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EDUCATIONAL REVIEW

Developmental respiratory physiology

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Abstract

Various developmental aspects of respiratory physiology put infants and young children at an increased risk of respiratory failure, which is associated with a higher rate of critical incidents during anesthesia. The immaturity of control of breathing in infants is reflected by prolonged central apneas and periodic breathing, and an increased risk of apneas after anesthesia. The physiology of the pediatric upper and lower airways is characterized by a higher flow resistance and airway collapsibility. The increased chest wall compliance and reduced gas exchange surface of the lungs reduce the pulmonary oxygen reserve vis-à-vis a higher metabolic oxygen demand, which causes more rapid oxygen desaturation when ventilation is compromised. This review describes the various developmental aspects of respiratory physiology and summarizes anesthetic implications.

KEYWORDS
airway, physiology, growth, child, control of breathing, airway obstruction, compliance

1 | INTRODUCTION

Significant differences in respiratory physiology between infants and adults explain the higher vulnerability of the infant respiratory system for decompensation and failure. In general, breathing efficiency is determined by the work of breathing per tidal breath and the gas exchange achieved per tidal breath. Numerous factors render the infants' respiratory system less efficient (Table 1), and a variety of counteractive mechanisms exist to compensate for the respiratory instability. However, anesthesia and/or severe illness may compromise these counteractive mechanisms or they may prove counter-productive (eg, laryngospasm). Respiratory adverse events are common in pediatric anesthesia and comprise more than three quarters of all critical incidents and half of all unplanned admissions to the pediatric intensive care unit, and approximately a third of cardiac arrests during anesthesia is attributed to respiratory complications.[1] Unsurprisingly, young age is a major risk factor, increasing the odds ratio of critical incidents in infants less than a year by a factor of four compared to older children.[2]

Following the path of a breathing cycle, pulmonary gas exchange requires.

- a functional neural control which includes the initiation and coordination of the breathing cycle, the maintenance of upper airway patency, and the generation of protective reflexes
- building-up of a pressure gradient to generate an airflow and to overcome the airway resistance, the viscoelastic forces, and the inertia of the lungs and the chest wall
- bronchiolo-alveolar gas mixing and diffusion of gas across the air-blood barrier
- renewal of oxygenated and decarbonized capillary blood.

All four functions are negatively affected by developmental characteristics.

TABLE 1 Aspects of developmental respiratory physiology contributing to respiratory vulnerability of infants (adapted from ref.[65])

Cause	Physiological and anatomic basis
↑ Metabolism	O_2 consumption ↑
↑ Risk of apnea	Immaturity of control of breathing
↑ Upper airway resistance	Preferential nose breathing
	Airway diameter ↓
	Airway collapsibility ↑
	Pharyngeal muscle tone ↓
	Compliance of upper airway structures ↑
↑ Lower airway resistance	Airway diameter ↓
	Airway collapsibility ↑
	Elastic recoil ↓
↓ Lung volume	Number of alveoli ↓
	Lack of collateral ventilation
	Rib cage compliance ↑
↑ Work of breathing	Metabolism ↑
	Airway resistance ↑
	Defense of FRC
	Respiratory rate ↑
↓ Efficiency of respiratory muscles	Efficiency of diaphragm ↓
	Horizontal insertion of the diaphragm at the rib cage
	Efficiency of intercostal muscles ↓
	Horizontal ribs
↓ Endurance of respiratory muscles	Fatigue-resistant type I muscle fibers ↓

2 | DEVELOPMENTAL ASPECTS OF BREATHING CONTROL

2.1 | Respiratory drive

Breathing activity starts with sporadic diaphragmatic movements toward the end of the first trimester and gains stability during gestation, but remains unstable *in utero*, with breathing activity occurring 30% to 60% of the time at term. Fetal breathing is important for fetal lung growth,[3] and breathing activity is already influenced *in utero* by the partial pressures of CO_2 and O_2 (pCO_2 and pO_2)—increasing pCO_2 and energy supply stimulate fetal breathing while hypoxia depresses diaphragmatic activity.[4]

At term, chemoreceptor pCO_2 sensitivity and its characteristics are almost mature, but minute ventilation at any pCO_2 is higher in neonates and infants compared with adults.[5] This is in contrast to prematurely born infants who show an attenuated sensitivity to increasing pCO_2.[6] In contrast, peripheral pO_2 receptors require readjustment to the higher oxygen levels *ex utero*, gaining sensitivity during the first days of life.[7]

