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CHAPTER 4

# Developmental Anatomy and Physiology of the Respiratory System

**Claude Gaultier**

In the first years of life, maturational changes in the respiratory system and breathing control are most marked, and respiratory disorders are particularly common and severe. Immaturity of the lung contributes substantially to the morbidity and mortality associated with prematurity. Respiratory control immaturity is involved in the pathophysiology of apnea of prematurity, apparently life-threatening events, and sudden infant death syndrome (SIDS). Immaturity of the chest wall limits the ability of infants to adapt to increased breathing loads during respiratory disorders.

Antenatal and postnatal environmental factors, such as malnutrition and chronic hypoxia, impair the development of the respiratory system and respiratory control mechanisms. Developmental abnormalities may be associated with increased vulnerability to insults such as viral infections, passive smoking, and air pollution.

Knowledge of the development of the respiratory system is currently moving from developmental anatomy and physiology to developmental cellular and molecular biology. The challenge for coming years will be to unravel the links among

dysregulation in gene expression and cellular phenotypes, abnormal physiologic function, and clinical symptoms of respiratory disorders in infants and children. Improved knowledge of the underpinnings of developmental processes will improve the ability to prevent antenatal and postnatal exposure to insults and devise effective treatment strategies.

## UPPER AIRWAYS

### Developmental Anatomy

The configuration of the upper airways changes with growth.[1,2] In the newborn, the epiglottis is large and can cover the soft palate, forming a low epiglottic sphincter and encouraging nasal breathing ("obligatory" nasal breathing of the newborn). A horizontal position of the tongue and an elevated position of the hyoid bone and laryngeal cartilage are other specific features. Over the first 2 years of life, changes in upper airway anatomy lead to formation of a dynamic velolingual sphincter that permits buccal respiration and speech. The epiglottis, larynx, and hyoid bone move downward. The posterior portion of the tongue becomes vertical during late infancy. The facial skeleton grows vertically, and the mandible lengthens from front to back.

### Developmental Physiology

#### *Function*

Newborn mammals, including human infants, have difficulty breathing through their mouths when the nasal passages are occluded. Although nasal breathing is considered obligatory in the newborn and infant, mouth-breathing can occur in the presence of nasal obstruction. Oropharyngeal structures have been examined using fluoroscopy during nasal occlusion in healthy infants.[3] Infants can breath through the mouth by detaching the soft palate from the tongue, thus opening the pharyngeal isthmus. However, the time required to establish mouth-breathing varies with age, the state of alertness, or both factors, with younger and sleeping infants responding more slowly than older and awake infants. When nasal passages are obstructed, mouth-breathing is established more slowly during rapid-eye-movement (REM) sleep than during non-REM sleep.[4,5]

Oropharyngeal dynamics in babies have been studied during life and at autopsy.[6-8] The relationship between pharyngeal pressure and oropharyngeal patency has been evaluated at autopsy in infants up to 3 months of age.[9] The closing pressure is 0.82 cm $H_2O$ on average and is generally lower than the opening pressure. The position of the neck is a significant determinant of oropharyngeal dynamics,[10] and neck flexion is thought to play a role in the occurrence of obstructive apnea.[11] During inspiration in normal children[12] and some normal premature infants,[13] phasic activity of the genioglossus muscle is absent; when pharyngeal pressure increases, phasic genioglossus activity appears or is augmented.[13]

Nasal resistance has been measured in Caucasian and black infants during the first year of life using an adapted posterior rhinomanometric method. The percentage contribution of nasal resistance to airway resistance is significantly higher in Caucasian infants than in black infants (mean values, 49% and 31%, respectively).[14] This difference probably reflects anatomic differences in nasal structures.

#### *Reflexes Originating in the Upper Airways*

In human infants and newborn animals, reflexes originating in the upper airways can induce apnea and bradycardia.[15,16] In anaesthetized puppies, the duration of apnea elicited by water instillation into the larynx decreased as age increased.[16] Studies in unanesthetized lambs have suggested that sensitivity of the respiratory system to superior laryngeal nerve inhibition decreases with development[15]; the cause for this maturation is still unclear. In premature infants, reflex apnea has been reported to occur after instillation of water or saline into the larynx during sleep.[17-19] Prolonged apnea in preterm infants may be a pathologic extreme that extends the normal spectrum of airway protective responses to upper airway fluids.[19] The laryngeal chemoreflex has been implicated in the pathophysiology of SIDS.[20] Studies in newborn animals noted that the degree of apnea and bradycardia elicited by the laryngeal chemoreflex was increased by upper airway infection,[21] anemia,[22] and infection by the respiratory syncytial virus.[23] Such an infection is associated with central and obstructive apneas during sleep in human infants.[24] The apnea and bradycardia elicited by the laryngeal reflex in human infants increase dramatically in the presence of hypoxia because of a cardioinhibitory effect on peripheral chemoreceptors during apnea with suppression of input from pulmonary stretch receptors.[20]

During the neonatal period, stimulation of other upper airway receptors can result in apnea. Activation of upper airway mechanoreceptors by negative pressure causes apnea in puppies but not in adult dogs.[25] In human infants, trigeminal airway stimulation can elicit a response similar to that seen during the diving reflex and can include apnea and bradycardia.[26] Studies of healthy infants tested during REM sleep showed that the ventilatory response to trigeminal stimulation became increasingly blunted as the infants mature.[27]

## CHEST WALL

### Developmental Anatomy

#### *Ribcage*

At birth, the ribs are mainly composed of cartilage and project at right angles from the vertebral column. As a result, the ribcage is more circular than in adults[28-30] (Fig. 4-1) and lacks mechanical efficiency.[31] In adults, ribcage volume can be increased by elevating the ribs. In infants, the ribs are already elevated, which may be one reason that ribcage motion during room air breathing contributes little to tidal volume.[31] Rib orientation (see Fig. 4-1) does not change substantially until the infant acquires the ability to assume the upright posture. This changes the forces acting on the ribcage. The action of gravity on the ribs and the pull of the muscles inserted on the ribs cause the ribs to slope caudally. This leads to relative lengthening of the thoracic cavity, which loses its circular cross section to acquire the ovoid adult pattern.[29,30] The thoracic index (anteroposterior/lateral diameter) decreases significantly with age during the first 3 years of life.[30] During the same period, gradual mineralization of the ribs occurs. These changes in shape and structure are extremely important because they stiffen the ribcage.

#### *Respiratory Muscles*

In the newborn, the diaphragm seems poorly adapted to the burden of respiratory work. The angle of insertion of the diaphragm in infants is different from that in adults (i.e., almost horizontal instead of oblique). This results in decreased contraction efficiency in infants. With its open angle of insertion and small area of apposition[32] (Fig. 4-2), the flat diaphragm of the newborn seems designed to suck the chest wall inward

rather than draw air into the chest cavity. In infants, the contracting diaphragm tends to pull the lower ribcage inward because of its almost horizontal insertion. For the same reason, the downward course of the contracting diaphragm is shorter, the abdominal pressure increase is smaller, and consequently, the ribcage expansion is less marked. The diaphragm tends to distort the floppy ribcage of infants, especially preterm infants (see section on thoracoabdominal motion).

With growth, there is a gradual increase in respiratory muscle bulk, as well as important changes in the composition, size, and oxidative capacity of respiratory muscle fibers. In preterm infants, the diaphragm contains less than 10% type I fibers[33] and a higher percentage of type II fibers, particularly type IIc.[34] The mean cross-sectional area of all fiber types increases after birth.[35,36] The total oxidative capacity of the diaphragm, defined as the succinyl dehydrogenase activity, is low at birth.[35,36]

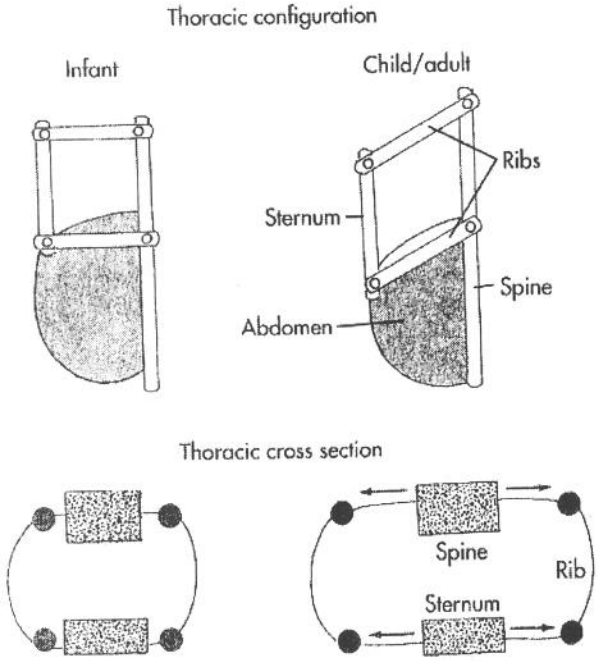


**Fig. 4-1.** Changes in configuration and cross-sectional shape of the thorax from infancy to early childhood. (Redrawn from Openshaw P et al: *Thorax* 39:624-627, 1984.)

## Developmental Physiology

### *Chest Wall Compliance*

High chest wall compliance relative to lung compliance is an inherent characteristic of newborn mammals.[37] Few studies have investigated chest wall mechanics in infants and children.[38-40] Data on the time pattern of changes in chest wall compliance during infancy and early childhood have been recently obtained.[40] In infancy, compliance of the chest wall is nearly threefold that of the lung. By the second year of life, the increase in chest wall stiffness is such that the chest wall and lung have similar compliances, as in adults.

### *Thoracoabdominal Motion*

Developmental changes in thoracic properties over time influence the pattern of thoracoabdominal motion during infancy and early childhood. The contribution of the ribcage to tidal breathing increases with postnatal age. Studies have found that this contribution is 34% during non-REM sleep at 1 month of age[41] and increases to adolescent levels (i.e., approximately 60%) by 1 year of age.

