by shivering can result in metabolic acidosis from anaerobic muscle metabolism. Significant hypothermia and shivering are also profoundly uncomfortable for the patient, often resulting in an unsatisfactory sedation experience in the case of older children, or agitation and crying behaviors in the younger children.

The neonate is a special case, as in most other organ systems, in that with significant hypothermia the neonate cannot shiver, but rather starts to metabolize special brown fat cells, mostly located between the scapulae, and in the mediastinum and perirenal areas, in order to generate heat to raise body temperature, in a process termed nonshivering thermogenesis [36]. This is accompanied by a significant catechohlamine discharge and anaerobic metabolism, resulting in lactic acidosis which can have profound secondary effects on other organ systems, i.e. the heart and circulation, resulting in hemodynamic instability. Non-shivering thermogenesis is either nonexistent or insignificant after the neonatal period.

Because of the high body surface area to weight ratio of neonates, which decreases to adult levels by 8–9 years of age, the young child is susceptible to hypothermia by radiation. Thus, an infant or young child who is uncovered and exposed to cool ambient temperatures, especially with a draft or in a room cooled because of medical equipment, e.g., MRI scanners, will cool rapidly.

Preventing hypothermia is a crucial task for every sedation procedure in children, and often the simplest method is to cover or wrap the child in warm blankets to prevent heat loss by convection. Warming the room or employing forced air

warming devices where possible, are other important measures to prevent hypothermia. Continuous temperature measurement during sedation procedures in patients at risk for hypothermia should be practiced, especially during lengthy procedures such as MRI scans in infants. Temperature should be taken along with other vital signs in the recovery area,

Drug Pharmacokinetics and Pharmacodynamics

All of the differences in organ system physiology discussed previously, especially cardiovascular, central nervous system, hepatic, renal, and body fluid composition, mean that response to sedative drugs, and initial dosage and interval dosing, are often very different especially in the infant, compared to the older child and adult.

Conclusion

Children, particularly the neonate and infant, have very substantial differences in physiology in all systems compared to the adult. The increased metabolic requirements for the rapidly growing young patient result in higher demand for oxygen and glucose, the major metabolic fuels. This increase in oxygen need limits the margin of error during sedation procedures, especially in patients less than 1 year of age, but to some extent in all growing children. The sedation practitioner must be well aware of these physiologic differences to ensure a safe and effective sedation procedure.

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