In summary, three distinct properties characterize the vulnerability of the newborn's ventilatory responses: (1) a hypoxic ventilatory depression which quickly reverts the initial hypoxic ventilatory stimulus to a level of ventilation below the normoxic level,[8] (2) a slower response rate to hypercapnia in preterm born babies,[9] and (3) a virtual absence of the potentiating, "more-than-additional" effect of concomitant hypercarbia on the hypoxic ventilatory response, which develops only during the first two months of life.[10] Hypoxic ventilatory depression persists up to 6 months postnatally.[11] A key point is that the arousal and ventilatory response to hypoxemia or airway obstruction is heterogenous and hardly predictable for the individual infant.[12]

Furthermore, breathing stability is influenced by the immaturity of respiratory cycling and the protective reflexes. Immature breathing control manifests as apneas, either as a single event or in series as periodic breathing. Both events are primarily considered a physiological phenomenon awaiting stabilization with evolving maturation. Concerns of possible associations with sudden infant deaths have so far remained unproven.[13]

Differentiating normal apnea from a pathological respiratory pause remains a clinical challenge. Typical physiological apneas result from the irregular breathing pattern in rapid eye movement (REM) sleep or follow deep sighs or movements, likely with the aim of opposing slow lung de-recruitment and maintaining functional residual capacity (FRC), respectively. According to the American Association of Sleep Medicine (AASM) manual, central apneas are scored if lasting ≥20 s or being accompanied by an arousal, a ≥3% oxygen desaturation, and/or a bradycardia.[14]

Frequency and duration of central apneas during sleep decrease over the first 12 months of life. Typical central apneas in neonates last 3–6 s,[15] but apnea durations of 20 s or more are not uncommon in healthy subjects <4 weeks of corrected gestational age.[13] In older infants, longer apneas are still seen in infants referred for observed apneas,[16] but apneas lasting more than 15–20 s become rare in unselected healthy infants,[17] while the 95th frequency percentile of shorter pauses ≥3 s remains at 15 events/hour at 12 months.[18] Healthy school-aged children and adolescents show an average of 1–2 apneas/hour of ≥10 s duration, most of which, however, are below the 20 s threshold of the AASM scoring rule.[19]

Periodic breathing in infancy is considered a distinct phenomenon of immaturity of breathing control, reflecting altered chemoreceptor reactivity and loop gains to changing pO_2 or pCO_2 levels, thus allowing larger breathing fluctuations.[20] The incidence of periodic breathing diminishes toward term, from 83% of cases at 37 weeks of corrected gestational age (in infants prematurely born at 34 weeks of gestation) to 41% at term in newborn babies one week after birth.[21] The reduction of periodic breathing, however, seems to depend on the respiratory stability during the preterm phase. Studies suggest that large pO_2 fluctuations typically seen in unstable preterm babies increase hypoxic chemoreceptor reactivity of the carotid bodies. The increased loop gain favors intermittent hyperventilation leading to hypocapnia and consequent apneas and periodic breathing,[22] interestingly a breathing pattern which continues to be a physiological

feature of breathing during sleep at high altitude.[23] Hypoxemia thus increases the time spent in periodic breathing,[24] while increasing pCO_2 reduces periodic breathing in infants.[25]

2.2 | Protective reflexes

Laryngeal and respiratory reflex responses (eg, laryngospasm, glottic spasm/closure, expiration reflex, apnea, spasmodic panting, and cough reflex) represent important defensive strategies securing the integrity of lower airways from aspiration of foreign bodies.[26] There is a lack of comprehensive scientific information regarding developmental aspects of these reflex responses in humans. However, experimental research in animals provides convincing evidence about the existence of developmental characteristics of these reflexes; for example, a discrete period of transient hyperexcitability was identified in pups 50–75 days postnatally resulting in an increased risk of laryngospasm. Suggested mechanisms include central synaptic maturation, changes in central latency, and transient reduction of central inhibition resulting in an imbalance of excitatory and inhibitory brainstem influences.[27]

It is important to distinguish between a coughing reflex and an expiration reflex. While a cough is a combination of an inspiration and a forceful expiration, expiration reflexes do not include an inspiration. Particularly in combination with glottic closure, expiration reflexes can lead to severe hypoxic episodes.[26]