Chest wall muscle contraction helps stabilize the compliant infant ribcage, minimizing inward displacement of the ribs during diaphragmatic contractions. However, when the stabilizing effect of intercostal muscles is inhibited (e.g., during REM sleep), paradoxic inward motion of the ribcage occurs during inspiration (Fig. 4-3).[31,42] Full-term newborns spend more than half of their total sleep time in REM sleep, and REM sleep is even more prominent in premature infants.[43]

Asynchronous chest wall movements during REM sleep are associated with a number of mechanical derangements in healthy newborns, including a decrease in functional residual capacity (FRC),[44,45] a decrease in the transcutaneous partial pressure of oxygen,[46] and an increase in the diaphragmatic work of breathing.[47] During REM sleep, a large proportion of the force of the diaphragm is wasted in distorting the ribcage rather than effecting volume exchange. Furthermore, infants can use their abdominal muscles to optimize diaphragmatic length, and this abdominal muscle activity is inhibited during REM sleep.[48] The increase in diaphragmatic work of breathing represents a significant expenditure of calories and may con-

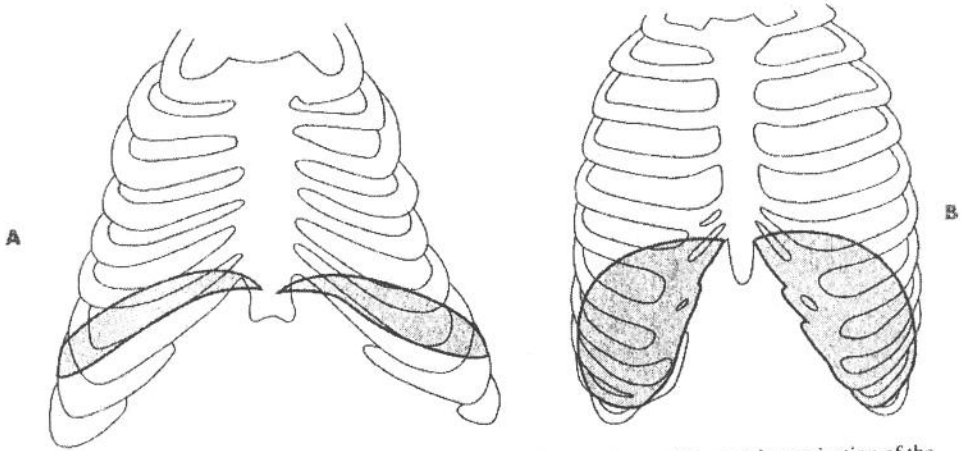


**Fig. 4-2.** Newborn **(A)** and adult **(B)** ribcage. The shaded areas represent the anterior projection of the diaphragm. (Redrawn from Devlieger H et al: *J Dev Physiol* 16:321-329, 1991.)

tribute to the development of diaphragmatic fatigue and ventilatory failure. Moreover, acidosis and hypoxia, both of which increase muscle fatigability, are not uncommon in sick premature infants.

With the changes in ribcage geometry and chest wall compliance that occur over time, the time spent with paradoxic ribcage motion during REM sleep decreases, nearing or reaching zero after 3 years of age.[49] In adolescents, no paradoxic movement is observed.[50]

The mechanical properties of the chest wall have clinical implications for respiratory adaptation during sleep in infants with respiratory disorders associated with increased resistive loads of breathing, such as upper airway obstruction and chronic lung diseases. In young infants suffering from such disorders, thoracoabdominal asynchronism occurs even during non-REM sleep.[51-53] As growth proceeds and the thoracic cage becomes less compliant, the increases in resistive load lead to the heightened activation of inspiratory thoracic muscles, which maintains inspiratory ribcage movement. However, inhibition of inspiratory intercostal muscles occurs during REM sleep, with the need for lower negative pressures during inspiration leading to the destabilized ribcage moving paradoxically.[54]

### *Pressures Generated by Respiratory Muscles and Respiratory Muscle Fatigue*

Maximum pressures exerted by infants are surprisingly high compared with adult values. This is probably related to the small radius of curvature of the ribcage, diaphragm, and abdomen because according to the Laplace's law, a smaller radius results in higher pressures. Esophageal pressures of up to $-70$ cm $H_2O$ have been reported during the first breath.[55] Inspiratory and expiratory pressures of about 120 cm $H_2O$ have been recorded during crying in normal infants.[56] During late childhood and adolescence, gradual increases in maximal static inspiratory and expiratory pressures occur, with substantial differences between male and female patients at all ages.[57,58]

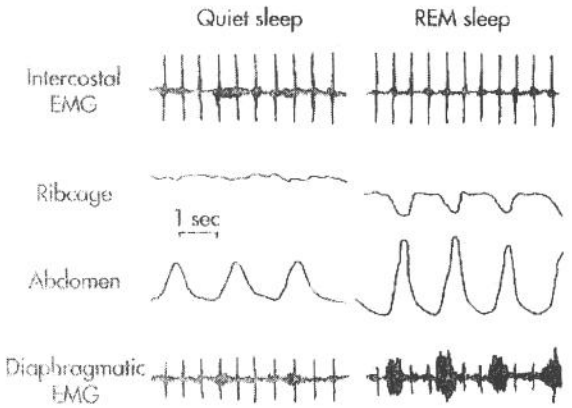


Fig. 4-3. Movement of the ribcage and abdomen measured with magnetometers and electromyograms *(EMG)* using surface electrodes on the intercostal muscles and the diaphragm of a newborn during non-REM *(left)* and during REM *(right)* sleep. During REM sleep, there is marked inward distortion of the ribcage with increased outward movement of the abdomen; the intercostal electromyogram is decreased, and the diaphragmatic electromyogram is increased. The inspiratory rate is increased. (Redrawn from Bryan AC, Gaultier CL. In Macklem PT, Roussos H, eds: *The thorax*, part B, New York, 1985, Marcel Dekker, pp 871-888.)

However, despite a relatively high maximum static inspiratory pressure, the inspiratory force reserve of respiratory muscles appears to be reduced during early infancy compared with that in adulthood because of the higher inspiratory pressures at rest.[59,60] The high pressure demand at rest in infants is due to the high minute ventilation and high metabolic rate normalized for body weight.[61] Occlusion pressure and inspiratory time measurements have been used to estimate the inspiratory pressure demand in children older than 4 years of age.[60] The ratio of mean inspiratory pressure to maximum static inspiratory pressure at FRC was 0.2 at 7 years of age (i.e., more than twice the value in adults).[59] It has been suggested that in healthy newborns the tension-time index of the diaphragm may be close to the fatigue threshold.[62]

Under any breathing conditions, two important parameters (i.e., pressure and time) determine the tension-time index, which allows the clinician to evaluate the position of the breathing pattern in relation to the critical level of muscle function or to the threshold of muscle fatigue[63-65] (Fig. 4-4). The small inspiratory force reserve places young children closer to the diaphragm fatigue threshold than older children. All conditions characterized by prolonged muscle contraction or increased pressure demand may lead to respiratory muscle fatigue. Young children with croup or epiglottitis are at especially high risk for fatigue because obstructed and prolonged inspiration is combined with a need for high pressures to produce adequate ventilation. Thus infants can develop ventilatory failure rapidly after small changes in mechanical loads. Infants are capable of using other muscles to unload (rest) the diaphragm. When the respiratory drive is increased because of

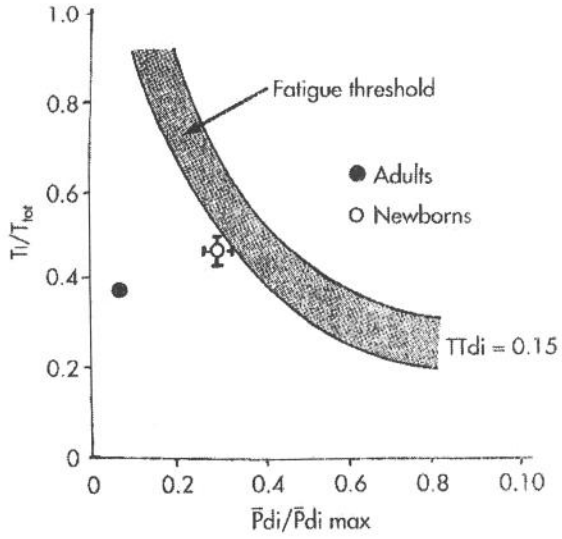


**Fig. 4-4.** Relationship between ratio of inspiratory time *(Ti)* over total duration of the respiratory cycle *($T_{tot}$)* and mean transdiaphragmatic pressure used to breathe at rest over maximal transdiaphragmatic pressure *($\bar{P}di\ max$)*. The gray area defines the diaphragmatic fatigue threshold and corresponds to the so-called tension-time index of the diaphragm *(TTdi = 0.15)*. Breathing patterns below the fatiguing threshold can be obtained indefinitely. Filled circle refers to the average value for normal adults during resting breathing. Open circle is the estimated value for normal infants. Bars indicate 1 standard deviation. (Redrawn from Milic-Emili J. In Cosmi EV, Scarpelli EM, eds: *Pulmonary surfactant system*, Rome, 1983, Elsevier Science, pp 135-141.)

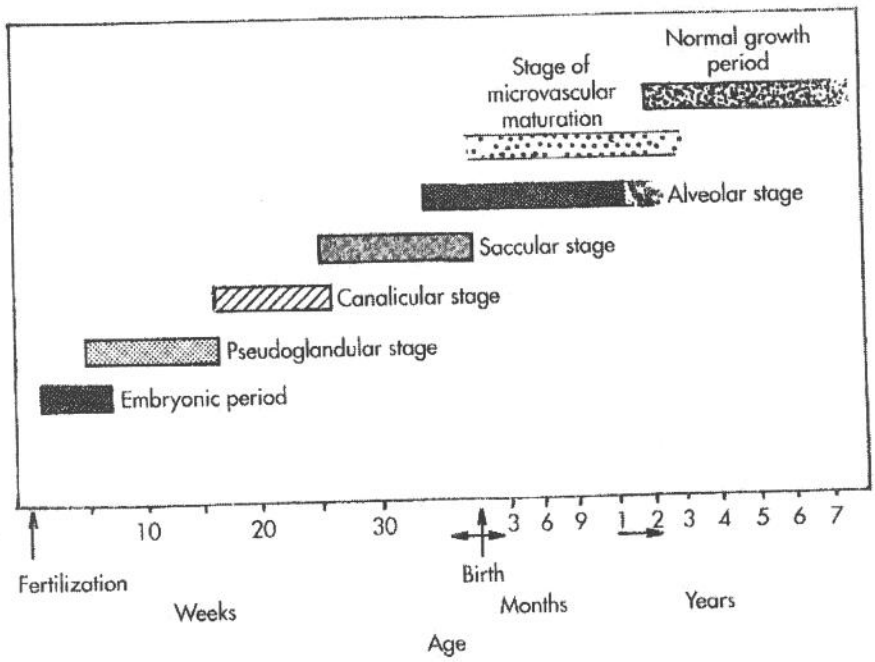


**Fig. 4-5.** Stages of lung development and growth with their respective timing. Open bars in the stages of alveolation and microvascular maturation indicate uncertainty as to exact timing. (Redrawn from Zeltner T, Burri P: *Respir Physiol* 67:269-282, 1987.)

carbon dioxide breathing or increased upper airway resistance, infants and young children recruit the intercostal muscles, abdominal muscles, or both sets of muscles.[48] However, this muscle recruitment aimed at preventing an increase in diaphragmatic work of breathing and diaphragmatic fatigue is suppressed during REM sleep.

