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Pathophysiologic Mechanisms Underlying Apnea of Prematurity

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Objectives After completing this article, readers should be able to:

1. Characterize the unique features of neonatal respiratory control mechanisms.
2. Clarify how immature respiratory control contributes to neonatal apnea.
3. Identify the contribution of upper airway obstruction to episodes of mixed apnea.

Introduction

Idiopathic apnea of prematurity is a common disorder that requires therapeutic intervention to avoid potential morbidity in preterm infants who require neonatal intensive care. Severe, recurrent apneic episodes may lead to multiple investigations to rule out secondary disorders leading to apnea (see accompanying article in this issue). Although the incidence of neonatal apnea is inversely related to gestational age and is probably as high as 100% in the most immature preterm infants, the onset may be delayed by the presence of lung disease in the first days of life. Apnea of prematurity, especially if severe or persistent, has been associated with poor developmental outcome in school-age children, although a cause-and-effect relationship is difficult to establish.

Definition and Classification

The definition of apnea varies among studies. Apnea of prematurity has been defined most widely as cessation of breathing in excess of 15 seconds' duration, typically accompanied by desaturation and bradycardia. However, shorter episodes of apnea, and even periodic breathing, may be accompanied by bradycardia or hypoxemia. Prolonged desaturation episodes also have been reported in the absence of apnea or bradycardia, both in healthy preterm infants and in infants who have chronic lung disease. These episodes might represent obstructive apnea, hypoventilation, or possibly intrapulmonary right-to-left shunting, although episodes of desaturation and bradycardia almost always are preceded by apnea or hypoventilation.

Apnea is classified traditionally into three categories based on the presence or absence of upper airway obstruction: central, obstructive, and mixed apneas. Central apnea is characterized by total cessation of inspiratory efforts with no evidence of obstruction. In obstructed apnea, the infant tries to breathe against an obstructed upper airway, resulting in chest wall motion without airflow throughout the entire apneic episode. Mixed apnea consists of obstructed respiratory efforts usually following central pauses, as seen in Fig. 1, and is probably the most common type of apnea. The contribution of obstruction to apnea was recognized by the observation that the frequency of apnea increased when the preterm infant's neck was flexed. Subsequently, upper airway obstruction was found to accompany apnea even in the absence of neck flexion. The site of obstruction in the upper airways is primarily in the pharynx, although it also may occur at the larynx and possibly at both sites. Mixed apnea typically accounts for more than 50% of long apneic episodes, followed in decreasing frequency by central and obstructive apnea. Purely obstructive spontaneous apnea in the absence of a positional problem is probably uncommon.

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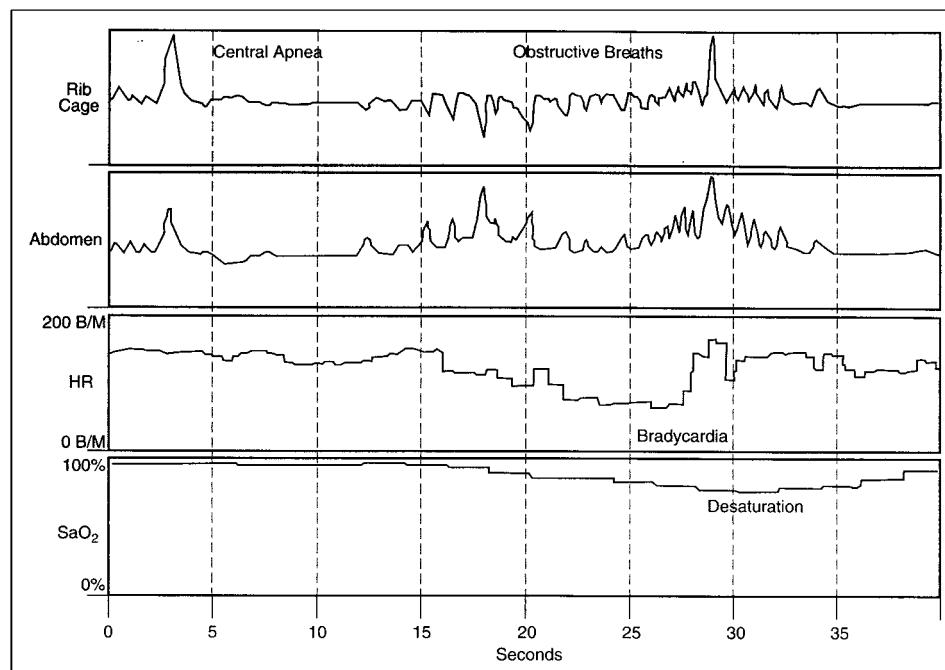