Protective reflexes also influence spontaneous breathing in the very young. Particularly in preterm babies, the pressure of a face mask may induce bradycardia and apneas by stimulating stretch receptors of the trigeminal nerve, known as trigemino-cardiac reflex.[28] This reflex is at the base of the diving reflex which is stimulated upon submersion into (cold) water and accompanied by laryngeal closure, and it is conceived as a powerful protective oxygen-preserving reflex increasing survival in hypoxic conditions.[29] The most powerful stimulus of the trigemino-cardiac reflex is a sudden mechanical tissue stretch, and predisposing risk factors in the anesthetic setting are young age, light anesthesia, and hypoxia and hypercapnia.[29] Placing a face mask in infants commonly elicits a transient change in breathing pattern consisting of an augmented tidal volume and reduced respiratory rate.[30]

The Hering-Breuer reflex represents a pulmonary volume-feedback loop affecting inspiratory muscle activity.[31] Lung distension not only reduces or even abolishes inspiratory muscle activity but also prolongs the respiratory cycle and hence the time of passive expiration.[32] This is referred to as the Hering-Breuer inflation reflex. Its primary physiologic function is thought to be the prevention of both overdistension at high lung volumes and de-recruitment at low lung volumes, as shortening of the expiration at lower lung volumes reduces the risk of de-recruitment and atelectasis.[32] This might explain why it is more active in the neonates and young infants.[33] The reciprocal aspect of the lung volume-feedback loop is the Hering-Breuer deflation reflex which delineates the increased inspiratory effort upon rapid lung deflation.[34]

2.3 | Anesthetic considerations about developmental physiology of breathing control

Control of breathing is prone to perioperative disturbances in all patients undergoing anesthesia, independent of the applied anesthetic technique (Table 2). Among children, young infants are more frequently affected by clinically relevant disturbances.[35] Prevention and handling of postoperative apnea in former preterm infants is a matter of continuous debate.[36,37] Of note, a large variability in the incidence of apneas is reported rendering firm conclusions and recommendations for the individual patient difficult. Nonetheless, identified individual risk factors for an association with postoperative apnea include decreasing gestational age at birth, anemia, a history of recent apnea, ever receiving methylxanthine, ever receiving mechanical ventilation, and ever needing oxygen support.[36,38] The GAS study demonstrated a lower incidence of early apnea requiring less interventions in the regional (spinal) anesthesia compared to the general anesthesia group.[38] However, the same study showed no difference between the odds of late apneas in the first 12 h postoperatively between infants allocated to a spinal anesthetic or a general anesthetic, which has implications for postoperative monitoring of these children. Interestingly, a brief anesthetic or sedation period in the patients with regional anesthesia in the GAS trial did not increase the overall incidence of observed apneas; 6.1% of preterm infants presented with apnea compared to only 0.3% of term infants (OR 21.9).[38] Furthermore, anesthesiologists have to keep in mind that early apneas are strong predictors of late apneic episodes, but they are nonetheless not a sensitive measure. During the preoperative planning, the relatively high failure rate of regional anesthesia of around 10% has to be considered.[39]

3 | DEVELOPMENTAL PHYSIOLOGY OF THE AIRWAYS

The infantile supraglottic airway is small and soft, and fundamental physical laws act together to make it vulnerable for inspiratory collapse. Laplace's Law implies that for any given surface tension the transmural pressure and thus the collapsing forces increase proportionally to the reduction of the airway radius, and Bernoulli's Law states that airflow streaming through a narrowing increases flow velocity and decreases pressure within the narrowing. Airway patency is thus dependent of the transmural pressures of parapharyngeal tissue and the distending pressures within the airways.[40] According to the Starling resistor model, the critical closing pressure of the pharynx during quiet unimpeded inspiration is smaller both than the upstream, atmospheric pressure and the downstream pressure within the large airways.[41] Once the critical pressure of the parapharyngeal tissue supersedes the downstream pressure, snoring occurs, and a further increase to above the atmospheric pressure results in complete obstruction. To counteract this inherent vulnerability, infants show an enhanced genioglossal electromyographic activity consequent to increasing inspiratory loading.[42] Immaturity, sleep, and