The paucity of fatigue-resistant type I fibers, the high proportion of fatigue-susceptible type IIc fibers, and the low oxidative capacity of the neonatal diaphragm suggest that the muscle may be relatively prone to fatigue. This hypothesis has been contradicted by in vitro[36] and in situ findings. However, an in vivo study in rabbits found that fatigue occurred more quickly in neonatal than adult animals.[66] Thus whether fatigability of the neonatal respiratory muscles is increased compared to those of adults remains controversial.

## LUNGS

## Developmental Anatomy

Lung development includes growth of lung structures and maturational cell differentiation processes. Three laws govern lung development: Alveolar development occurs both before and after birth, extraacinar airway development is complete by week 16 of gestation, and arterial development follows airway development for extraacinar arteries and alveolar development for intraacinar arteries.[67] Fig. 4-5 shows the timetable of antenatal and postnatal lung development.[68]

### *Antenatal Lung Development*

Antenatal human lung development can be subdivided into an early embryonic period, during which most organs are formed, and a fetal period that includes several stages.[68-70]

**Embryonic Development of the Lung.** The lung appears around day 26 as a ventral bud of the esophagus at the caudal end of the laryngotracheal sulcus. The epithelial components of the lung are thus derived from the endoderm and the enveloping connective tissue from the mesodermal germ layer. The tracheal bud rapidly divides into two branches that develop into the two main bronchi. The future airways continue to grow and branch dichotomously into the surrounding mesenchyma. By the end of the sixth week the lobar and segmental portions of the airway tree are preformed as tubes of high columnar epithelium. Simultaneously with the early stages of pulmonary organogenesis, vascular connections develop. The pulmonary arteries branch off from the sixth pair of aortic arches and descend to freshly formed lung buds, forming a vascular plexus in the surrounding mesenchyma. The pulmonary veins start to develop around the fifth week as a single evagination in the sinoatrial portion of the heart. Merging of the embryonic period into the fetal period is considered to occur on day 50. At that time, the lung resembles a small tubuloacinar gland, which is why the subsequent stage is called the *pseudoglandular stage.*

**Fetal Period.** The fetal period successively includes the pseudoglandular stage to week 16, the canalicular stage from weeks 24 to 26, and the saccular-alveolar stages to term.[68-70]

***Pseudoglandular stage.*** The pseudoglandular stage is characterized by formation of the extraacinar bronchi (Fig. 4-6) and arteries. The conductive airway system is formed through continuous growth and branching. The proximal airways are lined with a high columnar epithelium (Fig. 4-7) and the distal airways with a cuboidal epithelium. The cytoplasm of airway epithelial cells is poorly differentiated and rich in glycogen. Differentiation of the airway wall occurs in a centrifugal direction, so ciliated, nonciliated, and goblet cells first appear in the proximal airways. The luminal surfaces of the columnar cells have few microvilli with or without primary rudimentary cilia.[71] Precursors for neuroendocrine cells appear during this

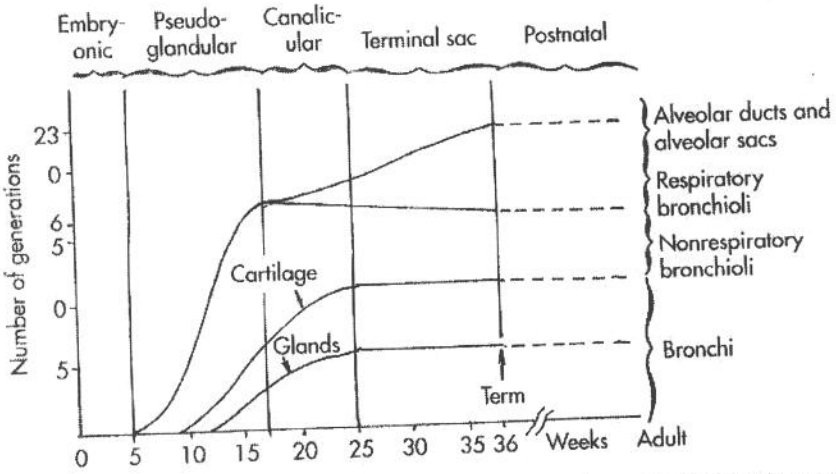


**Fig. 4-6.** Timetable for development of the airway tree, its generations, and typical wall structures. Generation numbers are fitted to the average airway tree of Weibel's dichotomous branching model. (Redrawn from Burri P. In Fishman P, Fisher A, eds: *Handbook of physiology*, Section 3: The respiratory system, vol 1: Circulatory and nonrespiratory functions, Bethesda, Md, 1985, Williams & Wilkins, pp 1-46.)

stage.[72] Mucus glands are also present.[73] Mesenchymal cells differentiate into chondrocytes[74] and smooth muscle cells. Capillaries are randomly distributed in the mesenchyme (Fig. 4-8). As a rule, the arteries develop and grow according to the same pattern as the airways. In contrast to the airway system, which averages 23 generations in adults, the arterial system has 28 to 30 generations. Arteries that follow the divisions of the airways are called *conventional arteries;* the smaller arteries with intermediate branchings that supply alveolar regions adjacent to airways are called *supernumerary arteries.*[75,76] By week 12, both types are present. The branching pattern of the veins matches that of the arteries.[77]

**Factors Controlling Branching Morphogenesis.** Epitheliomesenchymal interactions play a key role in regulating the growth and branching pattern. Transplantation experiments have shown that the mesenchyma is directly responsible for the branching pattern in the lung.[78] The branching process depends on interactions between cell-substrate adhesion molecules and underlying extracellular matrix (ECM) and intercellular adhesion molecules.[79,80] Epidermal growth factor may be an important mediator of this process.[81] The mechanisms responsible for the mesenchymal influences have not been fully elucidated but have been shown to depend on the synthesis of proteoglycans, collagen, laminin, and fibronectin.[79] Cellular attachment to the ECM is mediated by integrin receptors.[82] Branching is decreased in the presence of monoclonal antibodies against integrin receptors.[83] Integrin receptors appear to interact with fibronectin within the clefts that mark the branching points.[84] Transforming growth factor-$\beta_1$ colocalizes with fibronectin within these clefts and may regulate fibronectin deposition, thereby indirectly affecting branch formation.[85] Triamcinolone acetonide increases fetal rat airway branching in vitro.[86]

***Canalicular stage.*** Events during the canalicular stage include acini anlage formation and epithelial cell differentiation with formation of the air-blood barrier. Production of surfactant starts toward the end of this canalicular stage. The transition from the pseudoglandular stage to the canalicular stage is marked by the appearance of rudimentary acini. *Acinus* is generally defined as the portion of gas-exchanging tissue supplied by a terminal bronchus. The acinus margins become recognizable as a result of decreased density of the mesenchyma. At the end of week 17, the newly delineated acinus is composed of the anlage of the terminal bronchiole, two to four rudimentary respiratory bronchioles, and clusters of short tubules and buds. Over the following weeks, the clusters grow by further peripheral branching and by lengthening of each tubular branch. The epithelium differentiates into two cell types: secretory cells (type 2, containing lamellar bodies) and lining cells (type 1) characterized by low junctional complexes with neighboring cells and by close contact with capillaries (see Fig. 4-7). Peripheral growth is accompanied by an increase in capillarization. Capillaries begin to develop around the airspaces, subsequently establishing close contact with the lining cells to form the prospective air-blood barrier (see Fig. 4-8).

***Saccular-alveolar stages.*** The saccular-alveolar stage starts at weeks 24 to 26 of gestation. At this time, the fetal lung can theoretically function in air. However, because of a low level of surfactant synthesis, very premature babies are at high risk for respiratory distress syndrome. At the beginning of this stage, the airways end in clusters of thin-walled saccules. The saccules produce the last generations of airways (i.e., prospective alveolar ducts and alveolar sacs). Between weeks 28 and 36, there is a striking change in the appearance of the lung characterized by a marked decrease in interstitial tissue with thinning of saccule walls. Secondary crests divide the saccules into smaller units. The margins of the crests contain elastic fibers. The saccule walls retain their earlier double capillary network. The formation of alveoli marks the beginning of the alveolar phase. According to recent studies, alveolar develop-

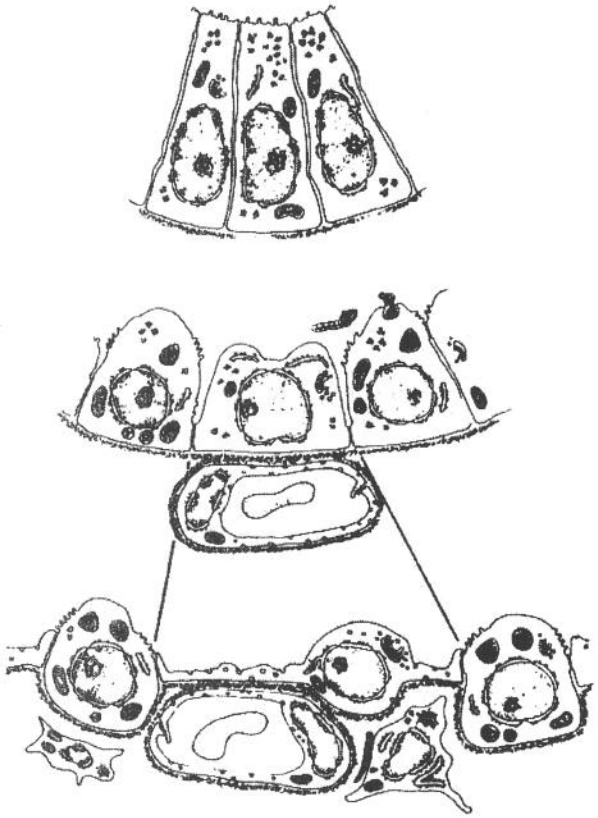

Fig. 4-7. Phases of epithelial transformation. *Top,* Pseudoglandular stage: high columnar epithelium and cells rich in glycogen. *Middle,* Canalicular stage: epithelium beginning to differentiate into two cells types, secretory (type 2, containing lamellar body) and lining cells (type 1), and characterized by the low position of the junctional complex with neighboring cells and close contact with capillaries. *Bottom,* Terminal sac stage: differentiation of type 1 and type 2 cells. (From Burri P. In Fishman P, Fisher A, eds: *Handbook of physiology,* Section 3: The respiratory system, vol 1: Circulatory and nonrespiratory functions, Bethesda, Md, 1985, Williams & Wilkins, pp 1-46.)

ment starts between weeks 29 and 32.[87,88] The internal surface area of the lung increases rapidly after the onset of alveolar development, from 1 or 2 to 3 or 4 $m^2$ at term.[87] The number of alveoli present at birth is still controversial. Early studies[89,90] examining only one lung found numbers ranging from $17 \times 10^6$ to $24 \times 10^6$. Larger mean numbers were found more recently[87,88]: $50 \times 10^6$ and $150 \times 10^6$. Despite these discrepancies, there is no doubt that the number of alveoli is lower at birth than in adulthood (i.e., $300 \times 10^6$ to $600 \times 10^6$).[91] During the saccular and alveolar phases, intraacinar blood vessels increase in width, length, and number.