Figure 1. Characteristic mixed apnea of approximately 20 seconds' duration commencing with a central component and prolonged by obstructed inspiratory efforts. In the absence of simultaneous measurement of rib cage and abdominal motion during routine impedance monitoring of chest wall motion, the obstructed inspiratory efforts would not be recognized. As noted in this tracing, bradycardia and desaturation are due to the cessation of effective ventilation during the mixed apnea. Reprinted with permission from Miller MJ, Fanaroff AA, Martin RJ. *Respiratory disorders in preterm and term infants*. In: Fanaroff AA, Martin RJ, eds. *Neonatal/Perinatal Medicine*. 7th ed. Philadelphia, Pa: Harcourt Publishers; 2001.

Apnea of Prematurity and Periodic Breathing

Periodic breathing is characterized by regular, recurring cycles of breathing of 10 to 15 seconds' duration that are interrupted by pauses of at least 3 seconds in duration. Although periodic breathing is considered a benign respiratory pattern for which no treatment is required, it shares some characteristics with apnea of prematurity. Both disorders tend to decline in frequency with advancing postconceptional age and with administration of theophylline. The respiratory pauses in both can be preceded by a decline in tidal volume and a decrease in respiratory frequency, indicating a decrease in central neural output. Obstructive breaths at the level of the pharynx can precede the onset of respiratory cycles in both disorders.

There also are important differences between the two disorders. During periodic breathing, the respiratory pauses appear to be self-limited, and ventilation does continue, albeit cyclically. In contrast, infants who have prolonged apnea may fail to reinitiate ventilation entirely or do so ineffectively. In addition, the respiratory pauses during apnea are associated with swallowing movements

that are not observed during periodic breathing. Periodic breathing can be resolved with an increase in environmental oxygen, but because of the benign nature of the disorder and the fact that it does not result in severe or persistent bradycardia or desaturation, this is not indicated clinically.

Maturation of Chemoreceptor-mediated Ventilatory Responses

Responses to CO_2/H^+

Spontaneous and sustained breathing movements alternating with episodes of apnea are well documented in the human fetus. Furthermore, breathing efforts in mature fetal lambs increase in response to elevated levels of arterial Pco_2 (Paco_2). Thus, even before birth, the mammalian fetus is equipped with the reflex input necessary to regulate the rate and depth of breathing. Experimental data derived primarily from fetal sheep indicate that fetal breathing is dependent on the presence of rapid eye movement sleep or wakefulness. Carotid body chemoreceptors are not essential for intrauterine breathing or the onset of effective breathing at birth. After birth, when the

placenta no longer is available for gas exchange, neonates presumably are dependent on an adequate ventilatory response to increasing P_{aCO_2} for their postnatal survival.

The ventilatory response to CO_2 has been shown clearly to increase with advancing postnatal and gestational age in preterm human infants. Therefore, the breathing response to CO_2 in preterm infants is impaired when compared with term neonates or adults, and it appears that this difference is both quantitative and qualitative. Whereas term neonates and adults increase their ventilation through an increase in both tidal volume and frequency, preterm infants do not appear to increase frequency in response to CO_2 . This somewhat unique response of respiratory timing during hypercapnic exposure is associated with prolonged expiratory duration. Physiologic studies employing various animal models, such as rat pups and piglets, have revealed that the prolongation of expiration associated with hypercapnia is centrally mediated at the brainstem level. Furthermore, the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) appears to be involved. Future studies are required to substantiate further the role of inhibitory neurotransmitters and neuromodulators such as GABA, opioids, and adenosine in contributing to this predisposition to respiratory inhibition, as manifested by an impaired CO_2 response, in early postnatal life.