TABLE 2 Potential implications of the developmental respiratory physiology for anesthesia in infants and toddlers

Physiological characteristics	Consequences for anesthesia in infants and toddlers
Immaturity of breathing control and reflex control	Consider risk of apnea postoperatively up to 12 h postintervention in newborns and premature infants (up to 60 postconceptional weeks)
	Expect apnea and bradycardia from forceful face mask application in preterm born babies (TCR)
	Expect hypoxic respiratory depression and bradycardia Expect transiently increased risk of laryngospasm in preschool children
Small anatomical dimensions of the laryngeal and tracheal airway	Increased risk for potential airway damage
	Age- and size-appropriate selection of laryngeal mask airways and endotracheal tubes
	Increased vulnerability for postextubation upper airway obstruction
Increased upper airway collapsibility and resistance	Expect airway occlusion from improper head positioning or inexpert execution of airway opening maneuvers during anesthesia
	Expect more rapid gastric inflation
	Increased risk for anesthetic complications during upper respiratory tract infections
Higher chest wall compliance	Expect rapid lung de-recruitment and atelectasis with anesthesia, particularly with neuromuscular blockade
	Use of PEEP and assisted ventilation early after induction
Decreased number of alveoli and lack of collateral ventilation	Decreased respiratory reserve and increased risk for atelectasis
	Consider using low FiO_2 (≤ 0.8 during induction) to prevent absorption atelectasis formation and pulmonary shunt
Increased lower airway collapsibility and resistance	Increased risk for anesthetic complications during lower respiratory tract infections
	Increased risk for airway collapse during agitation
	Expect less effect of inhaled bronchodilators particularly in infants
Higher metabolism	Expect more rapid oxygen desaturation with alveolar hypoventilation
	Expect more rapid hypercapnia due to increased CO_2 production

sickness reduce these counteractive mechanisms, which is associated with a marked reduction in minute ventilation.[43] Obstructive apneas occur as a physiological phenomenon in normal young infants with up to 3 obstructive events/hour being reported in the first 3 months of life,[16,44] and central apneas in newborns frequently end with short pharyngeal obstructions.[45,46] In addition, spontaneous neck flexion may induce obstructive apneas in preterm babies.[47] It has to be kept in mind that the adenoids continuously increase in size in the preschool and early primary school age before starting to regress toward adolescence, highlighting the higher risk of mechanical obstruction in this age group.[48]

While the parapharyngeal walls depend on tissue interdependence, muscle tone, and body position to keep the airspace open,[40,49] airways from the larynx down to the small bronchi are additionally stabilized by a cartilaginous scaffold. The basic construction principle of the lower airways resembles the fractal tree of Mandelbrot with dichotomous division of each airway for 20–23 generations, the airway diameter being reduced by each division by a factor of about 0.8.[50] This design implies that all gas exchange units are situated at approximately the same distance from the central airways, irrespective of the distance from the pleura, and that the cumulative cross-sectional area of all the bronchi increases from one generation to the next, thus decreasing the total airway resistance toward the periphery.[50] It appears that this stepwise airway diameter reduction by a factor of about 0.8 is the optimal trade-off between the competing interests of minimizing work of breathing and anatomical dead space.[50]

Airway smooth muscle contractility and reactivity to acetylcholine increase with age,[51] and airway smooth muscle tension stiffens the immature trachea.[52] Although airway smooth muscle tone is a determinant of airway caliber, data suggesting that the bronchial patency in infancy actually depends on airway smooth muscle tone are not convincing and should in our opinion be eliminated from the textbooks. While early reports did suggest that short-acting bronchodilators reduce maximum airflow at FRC by forced expiration maneuvers in some wheezy infants,[53] the findings were not replicated in healthy infants.[54] In addition, transient reduction of oxygenation after short-acting beta-agonist treatment in severely wheezy infants rather reflects worsening ventilation-perfusion matching in clinical practice,[55] and paradoxical deterioration of lung function to short-acting beta-agonists does not occur more often in children with tracheobronchomalacia.[56]