**FACTORS CONTROLLING GROWTH OF THE PERIPHERAL PART OF THE LUNG.** The exact mechanisms responsible for the growth and maturation of the periphery of the lung during the canalicular and saccular-alveolar stages have not been yet elucidated. They have been shown to depend on cell populations, cell-to-cell interactions, hormones, and growth factors. In rat fetal lung, epithelial cell proliferation slows during the transition between the canalicular and saccular stages.[92] This reduction in cell proliferation is accompanied by morphologic evidence of differentiation. There is increased proliferation of fibroblasts and endothelial cells. The mesenchymal tissue influences epithelial cell function. An endogenous steroid may cause fetal fibroblasts to secrete a lung maturation factor (fibroblast pneumocyte factor) that promotes lipid synthesis by type 2 cells.[93] Epithelial cell–fibroblast interactions also involve direct intercellular contact.[94] Foot processes from epithelial cells cross the basal membrane and come into close contact with fibroblasts. They are most prominent at the onset of surfactant synthesis.[95,96] The ECM contributes to the regulation of surfactant synthesis.[79] Surfactant apoprotein gene expression appears to require cell-matrix contact and cell-to-cell contact. A variety of hormones and growth factors, most notably glucocorticoids, thyroid hormone, epidermal growth factor, insulin-like growth factor,[97-99] and gastrin-releasing peptide,[100] participate in the regulation of surfactant synthesis.[101] The factors that modulate endothelial growth in the fetal lung have not been identified. Growth factors, such as transforming growth factor-β, fibroblast growth factors, and platelet-derived growth factor, may be involved.[79,102]

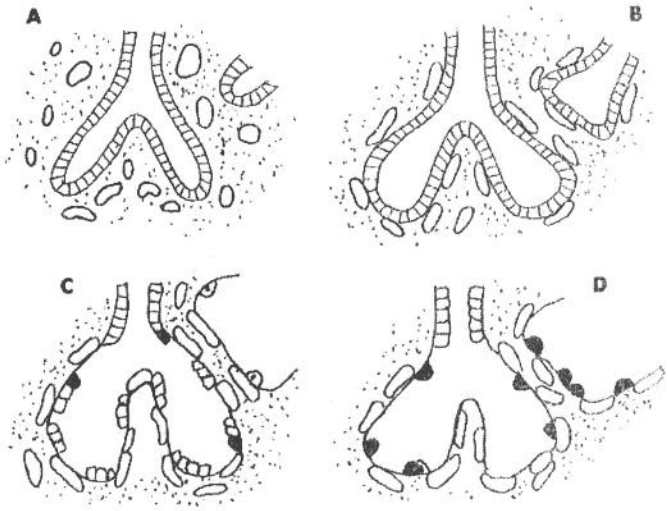


Fig. 4-8. Development of the pulmonary capillaries. **A,** Pseudoglandular stage: Capillaries are randomly distributed in mesenchyme. **B,** Beginning of the canalicular stage: Capillaries start to arrange around the epithelial tubes. **C,** Capillaries establish close contacts to the lining epithelium, which flattens to form thin air-blood barriers. **D,** Saccular stage: Epithelium is differentiated in type 1 and type 2 cells. (Redrawn from Burri P. In Fishman P, Fisher A, eds: *Handbook of physiology,* Section 3: The respiratory system, vol 1: Circulatory and nonrespiratory functions, Bethesda, Md, 1985, Williams & Wilkins, pp 1-46.)

### *Postnatal Lung Development*

**Alveolar Development.** At term, the internal surface area of the lung is to 3 to 4 $m^2$,[87] and the in vitro lung volume with a transpulmonary pressure of 25 cm $H_2O$ is 150 ml.[87] Alveolar multiplication continues after birth. Early studies suggested that postnatal alveolar multiplication ends at 8 years of age.[90] However, more recent studies have shown that it is terminated by 2 years of age and may even end earlier, possibly between 1 and 2 years of age.[68,70,103] During postnatal alveolar multiplication, the capillary network of the septa is remodeled from the initial double pattern to the single pattern seen in adults.[104] This process continues after the end of alveolar multiplication, stopping between 3 and 5 years of age.[68,70] At 2 years of age, the number of alveoli varies substantially among individuals. After 2 years of age, boys have larger numbers of alveoli than girls. After the

end of alveolar multiplication, the alveoli continue to increase in size until thoracic growth is completed.[103]

Factors controlling postnatal alveolar multiplication have been studied in rats. In rats, alveolar multiplication starts on day 4 and peaks between days 7 and day 12.[104,105] This period is characterized by fibroblast proliferation and accumulation of ECM components (lectin, fibronectin, elastin, collagen).[106,107] TGF-β is involved in elastin production.[108] Dexamethasone impairs postnatal alveolar multiplication by decreasing fibroblast proliferation, lectin accumulation, and acceleration of capillary remodeling.[109,110]

**Airway Development.** Hislop and Haworth[111] have recently described airway size and structure in the normal lungs of fetuses and infants. The mean airway lumen diameter from the main bronchi to the respiratory bronchi increases linearly with postconceptional age. Each type of airway shows a similar relative increase in diameter of 200% to 300% from birth to adulthood. The absolute amount of cartilage increases until 8 months of age. The area of the submucosal glands (expressed in relation to the lumen perimeter as millimeters squared per millimeter) increases linearly from birth to 8 months of age. The area of the hilar bronchi continues to increase until adulthood. At birth, submucosal glands are innervated by nerves containing peptides. Bronchial smooth muscle is present at birth, even at the level of respiratory bronchioles (Fig. 4-9). The bronchial smooth muscle area increases from birth to 8 months of age in all airways from the main bronchi to the respiratory bronchioles. In proximal airways only, this area increases from 8 months of age to adulthood. In premature infants, airway size is appropriate for the postconceptional age, and airways contain increased amounts of bronchial smooth muscle and goblet cells. At birth, smooth muscle is innervated by nerves containing peptides (neuropeptide-tyrosine, vasointestinal peptide, substance P, neuropeptide Y, somatostatin, and gene-related peptide).[112] Smooth muscle innervation appears to change with age because the relative number of peptide-containing nerves within the respiratory unit decreases from infancy to adulthood. No developmental changes in myosin chain isoforms have been demonstrated in human airway smooth muscle.[113]

**Arterial Development.** Pulmonary vascular resistance falls rapidly at birth as a result of dilation of the small muscular arteries and reduction in the amount of vascular smooth muscle in the lungs.[114] Postnatal adaptation of the pulmonary circulation is thought to be related to changes in endothelial cell function, including an increased capability for synthesis and release of endothelium-derived relaxing factor identified as nitric oxide.[115,116] Ultrastructural studies have found evidence of postnatal smooth muscle maturation with changes in contractile myofilaments[114] and the types of cytoskeletal proteins.[117] The number of arteries increases rapidly during the first 2 months of life.[118] Subsequently, arteries multiply at the same rate as alveoli, and the alveolar-arterial ratio remains fairly constant. Arterial size increases are most marked during the first 2 months of life but remain substantial during the first 4 years.

Studies of the structure of the arteries that accompany the peripheral airways have demonstrated that the respiratory bronchiolar arteries acquire a muscle coat as they increase in size during the first year of life. From birth to 6 months of age, the mean number of arteries surrounded by muscle cells is 58% among the arteries accompanying terminal bronchioli vs. only 23% among arteries accompanying alveolar ducts. These mean proportions

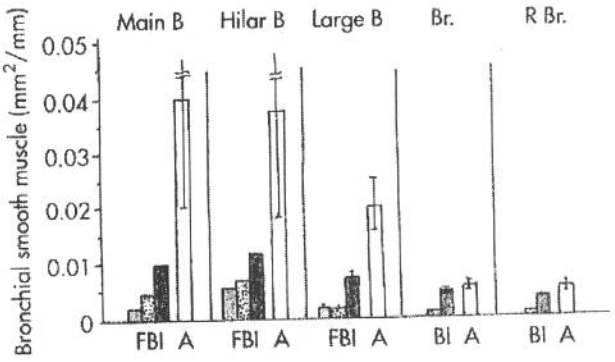


**Fig. 4-9.** Area of bronchial smooth muscle related to airway perimeter at four representative ages: *F*, Fetus at 22 weeks' gestation; *B*, fetus at term; *I*, infant at 8 months; *A*, adult. Bars indicate standard error of the mean. *B*, Bronchus; *Br.*, bronchioli; *R Br.*, respiratory bronchioli. (Redrawn from Hislop AA, Haworth SG: *Am Rev Respir Dis* 140:1717-1726, 1989.)

reach 92% and 40%, respectively, between 1 and 4 years of age and increase further to 96% and 71%, respectively, after 5 years.

Remodeling of the arterial wall within the acinus is accompanied by an increase in the nerve supply to the arterial wall during childhood.[119] Many respiratory unit arteries do not have accompanying nerve fibers in infants 1 to 4 months of age. The proportion of innervated vessels increases with age. In all age groups, the vasoconstricting neuropeptide tyrosine is the predominant neuropeptide associated with perivascular nerves. In infants with pulmonary hypertension, respiratory unit arteries are prematurely innervated by sympathetic-like nerve fibers. In both the normal and the pulmonary hypertensive lung, the development of sympathetic innervation seems to occur in parallel with an increase in the amount of smooth muscle in peripheral arteries.

## Developmental Physiology

### *FRC*

During breathing in the resting state, the volume of gas in the lungs at FRC represents lung oxygen stores. The FRC is determined by the static passive balance of forces between the lung and the chest wall. In infants, the outward recoil of the chest wall is very small and the inward recoil of the lung slightly less than in adults.[37] Consequently, the static passive balance of forces dictates a very low ratio of FRC over total lung capacity (TLC) in infants, which would be inadequate for gas exchange. Measured FRC and estimated TLC values in infants[120] indicate that the dynamic FRC/TLC ratio is about 40%, a value similar to that in supine adults. Thus it is very likely that in newborns and infants with little outward recoil of the chest wall, the dynamic end-expiratory volume is substantially greater than the passively determined FRC.[121]

Infants, in contrast to adults, terminate expiration at substantial flow rates[122] (Fig. 4-10). This suggests active interruption of relaxed expiration. The newborn may use two active mechanisms to slow expiration and maintain FRC. One is the postinspiratory activity of the diaphragm,[123,124] and the other is laryngeal narrowing during expiration,[125] the extreme form of which is the grunting observed in newborns with respiratory distress syndrome. Laryngeal braking of expiration has an effect like auto–positive end-expiratory pressure, which increases FRC. FRC would be expected to fall during REM

sleep. It has been firmly established that expiratory airflow braking mechanisms are disabled during REM sleep in preterm infants. Postinspiratory diaphragmatic activity is reduced during REM sleep, and animal studies have demonstrated that expiratory laryngeal adduction is substantially diminished during REM sleep.[125] Furthermore, flow studies in human preterm newborns show clear evidence of expiratory braking during non-REM sleep but suggested passive airflow without expiratory braking during REM sleep.[126] The transition from dynamically maintained to passively determined end-expiratory lung volume has been estimated to occur during the second half of the first year of life.[127]

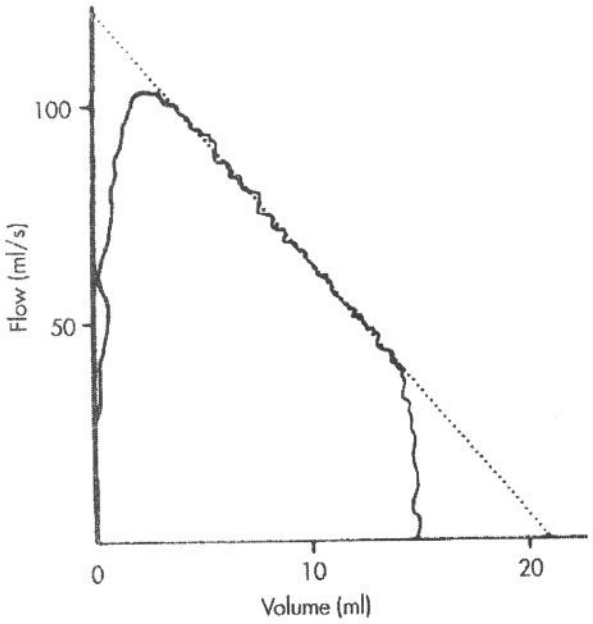


**Fig. 4-10.** Passive flow-volume curve in an infant, showing abrupt inspiration substantially above passive FRC. (From Le Souëf PN et al: *Am Rev Respir Dis* 129:552-556, 1984.)

### *Mechanical Properties of the Lung*

**Elastic Properties.** Changes in pressure-volume relationships have been related to changes in the amount, distribution, and structure of elastin and collagen in the growing rat lung.[128] In humans, little is known about the development of the elastic properties of the lung. One study has shown that the true elastin content of the lung increases up to a plateau during the first 6 months of life.[129] Measurements of the pressure-volume relationship of the lung have been performed in excised lungs of infants and a few children[130-132] and in vivo in older children using esophageal balloons to measure transpulmonary pressure. In excised preparations, lung pressures of up to 30 cm $H_2O$ have been used; in vivo, the TLC is taken to represent full inflation. Fig. 4-11 shows the changes in the shape of the pressure-volume curve that accompany pulmonary maturation.[133] In excised lungs, when lung volume is expressed as a fraction of the lung volume at 30 cm $H_2O$, there is a marked change in the overall shape of the pressure-volume curve within the age range examined. The younger lung holds a greater fraction of this volume at low pressure than the older lung. The in vivo quasistatic pressure-volume curves during deflation show that lung recoil increases with age in children older than 6 years of age.[134]

Studies in animals and in humans have shown that antenatal and postnatal environmental factors modify the elastic properties of the lungs. Protein malnutrition impairs elastin deposition in the lungs and is associated with a shift of the pressure-volume curves upward and to the left.[135] Neonates born to mothers liv-

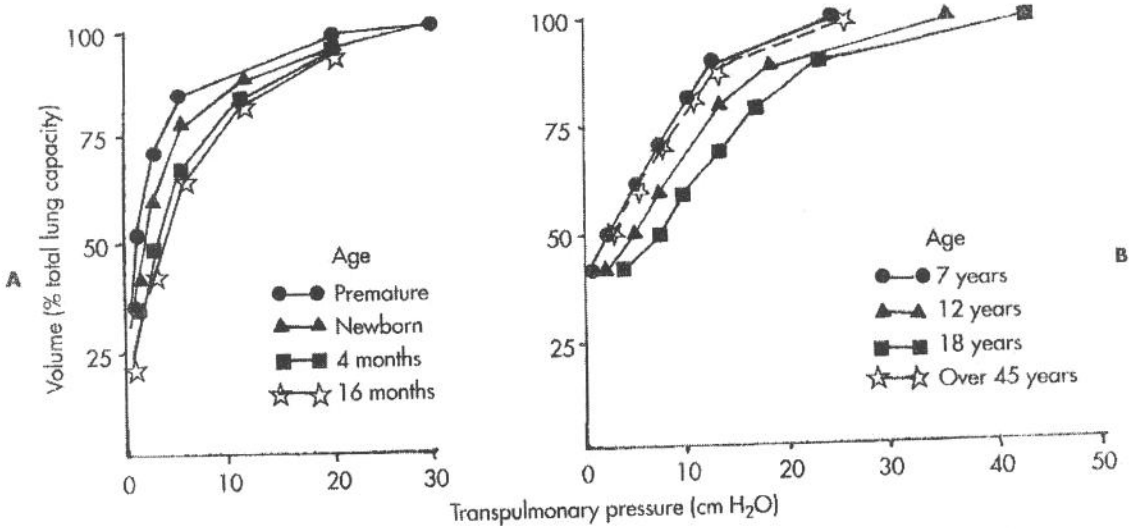


**Fig. 4-11. A,** Pressure-volume curves obtained from excised lungs. Curves are grouped by length. Lengths of 30 to 45, 46 to 55, 56 to 65, and 66 to 90 cm correspond to premature infants, infants 1 month of age, infants 4.4 months of age, and infants 16 months of age, respectively. **B,** Pressure-volume curves obtained from children. Heights of 115, 150, and 180 cm correspond to 6, 12, 13, and 17 years, respectively, as estimated from growth charts. (**A** data from Fagan DG: *Thorax* 31:534-543, 1976; and Fagan DG: *Thorax* 32:198-202, 1977. **B** data from Zapletal A et al: *J Appl Physiol* 40:953-959, 1986. **A** and **B** redrawn from Bryan AC, Wohl MEB. In Fishman P, Fisher A, eds: *Handbook of physiology*, Section 3: The respiratory system, vol 1: Circulatory and nonrespiratory functions, Bethesda, Md, 1985, Williams & Wilkins, pp 179-191.)

ing at high altitudes have higher total respiratory system compliance than those born to mothers living at sea level.[136]

**Compliance, Resistance, and Time Constant of the Total Respiratory System.** Compliance of the respiratory system increases during the first year of life. This increase has been estimated at 152%.[137] The rate of increase in lung compliance exceeds that of chest wall compliance and accounts in large part for the increase in compliance of the respiratory system during the first year of life. During the same period, total resistance of the respiratory system decreases by 42%, a noticeably less considerable modification than the change in compliance. The difference between rates of change in compliance and total resistance of the respiratory system corresponds with anatomic findings that alveolar formation is substantial during the first year of life whereas the total number of conducting airways is present at birth. In the human infant, measurements have shown that the expiratory time constant of the total respiratory system increases during the first year of life and then reaches a plateau.[138-141] This change may reflect the increase in compliance caused by rapid alveolar growth. After 1 year of age, the relative stability of this constant suggests that changes in compliance and resistance are balanced after infancy.

**Flow-Resistive Properties.** During postnatal life, airway growth results in increases in the radius and length of airways and in changes in the mechanical properties of airway walls. Airway compliance is greater in infants and young children than in adults. In excised preparations, the trachea of the newborn is twice as compliant as the adult trachea.[142] Radiographic studies in normal infants have shown variations of 20% to 50% in the anteroposterior diameter of the intrathoracic trachea during exertion.[143] This may be related to the decreased amount of cartilage.[111]

Measurements of airway, pulmonary, and respiratory resistance have been performed in newborns, infants, and children 5 years of age and older.[135] Airway resistance falls tenfold on average from term to adolescence. The inverse of airway resistance, airway conductance, corrected for differences in upper airway resistance and divided by the lung volume at which it was measured (specific airway conductance), decreases during the first years of life and remains constant beyond the age of 5 years (Fig. 4-12).[144,145] This profile of the specific airway conductance strongly suggests that the airways are well formed and relatively large in newborns but that during the early period of life, lung volume increases disproportionately with the size of the airways.

The total resistance of the respiratory system includes resistance of the airways, lung tissue, and chest wall. Little is known about the changes in the lung and chest wall components of total resistance. A recent study investigated growth-related changes in the viscoelastic properties of the total respiratory system by measuring pressure variations after airway occlusion in paralyzed subjects 3 weeks to 15 years of age.[146] This measure decreases during the first 2 years of life and increases after age 5. These changes have been interpreted as indicating greater influence of the lung tissue during the early period of life and greater influence of chest wall viscoelastic properties at older ages.

The distribution of resistance along the central and peripheral airways has been studied in excised lungs from infants, children, and adults.[147] The central airway conductance per gram of lung weight remained unchanged from the neonatal period to adulthood, whereas the peripheral airway conductance per gram of lung weight increased with age in subjects older than 5 years of age. These data suggest that peripheral airways may be disproportionately narrow in children younger than 5 years of age. Disproportionately low peripheral airway conductance values in infants as compared with older children should be accompanied by low maximum expiratory flows at low lung volumes. However, relatively high flows at low lung volumes have been observed in healthy, anaesthetized infants and children.[148] Furthermore, the maximum expiratory flow at FRC measured from partial expiratory flow-volume curves was higher in neonates and similar in infants compared with those reported in children and adults.[149,150] Thus physiologic data do not support the hypothesis suggested by pathologic findings that peripheral airways are disproportionately smaller in infants than in adults.

Abnormal growth of conducting airways (e.g., in lung hypoplasia) is associated with low airway resistance values during infancy.[151] Conceivably, dysregulation during the processes involved in morphogenesis (see section on the fetal period in developmental anatomy) may be responsible for the substantial interindividual variability in postnatally measured indexes of pulmonary flow-resistive properties.