The lower airways show a growth spurt during the first 3 years, becoming less compliant with age.[57] The infant's tracheal length is already at about 40% of its adult size, but only at 10%–15% of its cross-sectional area.[57] The tracheal and bronchial diameter correlates best with age, while the airway length correlates better with body length. Airway parameters correlate poorly, in contrast, to body weight.[58] The cartilaginous scaffold lengthens and stiffens with maturation during childhood. While new airway cartilages are

formed until the 25th week of gestation only,[59] progressive reduction in water and proteoglycan content render the airway cartilages increasingly stiffer with age.[60] This is reflected, for example, by the common functional improvement of congenital laryngomalacia during the first months in affected infants.[61] Importantly, cartilage growth and maturation are influenced by excessive intrinsic or extrinsic pressure application, causing localized or long-stretch airway malacia.[62] Children with bronchopulmonary dysplasia and a history of positive pressure ventilation, for instance, are at risk of developing trachea-bronchomalacia. This results in an increased work of breathing and a higher risk of recurrent hospitalization during infancy, but usually resolves in the first 2–3 years of live.[63] In addition, prolonged positive pressure ventilation in very immature children has been associated with larger airway diameters and mild tracheomegaly.[64]

The connective tissue network of the surrounding lung parenchyma is crucial to maintain small airways open, especially the terminal and respiratory bronchioli which lack cartilages (Figure 1, from ref.[65]).[66] Due to this pulmonary interdependence, the airway dimensions change *within limits* proportionally to cube root of the changes in lung volume. That is, the airway diameter of airways sized >2 mm increases proportionally with lung inflation until the transpulmonary pressure has reached approximately −5 to −7 cmH_2O, which is about half the intrapleural pressure reached during normal tidal breathing, that is, at the end of a normal inspiration.[67] Pulmonary derecruitment (below FRC) thus significantly affects airway resistance R_{aw}, which is inversely proportional to the 4th power of the airway radius with laminar flow. To account for this dependence of lung inflation, R_{aw} is commonly indicated as specific resistance at FRC, that is, R_{aw}/FRC. Importantly, as lower lung volumes reduce the resistive load against which the constricting airway smooth muscle work, lung inflation has also a direct impact on the degree of bronchoconstriction following airway smooth muscle activation.[68] In other words, there is an inverse relation between the strength of the elastic recoil of the connective tissue and the severity of bronchoconstriction upon airway smooth muscle activation.

Due to the collapsibility of human airways and the pulmonary interdependence, increasing the pleural pressure with forced expiration leads to dynamic airway compression and, eventually, airflow limitation. The importance of the elastic recoil forces to airway patency is exemplified by the significant bronchial obstruction seen in adult patients with severe emphysema. Similarly, the fewer alveoli and interstitial septa of immature lungs offer considerably less suspension forces, such that forced expiration and coughing readily lead to peripheral airway collapse in babies.[69] During early childhood, continued alveolarization by the formation of new alveolar septa increases the fine interstitial network suspending collapsible airways (Figure 1).

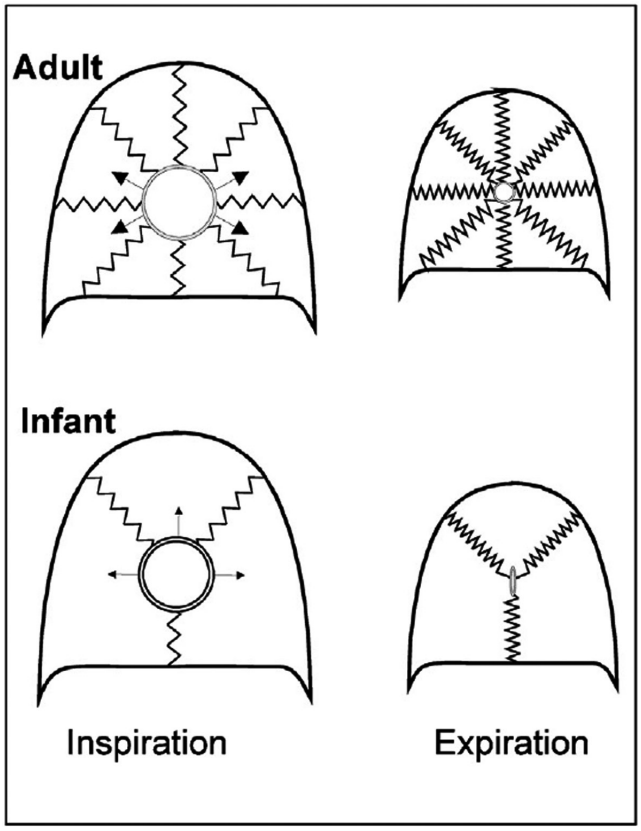

FIGURE 1 Model of pulmonary interdependence and elastic recoil forces infants and adults (from ref.,[65] copyright Elsevier, with permission)