Postmortem evaluations of airway size in preterm infants have shown that airway size is normally related to postconceptional age.[111] However, data obtained during childhood suggest that premature birth is associated with impaired airway growth.[152]

**Gas Exchange.** In the newborn, the partial pressure of oxygen in arterial blood ($Pa_{O_2}$) is approximately 70 mm Hg.[153] The alveolar-arterial difference in $Pa_{O_2}$ is about 30 mm Hg while a person breathes room air and 120 mm Hg while a person breathes oxygen.[153] The $Pa_{O_2}$ in arterialized blood samples rises rapidly during the first 2 years of age and then slowly up to the age of 8 years[154,155] (Fig. 4-13). Thereafter, $Pa_{O_2}$ values remain stable and similar to those seen in adults.[156]

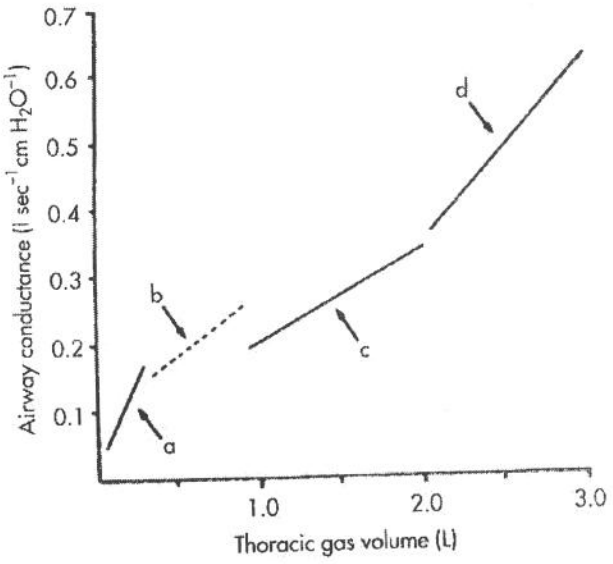


**Fig. 4-12.** Comparison of regression lines of airway conductance during mouth-breathing vs. thoracic gas volume from infancy to adulthood. Regression lines refer to data in infants *(a)*, in children 1 to 5 years of age *(b)*, and in older children *(c)* and adults *(d)*. (From Bryan AC, Wohl MEB. In Fishman P, Fisher A, eds: *Handbook of physiology*, Section 3: The respiratory system, vol 1: Circulatory and nonrespiratory functions. Bethesda, Md, 1985, Williams & Wilkins, pp 179-191.)

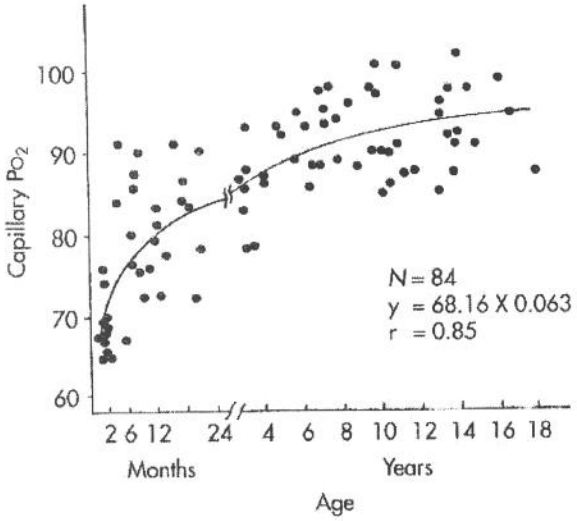


**Fig. 4-13.** Arterialized partial pressure of oxygen in the capillaries in 84 infants and children from 20 days to 18 years plotted against age. *X*, Age expressed in months and years. (Redrawn from Gaultier CL et al: *Bull Eur Physiol Respir* 14:287-297, 1978.)

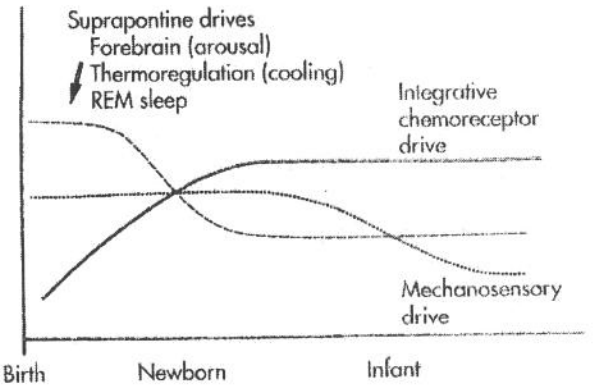


**Fig. 4-14.** Relative importance of different respiratory drive mechanisms after birth. (From Lagercrantz H et al. In Crystal RG, West J, eds: *The lung: scientific foundations*, New York, 1991, Raven, pp 1711-1722.)

The lung volume at which some of the intrapulmonary airways are closed (closing volume, an index of susceptibility to hypoxemia) decreases with age.[157,158] In infants and young children, the closing capacity (closing volume plus residual volume) is sometimes greater than the FRC and some areas of the lung may be closed throughout part or all of the tidal volume, resulting in impaired gas exchange.

Mechanisms that result in improvements in pulmonary gas exchange during growth have been more extensively investigated in piglets than humans. Using the multiple inert gas technique in the awake, growing piglet, researchers have shown that low $Pa_{O_2}$ values were due to two mechanisms: ventilation-perfusion mismatch and diffusion limitation for oxygen.[159] The impaired oxygen diffusion in piglets was related to the inadequate diffusion-perfusion equilibrium of oxygen.[160] This suggests that the capillary transit time in newborns may be too short to permit alveolar-capillary diffusion equilibrium, implying that newborns have little pulmonary vascular reserve for gas exchange. In newborns, the ratio of pulmonary diffusing capacity to FRC is close to that obtained in 11- to 13-year-old boys during submaximal exercise.[161]

The fairly low $Pa_{O_2}$ values in infants and young children are close to the steep part of the oxygen-hemoglobin dissociation curve. Any further decrease in $Pa_{O_2}$ can induce severe oxygen desaturation. During sleep, especially REM sleep, decreases in the arterial oxygen saturation ($Sa_{O_2}$) to less than 90% have been demonstrated in healthy full-term infants.[162] Drops to less than 90% become less common with advancing age and are not observed in healthy children older than 9 years of age.[163,164]

## RESPIRATORY CONTROL

### Development of the Neuronal Network Controlling Respiration

Breathing in mammals relies on a neuronal network located within three brain stem complexes (dorsal respiratory group in which nucleus of the tractus solitarius is located, ventral respiratory group, and pontine respiratory group).[165] The respiratory neuronal network receives suprapontine influences[166] from the systems involved in thermoregulation, sleep-wake and arousal patterns,[167] and circadian rhythms.

At birth, the control of breathing switches from discontinuous and metabolically less dependent fetal breathing to continuous metabolically dependent breathing. Fig. 4-14 shows the relative importance of various respiratory drive mechanisms after birth.

Although there is a substantial body of data on the control of respiration by the neuronal network in adult mammals, less is known about the structural organization of the central respiratory neurons in human newborns. The neurons of the bulbopontine respiratory complexes are probably formed during the proliferative phase between gestational weeks 10 and 20 in human fetuses. Significant differentiation of respiratory neurons and formation of the respiratory neuronal network probably also occurs during the neonatal period.[168] The dendritic spines of respiratory neurons of some brain stem nuclei (nucleus of the tractus solitarius) increase before birth, with the highest densities being observed shortly before. These dendritic spines represent areas with high synaptic densities. After birth, the density of synaptic connections decreases gradually. Interestingly, SIDS victims have higher dendritic densities in the brain stem than infants who die from other causes,[169] suggesting that brain stem immaturity is involved in the pathophysiology of SIDS.

So that the understanding of respiratory rhythm generation can be improved during the early period of life, there is a need for studies on neuronal differentiation and organization, on gene expression associated with the many different neurotransmitters that determine cell phenotypes, and on membrane proteins that affect sensitivity and responsiveness to specific stimuli.[170] Experimental studies on maturational changes in the nucleus of the tractus solitarius have shown that some neurotransmitter mechanisms (such as those involving *N*-methyl-D-aspartate receptors) are mature at birth[171] whereas other processes relevant to morphologic and bioelectrical properties are still immature.[172,173] Abnormalities in the timing of the maturation of synaptic relationships with respect to that of cellular metabolism may be involved in the pathophysiology of SIDS.

Among neurotransmitters involved in the function of the respiratory central pattern generator, some are excitatory (e.g., glutamate, aspartate), whereas others are inhibitory (e.g., γ-aminobutyric acid).[165] The central generator is controlled by neuromodulators (acetylcholine, biogenic amines, neuropeptides).[165] Inhibitory amino acids seem to be expressed at an earlier stage than excitatory amino acids.[174] There may be some dominance of inhibitory neuroactive agents terminating at the respiratory neurons before birth, possibly as a result of the low fetal $PaO_2$ values.[174] Experiments in rabbits have shown that reorganization of synapses occurs immediately after birth. Neuropeptides increase in respiratory brain structures in the newborn rabbit compared to the fetus. This may be related to the postnatal increase in $PaO_2$.[175] Further peptide phenotype changes occur after birth in respiratory areas of the brain stem.[168] The plasticity of the peptide system during the early period of life may contribute to adaptation to environmental disturbances.

The fetal and perinatal environment may influence developmental processes in the brain stem. Interestingly, preliminary data have shown that chronic hypoxia during the perinatal period in rats is associated with alterations in the maturation of brain stem neuronal neurotransmitters and with a shift in the balance of excitatory and inhibitory neurotransmitters toward inhibition.[176] It has been postulated that neuronal immaturity may be the main cause of respiratory instability in the newborn. This hypothesis is consistent with the finding that brain auditory response latency is correlated with the frequency of apneas in preterm infants.[177] Brain stem auditory response latency is thought to be related to neuronal conductivity. The auditory pathways are located in the immediate vicinity of the respiratory neurons in the brain stem. Therefore maturation of the auditory pathways may parallel development of breathing pattern stability.

## Pattern of Breathing, Apnea, and Periodic Breathing

Over the last decades, many studies have shown that apneas of short duration (<10 seconds) are common in early life. Apneas are more frequent in preterm than in full-term infants[178] (Fig. 4-15). Apneas in preterm infants are related to underlying oscillatory breathing patterns.[179,180] Although obstructive apneas have been reported more frequently in preterm infants, there is no consensus regarding the incidence of such events. The incidence of obstructive apneas was very low in two studies.[181,182] Higher incidences were found in other studies.[183] Upper airway obstruction may be an important risk factor for apnea in preterm infants. Continuous positive airway pressure selectively reduces obstructive apneas in preterm infants.[184] There is a general consensus that the occurrence of obstructive apneas decreases with increasing postconceptional age.[185] This may result from the improvement in extrathoracic airway stability with maturation.[186] In full-term newborns, most apneas are central.[187]

Some studies on apneas in early life have focused on variations in its occurrence across sleep states. In all such studies except one,[188] apneas were more frequent during REM sleep than during non-REM sleep in both preterm and full-term newborns[178,185,187] (see Fig. 4-15). The higher frequency of apneas during REM sleep in newborns contrasts with the fact that few apneas occur in children and adolescents, especially during stage 1 non-REM sleep.[189]

The observation that REM sleep is associated with greater respiratory instability than non-REM sleep during early life

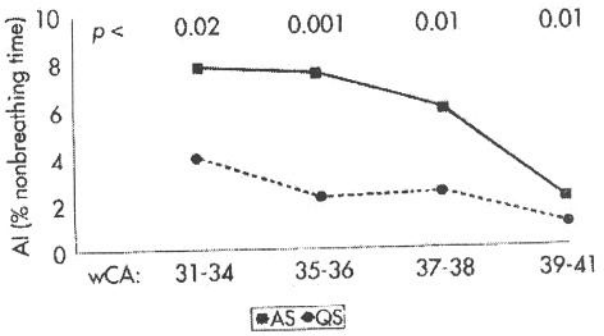


**Fig. 4-15.** Apnea index *(AI)* (the percentage of nonbreathing time calculated by dividing the sum of all respiratory pauses by the time spent in the given state multiplied by 100) in four groups of infants from 31 to 40 weeks' postconceptional age *(wCA)*. *p* values indicate the level of significance between sleep states. *AS*, Apnea index during active (REM) sleep; *QS*, apnea index during quiet (non-REM) sleep. (Modified from Curzi-Dascalova L., Christova-Guergueva E: *Biol Neonate* 44:325-332,1983.)

may result either from overall immaturity of brain stem centers and the respiratory pump or from phasic inhibitory mechanisms inherent to REM sleep.[190] In preterm infants, apneic spells occur predominantly during the period of decreased spinal motoneuron excitability that occurs during REM sleep.[191] Frequent apneas during REM sleep early in life may reflect an exaggeration of normal phasic inhibitory-excitatory central mechanisms that occur during this sleep state. Irregular phasic respiratory patterns of REM sleep occur synchronously with other brain stem phasic activities, such as REMs. Tidal volume and total respiratory cycle duration decrease with increasing frequency of REMs in infants.[192] Inhibitory mechanisms during REM sleep affect the muscles involved in respiratory adaptation, such as the upper airway muscles. Upper airway muscle inhibition may increase the risk of upper airway obstruction. This may play a key role in prolonging apneic events.

Periodic breathing is frequent in preterm infants. Infants of 30 weeks' postconceptional age spend about 25% of their time in periodic breathing.[193] Periodic breathing is even more prominent at younger gestational ages. Studies of periodic breathing in full-term infants have yielded variable results. The time spent in periodic breathing was found to decrease during the first year of life.[194]

Many factors may increase the occurrence of apnea, periodic breathing, or both in neonates and infants; these include medications taken by the mother (meperidine[195]) or infant (phenothiazine[196]), metabolic disorders,[197] anemia,[22] hypoxia,[198] upper airway infections, viral infections,[23] gastroesophageal reflux,[199] hyperthermia (which increases the time spent in periodic breathing),[200] and sleep deprivation (which increases the number of obstructive events)[201] (Fig. 4-16). The influence of three of these factors (i.e., administration of meperidine to the mother, hyperthermia, and sleep deprivation) is significantly greater during REM than non-REM sleep. Therefore in infants whose homeostasis is disturbed, the risk of increased respiratory instability may be greater during REM sleep than during non-REM sleep. Any factor that increases respiratory instability is a potential risk factor for acute life-threatening events and SIDS. The sleeping position (prone or supine) was not found to affect the incidence, duration, or type of apnea in healthy infants or in infants with a history of apnea.[202]

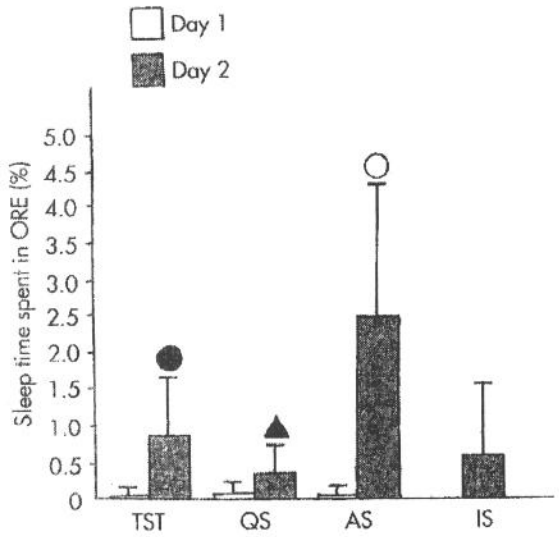


**Fig. 4-16.** Sleep spent in an obstructive respiratory event *(ORE)* during total sleep time *(TST)*, quiet (non-REM) sleep *(QS)*, active (REM) sleep *(AS)*, and indeterminate sleep *(IS)*. The values are expressed as percentages. Day 1 is the baseline; day 2 figures were taken after a sleep deprivation recovery nap. Bars indicate the standard deviation. Percentage of time spent in an obstructive respiratory event significantly increased after sleep deprivation during total sleep time *(full circle, $p < 0.01$)*, quiet sleep *(triangle, $p < 0.05$)*, and active sleep *(open circle, $p < 0.002$)*. (Redrawn from Canet E et al: *J Appl Physiol* 66:1158-1163, 1989.)

## Reflexes Originating from the Lung and Chest Wall

Reflexes originating from the tracheobronchial tree and within the lung parenchyma have significant effects in newborns, who differ in this respect from adults. The vagally mediated Hering-Breuer inspiratory inhibitory reflex is an important mechanism for regulating the rate and depth of respiration in newborn mammals.[203-205] The activity of this reflex can be expressed as the relative change in expiratory time after end-expiratory occlusion compared to the resting expiratory time during spontaneous breathing. This parameter has been measured during non-REM sleep in infants younger than 1 year of age. Results showed that the reflex persisted beyond the neonatal period and showed no variation in activity during the first 2 months of life.[205] Later, activity of the reflex was negatively correlated with age.[137] The reflex is less potent during REM sleep than during non-REM sleep in newborns.[206]

The functional immaturity of pulmonary irritant receptors has been reported in preterm infants younger than 35 weeks' postconceptional age.[207] Apnea occurred when the receptors were stimulated. This paradoxic response to irritants may be related to incomplete vagal myelinization.[208] Rapid lung inflation can initiate an augmented inspiratory effort, called *Head's paradoxic reflex*, which been observed during the neonatal period.

In adult animals, various reflexes that arise in the ribcage influence intercostal and phrenic motoneurons.[209] These reflexes are of potential importance in the newborn with a compliant ribcage prone to distortion during REM sleep. Ribcage distortion is associated with breathing pattern changes, including decreases in inspiratory time and tidal volume, prolongation of expiratory time, irregularity of breathing,[209-211] and even apnea.[155]

## Chemoreception

### *Peripheral Chemoreceptors*

Oxygen-sensitive chemoreceptors are activated by changes in the partial pressure of oxygen and trigger respiratory drive changes aimed at maintaining normal partial pressure levels. Studies in fetal lambs have demonstrated that peripheral chemoreceptors can be activated by further decreasing the already low fetal $Pao_2$.[166] The initiation of breathing at birth immediately results in a very substantial increase in $Pao_2$. Consequently, the chemoreceptors have to be reset at a higher $Pao_2$ level. The mechanisms underlying this resetting have not yet been elucidated. Recent studies in newborn rats suggest that dopamine may be involved.[212] The turnover rate of dopamine is high immediately after birth and decreases markedly a few hours later when the peripheral chemoreceptors start to reset[212] (Fig. 4-17). Resetting of peripheral chemoreceptors is essentially complete approximately 24 to 48 hours after birth in healthy human full-term newborns tested during non-REM sleep using breath-by-breath alternations in inspired oxygen[213] or single breaths of 100% oxygen.[214] Interestingly, delayed resetting of peripheral chemoreceptors has been demonstrated in kittens subjected to hypoxia during the perinatal period.[215] A similar delay has been recently reported in infants with chronic hypoxia resulting from bronchopulmonary dysplasia.[216] Because peripheral chemoreceptors play a key role in initiating the ventilatory, cardiovascular, and arousal responses to hypoxia and asphyxia, this delay may be among the factors that place infants with bronchopulmonary dysplasia at greater risk for SIDS. The ventilatory response to a single breath of 100% oxygen was not significantly different between REM and non-REM sleep in human newborns.[217]

In newborns, steady-state hypoxia produces a transient increase in ventilation followed by a decrease to or below the baseline level[218] (Fig. 4-18). The profile of this biphasic response is affected by the sleep state in preterm infants, with the initial hypoxia-induced increase in ventilation being smaller during REM than non-REM sleep.[219] The initial increase in ventilation in response to steady-state hypoxia has been ascribed to peripheral chemoreceptor stimulation, and the subsequent decrease has been ascribed to other mechanisms, including a decrease in metabolic rate, changes in lung mechanics, and the central depressant effect of hypoxia. Hypoxia may activate neurochemical mechanisms that affect breathing. Endorphins, γ-aminobutyric acid, adenosine, and dopamine have been suggested as possible neurotransmitters and modulators of hypoxia-induced depression.[220] Furthermore, chemoreception interacts with thermometabolism. The ventilatory response in kittens tested at or close to thermoneutrality increases in parallel with thermal efficiency.[221]

The carotid body response to carbon dioxide is quite different. In the newborn, the carotid body responds to rapid changes in the partial pressure of arterial carbon dioxide, even at an age when there is little sensitivity to hypoxia because resetting has not yet occurred.[222]

### *Central Chemoreceptors*

Hypercapnia is a respiratory stimulant during late fetal life. At birth, the ventilatory response appears to be more mature than the response to hypoxia. Studies of the response of newborns to carbon dioxide have shown that the curve plotting minute ventilation against the alveolar partial pressure of carbon dioxide has a slope similar to that seen in adults, although the curve is shifted to the left because of lower resting carbon dioxide levels.[223] The tidal volume component of the ventilatory response takes on greater importance with postnatal development. The

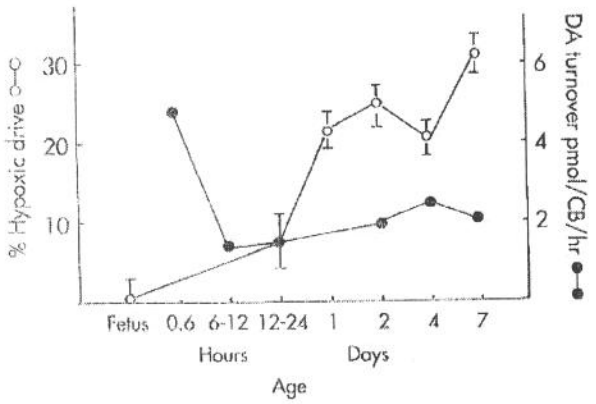


Fig. 4-17. Peripheral chemosensitivity was tested by giving oxygen to unanesthetized rat pups. Respiration was monitored using plethysmography, and the relative decrease during oxygen exposure was used as an index of peripheral chemoreceptor activity. From day 1, ventilation decreased significantly, suggesting an increase in chemoreceptor activity with increasing age. Dopamine *(DA)* turnover in the carotid bodies *(CB)* was relatively high immediately after birth and markedly decreased a few hours later. (Redrawn from Hertzberg T et al: *J Physiol* 425:211-225, 1990.)