3.1 | Anesthetic considerations about developmental physiology of the airways

In children, establishing and maintaining airway patency is a cornerstone of safe anesthesia and also a key feature during resuscitation. During anesthesia in children, upper airway obstruction is a frequently encountered problem,[70] and failure to maintain the airway open may rapidly result in hypoxemia, bradycardia, or cardiac arrest.[70] Anesthesia-related narrowing of the upper airways is most likely to appear in pharyngeal structures.[71] In particular, obstruction is caused by a posterior displacement of the hyoid bone which reduces airway dimension mainly during inspiration when the rims of the epiglottis approach the posterior pharyngeal wall.[72]

Young children are particularly susceptible to upper airway obstruction not only because of the smaller dimensions of their airways but also due to the physiological tonsillar and/or adenoidal hypertrophy.[73] A substantial number of children, especially those undergoing ear-nose-throat surgery, present with a clinically significant narrowing of their upper airways, which may manifest as obstructive sleep apneas (OSA). MRI studies show that children with OSA have a significantly smaller volume of their upper airway along with significantly larger adenoids and tonsils compared to patients without OSA.[74] Additionally, in children with OSA, the soft palate is thickened and consequently contributes to the restriction of the upper airway.[74]

Airway occlusion due to improper head-neck position during resuscitation potentially contributes to increased neonatal mortality. Various head positioning and airway maneuvers are described to maintain airway patency during anesthesia and resuscitation in children. In neonates, an MRI-based examination revealed that the probability of a

patent airway progressively increases with increasing head-tilt angle.[75] Nonetheless, there is a large overlap of specific positions, making critical assessment of the clinical condition necessary.[75] A comparison of preschool vs. school children showed that the optimal head-tilt position for airway patency differed between the two groups; while in younger children a neutral position proved to be the ideal condition, a head extension of about 15° was superior in school children.[49]

In sedated, spontaneously breathing children aged 2–12 years, lateral positioning increases cross-sectional area and total upper airway volume compared with supine positioning.[72] Here, the area between the tip of the epiglottis and the vocal cords demonstrates the greatest relative percent increase in size. However, simple head rotation may already elicit a significant increase in the ante-posterior distance and hence the cross-sectional area in the retroglossal region, along with a volumetric increase of the upper airway.[76]

Simple methods to maintain airway patency include airway maneuvers such as chin lift, jaw thrust, or the use of continuous positive airway pressure (CPAP). Jaw thrust is the most effective maneuver to open an obstructed airway and improve ventilation in anesthetized and unconscious patients, irrespective of the age of the patient.[77] While chin lift is effective in healthy children without tonsillar hypertrophy, it has, however, the potential to obstruct the airway in children with hypertrophic tonsils and adenoids when the mouth is closed. CPAP with or without jaw thrust and chin lift can further improve upper airway patency in sedated or anesthetized children, but may decrease ventilation in some patients.[77] The effectiveness of oro-pharyngeal, naso-pharyngeal, and laryngeal mask airways depends on the correct positioning of the devices in the pharynx. Due to the large and age-dependent variability of the palatal and oro-pharyngeal morphology,[78] the design of these devices, for example, the radius of the curvature or the length of the distal portion of oro-pharyngeal airways, determines the effectiveness in the individual patient. Landmark rules, formulas, or nomograms thus may help choosing the appropriate size but need validation in the clinical setting.

4 | DEVELOPMENTAL PHYSIOLOGY OF THE LUNG PARENCHYMA

Alveolarization is the formation of new alveoli, a developmental process that starts in the beginning of the 3rd trimester and continues postnatally. While earlier morphometric studies suggested continued alveolarization until the age of 2–3 and 7–8 years, respectively, newer techniques suggested ongoing formation of new alveoli into adolescence, to a final count of 270–790 million.[79–81] The size of the alveoli is estimated to roughly double during growth and be independent of body size.[81] The primary goal of alveolarization is the enlargement of the gas exchange area from <10 m^2 to about 80–130 m^2 in an average adult.[50]