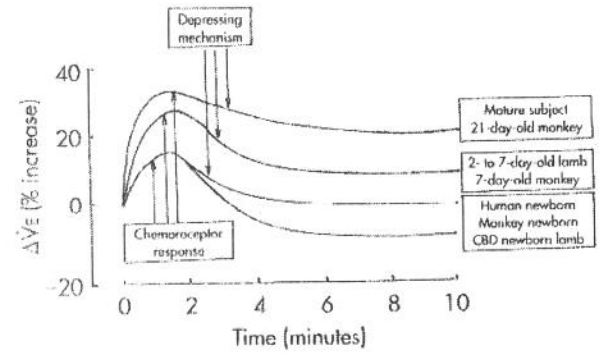


Fig. 4-18. Ventilatory response to steady-state hypoxia in the newborn. The newborn has a diphasic response to hypoxia. $\Delta \dot{V}_E$, Change in expiratory gas flow. (Redrawn from Davis GM, Bureau MA: *Clin Perinatol* 14:551-579, 1987.)

neonatal ventilatory response to carbon dioxide appears to have a number of limitations. In contrast to adults who can produce tenfold to twentyfold increases in minute ventilation in response to inhaled carbon dioxide, neonates cannot increase the minute ventilation more than 3 to 4 times the baseline level.[218,223]

Data conflict on the influence of the sleep state on the carbon dioxide–induced ventilatory response in newborns. Studies using the steady-state technique generally failed to detect any significant difference in the ventilatory response to carbon dioxide between REM and non-REM sleep.[224] In contrast, four studies using the rebreathing technique with either hyperoxic[48,225-227] or normoxic[227] gas mixtures reported a significantly decreased ventilatory response to hypercapnia during REM sleep compared with non-REM sleep in preterm and full-term newborns[225-227] (Fig. 4-19). The ventilatory response to hypercapnia varies widely among individuals and in a given individual within the same sleep state.[227] Mechanisms that contribute to the decreased ventilatory response to carbon dioxide during REM sleep include a decrease in the contribution of the ribcage to ventilation,[225] a decrease in central output to the diaphragm,[48,226] and inhibition of abdominal muscle recruitment by carbon dioxide breathing during REM sleep as compared with non-REM sleep.[48]

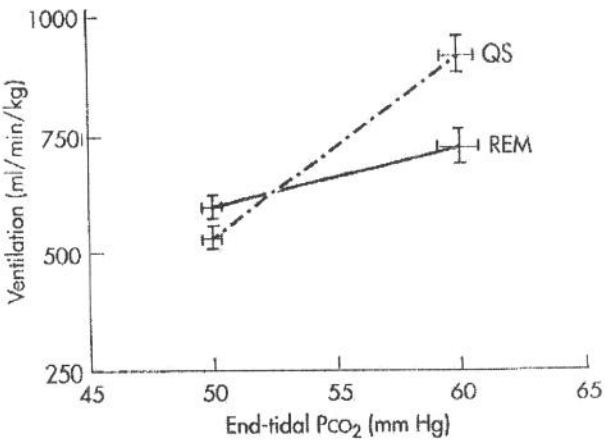


Fig. 4-19. Partial end-expiratory pressure of carbon dioxide vs. minute ventilation for REM sleep and quiet (non-REM) sleep *(QS)*. Data are means plus or minus 95% confidence intervals for position. Data are from 46 tests in five full-term babies. (Redrawn from Cohen G et al: *J Appl Physiol* 71:168-174, 1991.)

## Thermoregulation

Hypothalamic mechanisms that increase ventilation are active before birth.[228] Cooling of the skin provides a potent drive to breathing in the neonatal period. Ambient temperature is closely linked to metabolic rate, especially in the early period of life, when the basal metabolic rate is high and provides an important tonic sensory input that directly influences the stability of breathing.[229] The effects of ambient temperature changes are complex; these changes alter the metabolic rate, which is a major stimulus for breathing during the neonatal period and probably also contributes to maintain breathing in infants. Under resting conditions, the most important determinant of metabolic rate is environmental temperature. Metabolic rate is lowest when environmental temperatures are within the neutral range. In adults, thermoregulatory mechanisms are impaired during REM sleep. In contrast, in newborns, REM sleep seems to be associated with the maintenance of homeothermia in cool as well as in warm environments.[230] Metabolic responses are more active during REM sleep than during non-REM sleep.[231] A more active metabolic response during REM than non-REM sleep may increase the instability of breathing. In fact, small increases in body temperature are associated with significant increases in the time spent in periodic breathing during REM sleep but not during non-REM sleep.[200] High body temperature was associated with decreases in the threshold and latency for reflex contraction of the laryngeal adductor in newborn dogs,[232] suggesting that hyperthermia may permit reflex laryngeal closure in newborns. Interactions between developmental changes in thermoregulation and control of breathing may influence the risk of SIDS.[233]

## Circadian Rhythms

Circadian rhythms are apparent for many physiologic phenomena, such as sleep-wakefulness, body temperature, release of hormones, and activity of neurotransmitters. A biologic clock in

the anterior hypothalamus (i.e., the suprachiasmatic nucleus) harmonizes these rhythms. The suprachiasmatic nucleus regulates activity of the pineal gland, which produces melatonin.

Perinatal animal studies and data from human fetuses and preterm infants have shown that human circadian rhythms are present as early as 30 weeks' gestation.[234,235] In preterm infants during early life, circadian rhythmicity is present for some physiologic variables (e.g., body temperature, heart rate) but not others (e.g., respiratory rate).[236,237] The emergence of circadian variations in the respiratory rate has been studied in full-term infants.[238] The age at which the circadian pattern appears, which is characterized by a lower respiratory rate between 10 PM and 1 AM, was 1 month for REM sleep and 3 months for non-REM sleep. One study reported more frequent respiratory pauses during the early morning hours.[239]

Additional investigations are needed to gain further insight into the maturation of circadian rhythms of physiologic variables, including those related to control of breathing. Impaired maturation of the pineal gland may be involved in the pathophysiology of SIDS.[240]

## Arousal Responses

Arousal from sleep is the most important protective response to danger-signaling stimuli during sleep.[167] Arousal responses to hypoxia, hypercapnia, apnea, gastroesophageal reflux, and auditory stimuli, as well as spontaneous arousals, have been studied in infants. However, whether arousal responses change with maturation remains unclear for a couple of reasons: Many studies included only infants within the peak age range of SIDS occurrence (i.e., 2 to 4 months of age), and criteria for arousal vary across studies. Different types of arousal have been considered: behavioral arousal, electroencephalographic (EEG) arousal, movement arousal,[241] and miniarousal.[185] Full-term and preterm newborns have similar rates of spontaneous arousals lasting longer than 5 seconds.[242] In full-term newborns, the rate of spontaneous behavioral arousals was similar to the rate of EEG arousals lasting longer than 2 seconds.[243]

Although apnea occurs in almost all preterm and full-term infants, little is known about the mechanisms that terminate an apneic episode. The occurrence of behavioral arousals has been studied in preterm apneic infants.[244] Less than 10% of apnea episodes ended with an arousal. Arousal was significantly more common in long vs. short, mixed vs. central, and severe vs. mild apneas. *Miniarousals,* defined as the occurrence of movements after an obstructive apnea, have been reported to prevent prolonged apnea in preterm infants.[185]

Behavioral arousal to hypercapnic stimuli has been studied in healthy infants and young children during non-REM sleep.[244-246] Hypercapnia is a potent stimulus causing arousal from non-REM sleep. All tested infants and young children had behavioral arousal from sleep when the end-tidal partial pressure of carbon dioxide was between 48 and 52 mm Hg. One study reported the occurrence of behavioral arousal at the end of a carbon dioxide rebreathing test during non-REM and REM sleep in preterm infants. Behavioral arousal occurred in only one third of tests during REM sleep vs. 93% during non-REM sleep.[48]

Compared to hypercapnia, hypoxia is less effective in causing arousal from sleep. Few studies have reported the incidence of behavioral arousal during non-REM sleep in response to hypoxic stimuli. One study in healthy infants (mean age 8.4 ± 3.2 months) found that arousal occurred consistently.[245] Only a few of the infants in the other studies exhibited arousals.[244,247,248] Thus the absence of hypoxic arousal cannot be ascribed to a deficient arousal response to hypoxia in infants. Studies in lambs have shown a delayed arousal response to severe hypoxia during REM sleep compared to non-REM sleep.[249]

Other stimuli can lead to arousal from sleep in infants. In near-term infants, the esophageal acid infusion test induced significant increases in the rate and duration of EEG arousals during REM sleep.[250] The auditory arousal threshold decreases with maturation between 44 and 52 weeks' postconceptional age.[251]

Several factors may impair arousal from sleep. Arousal was found to be less common in infants who slept in the prone rather than the supine position.[202] Drugs such as phenothiazine can depress arousal mechanisms in infants.[196] Arousal response habituation may occur with exposure to repetitive stimuli during sleep, as shown in lambs for airway obstruction.[252] Finally, sleep fragmentation or deprivation may impair arousal responses from sleep.[253]

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CHAPTER 5

# Lung Cell Biology

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The lung consists of diverse cell types that function with one another and with the cardiovascular and hematopoietic systems to efficiently eliminate the carbon dioxide produced by cellular metabolism and to resupply the cells with oxygen. Within the adult human lung parenchyma, alveolar type I cells account for 93% to 96% of the alveolar surface area and 6% to 9% of the total cell population. Alveolar type II cells account for 4% to 7% of the alveolar surface area and 13% to 19% of the total cell population. The remainder of the cell population within the lung is about 35% to 39% endothelial cells, 34% to 40% interstitial cells (fibroblasts), and 2% to 5% macrophages.[1] Specific structural and functional duties are performed by each of these cells. Important interaction and communication among various lung cell types is ongoing and essential for normal cellular and lung function.

Airways conduct gas into and out of the alveoli and are lined with cells that optimize this process and protect the airways and distal lung parenchyma from damage. Eight different cell types line the conducting airways: ciliated cells, serous cells, basal cells, small mucous granule cells, Clara cells, neuroendocrine cells, brush cells, and mucous goblet cells.[2] Once the gas reaches the alveoli, the alveolar lining cells, interstitial cells, and endothelial cells are responsible for the maintenance of alveolar-capillary integrity and the enhancement of gas exchange. Blood vessels composed of endothelial cells, smooth muscle cells (SMCs), and adventitial fibroblasts regulate blood flow to the gas-exchange units and also actively participate in a number of other metabolic, immunologic, hemostatic, and host defense functions performed by the lung.

## LUNG GROWTH AND DEVELOPMENT

### Basic Concepts

The lung begins to form in humans at 21 to 24 days' gestation as a bud of the primitive foregut[3] (Fig. 5-1). This process evolves rapidly during the first, or pseudoglandular, phase of lung development, with rapid and complete formation of all the airways through the terminal bronchioles by week 16 of gestation. The lung then begins to form the primitive gas-exchanging units (acini) during the second, or canalicular, phase