The term dysanaptic growth refers to the disproportionately larger absolute growth of the lung parenchyma relative to the growth of the conducting airways.[82] It is primarily a physiologic phenomenon that leads to a lower dead space-to-alveolar volume ratio (V_D/V_A) and thus an improved ventilatory efficiency during exercise, as a higher proportion of each tidal breath reaches the gas exchanging area V_A. A further decrease of the V_D/V_A ratio during the first years of life results from a relative decrease of the extrathoracic anatomic dead space from 2.3 ml/kg to 0.8 ml/kg, while the intrathoracic dead space is independent from age at approximately 1 ml/kg.[83] During quiet breathing, however, dead space related to tidal volume (V_D/V_T) remains age-independent at roughly 33%.[84]

Dysanaptic growth is discussed as a pathological process when airway growth seems to exceedingly lag behind lung growth. This is commonly assumed if flow parameters by pulmonary function testing are disproportionally low compared to the lung volume in the absence of active bronchoconstriction, for example, by a lower than normal FEV_1/VC ratio, particularly in the presence of a normal FEV_1. It has been discussed in the context of asthma and obesity,[85] lung growth after pneumonectomy,[86] and in prematurity and bronchopulmonary dysplasia,[87] and it may be hypothesized after congenital diaphragmatic hernia repair, after resection of congenital lung anomalies and with long-standing tobacco exposure. It implies that hypoplastic conducting airways have limited capacity of catch-up growth. The main implication of pathological lung dysanapsis is the potential impact on lung function decline with aging and the development of chronic obstructive pulmonary disease (COPD).[88]

Alveolarization is associated with a re-arrangement of alveolar capillaries, enhanced surfactant production, and a thinning of the alveolar septa with a reduction of the interstitial lung tissue.[89] During the first years of live, this thinning of the alveolar walls allows the formation of pores of Kohn and later on the pores of Lambert,[90] inter-alveolar and bronchiolo-alveolar shortcuts that enable collateral ventilation, and thus aeration of ventilatory units distal to obstructed conducting airways. During the early stage of alveolarization, the capillary network within the alveolar septa is arranged in a double layer, and thinning of the alveolar septa in the mature lung is accompanied by a re-arrangement of the capillaries into a single layer.[89] Although this facilitates gas transfer into the blood, resting diffusing capacity of the lung correlates to and linearly increases with lung volume, and is not different in neonates than in adults,[91] that is, the gas exchange surface of a healthy newborn already provides the same weight-adjusted oxygen-uptake capacity *at rest* as the lung of an adult.

A significant determinant of diffusing capacity is the ventilation/perfusion (V/Q) matching. While in adults, ventilation and perfusion are mainly directed into the dependent lung areas by gravity,[92] ventilation in children is more often directed toward the nondependent part of the lungs, or variable during breathing.[93] V/Q matching is thus weaker in children than adults.

5 | DEVELOPMENTAL PHYSIOLOGY OF THE CHEST WALL AND DIAPHRAGM AND ITS INTERACTION WITH LUNG

Lung growth follows the growth of the thoracic cage, which is determined by elongation of the spine and expansion of the chest. The

thoracic spine lengthens by 50% during the first 5 years and ends at approximately 2.5 times the length at birth.[94] Simultaneously, the chest volume grows from an original 6% of its final volume at birth to 30% at 5 years and 50% of the final thoracic space at 10 years of age, respectively.[94] Severe thoracic restriction obviously is associated with smaller lungs, but whether chest expansion surgery which increases the thoracic volume by radiographic volumetry and thus the *space available for lungs* just leads to lung tissue expansion or also stimulates growth and alveolarization remains debated.[95]

The two important changes in chest physiology occurring during the early years of life are the stiffening of the chest wall and the sternal downshift of the more horizontally positioned ribs of the infant into a slanting position in the older child.[96] Activation of the auxiliary respiratory muscles leads to effective thoracic breathing in the older individual by elevating the ribs into a horizontal position, which increases the thoracic volume both in the anterior-posterior dimension (pump-handle movement of the ribs) and in the lateral dimension (bucket-handle movement).[95] Infants less than 12 months are more dependent of diaphragmatic breathing,[97] and the intercostal muscles are pivotal in stabilizing the chest during inspiration as evidenced by the paradoxical breathing in severe spinal muscle atrophy.

The interaction of chest wall stiffness and lung compliance is a major component of developmental respiratory physiology, and it is reflected by age dependency of the volume-pressure curve of the respiratory system. In the first year of life, the chest wall is nearly three times as compliant as the lung.[98] With the progressive stiffening of the chest wall during the first year of life the lung volume-adjusted compliance of the respiratory system slightly decreases.[99] Toward the end of the second year, the chest wall compliance has decreased to nearly equal the lung's compliance.[98] From this timepoint on, the lung's elastic inward recoil and the chest wall's outward movement stay in balance at a site on the pressure-volume curve, where breathing efficiency is at an optimum. In addition, it is at the nadir of the U-shaped pulmonary vascular resistance curve that increases both toward lower and higher lung volumes.

During infancy, the compliant chest wall offers less resistance to the lung's inward recoil. Hence, the relaxation volume of infants is reduced and estimated at only 10%–15% of total lung capacity, as opposed to 30%–35% in adults.[100] As this moves the lungs toward or below the closing volume,[69] that is, the volume at which atelectasis ensues, the infant actively defends its FRC, mainly by sustained tonic diaphragmatic activity during the entire respiratory cycle.[101] This is associated with an increased work of breathing.[102]

5.1 | Anesthetic considerations about developmental physiology of the lungs and the chest wall

As infants and young children are dependent of their active FRC defense, anesthesia and deep sedation, which counteract the lung volume-preserving strategy, cause a reduction of FRC which may lead to small airway closure, atelectasis, ventilation-perfusion mismatch, and eventually hypoxemia.[103] This is even more pronounced with the use of neuromuscular blockade.[104] In fact, the majority of children under 3 years of age, particularly when using neuromuscular blockade, develop atelectases immediately after induction of general anesthesia.[105] Both the application of PEEP and recruitment maneuvers may reverse atelectasis and restore FRC and ventilation homogeneity.[106]

Volatile anesthetics reduce respiratory muscle activity and tone, starting with the glossopharyngeal muscles, involving then the intercostal muscles and finally the diaphragm.[107] Thus, an increased resistance of the upper airway is followed by thoraco-abdominal asynchrony, presenting with an inspiratory inward movement of the ribcage and a simultaneous abdominal expansion.[107] Except from desflurane, volatile anesthetic agents reduce FRC, particularly in young children with highly compliant chest walls. Conversely, desflurane may lead to bronchoconstriction in children with hyperreactive airways.[108]

Propofol leads to a dose-dependent reduction of FRC and increasing ventilation inhomogeneity in spontaneously breathing preschool children.[109] Midazolam, when used as a premedication in preschool children, may cause a small reduction of FRC and respiratory compliance as well as an minor increase ventilation inhomogeneities.[110] In addition, benzodiazepine-induced muscle relaxation increases upper airway resistance, which may further compromise breathing.[111] Ketamine is unique among hypnotic drugs with regard to its effects on respiration, as increasing doses have little impact on FRC and ventilation homogeneity, whereas the effect on breathing frequency is variable, ranging from apnea to an increased respiratory rate.[112] Opioids may activate chest and abdominal wall muscles, potentially leading to chest wall rigidity in adults.[103] In children, the phenomenon is less well described, and difficult mask ventilation may be caused by active upper airway obstruction after sufentanyl in some children.[113]

During anesthesia, high inspired fractions of oxygen (FiO_2) are used at induction of anesthesia or during the treatment of adverse events in order to increase the oxygen reserve and maintain oxygenation. However, a high FiO_2 leads to lung de-recruitment, ventilation in homogeneities, and ventilation/perfusion mismatch.[114] FiO_2 >80% during the induction and emergence of anesthesia leads to decreased lung volumes in the immediate postoperative period and persistent ventilation inhomogeneity, which normalizes 24 h later.[115] Recruitment maneuvers can be successfully used to reverse this effect. Recruitment maneuvers and atelectasis in pediatric anesthesia are discussed in detail in another article of this special issue.[116]

6 | REFLECTIVE QUESTIONS

1. How does immature breathing control manifest in newborns?
2. How do central apneas change over the first 12 months of life?
3. Describe potential developmental aspects of laryngospasm.

4. How does airway configuration change when bringing children in lateral positioning?
5. What are the physiologic consequences of dysanaptic lung growth?

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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