Over many years, research also has focused on the localization of chemosensory sites. These studies have revealed that the chemosensitive neural elements of the ventrolateral surface of the medulla play a pivotal role in regulating respiratory activity and ventilatory responses to CO_2 . Although more recent physiologic data demonstrated the presence of chemosensitive sites in regions outside of the ventrolateral aspect of the medulla oblongata, physiologic studies have established primary importance for the ventral medullary chemosensitive regions.

Few detailed maturational studies have focused on changes in the distribution of medullary chemosensory structures that might explain the observed differences in hypercapnic ventilatory responses during development. These issues have been difficult to address because a clearly structured organization of the chemosensory system at the single-cell level has not been defined. Methods used to identify chemosensory neurons, such as the single-cell recording technique, do not allow sampling of a large number of functionally active cells under awake, nonsedated experimental conditions. One method of circumventing these difficulties is to examine hypercapnia-induced expression of encoding transcription factors, such as the *c-fos* gene, a member of the immediate early genes, and its product Fos protein (Fos).

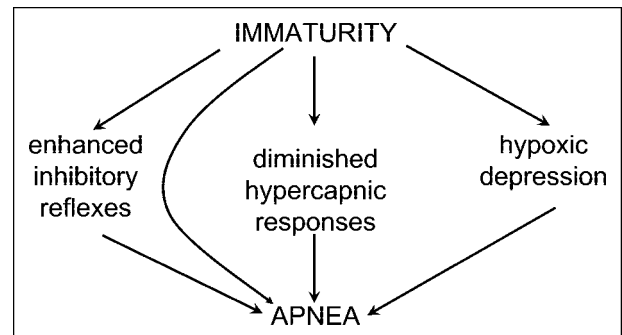


Figure 2. Proposed pathophysiologic mechanisms predisposing or leading to apnea of prematurity.

This technique has been used as a cellular marker to identify activated neurons within the central nervous system (CNS), as during CO_2/H^+ exposure. It has been demonstrated that neurons activated by increases in CO_2/H^+ concentrations appear to be well developed from the first days of postnatal life in maturing rat pups. Therefore, deficiency in the neuronal network for sensing increases in CO_2/H^+ does not appear to play a major role in the decreased CO_2 responses observed during early maturation. However, it is still possible that postnatal maturation may influence the relative importance of discrete chemosensitive sites beyond the ventrolateral medulla, such as the medullary caudal raphé nucleus, which appear to play an important role in the full expression of both phrenic and hypoglossal responses to CO_2 .

There is little available information on the role of second messenger systems in modulating ventilatory patterns and CO_2 responses during early development. Protein kinase C (PKC) appears to be involved in CO_2 -induced *c-fos* mRNA expression in the CNS. Recent data suggest that PKC modulates respiratory timing mechanisms in rats and that the neural substrate mediating respiratory output may be more critically dependent on PKC activity in the immature animal. Future studies should clarify the role of this and other second messenger systems during normal and abnormal respiratory patterning and their roles in modulating the neurotransmitter-mediated pathways described earlier.

It has been assumed for some time that apnea of prematurity is due to immaturity of brainstem centers that regulate breathing and are the major site of central chemosensitivity. This immaturity in breathing regulation is manifested by immaturity in the respiratory responses to hypercapnia and hypoxia and an exaggerated inhibitory response to stimulation of airway (eg, laryngeal) receptors (Fig. 2). Histologically, immaturity of the preterm brain is manifested by a decreased number of

synaptic connections, dendritic arborizations, and poor myelination. Functionally, auditory evoked responses are reported to be longer in infants who have apnea than in matched preterm controls, suggesting a delay in brainstem conduction time. Furthermore, multiple inhibitory neurotransmitters and neuromodulators, including dopamine, adenosine, endorphins, GABA, and prostaglandins, have been implicated in the pathogenesis of disturbances of breathing both at the peripheral and central chemoreceptors, and these substances may be upregulated in early life.

When compared with nonapneic controls, an even greater impairment of the hypercapnic breathing response is seen in preterm infants who have apnea. The CO_2 response in preterm infants who have apnea is shifted to the right and has a lower slope than in unaffected infants. In other words, at the same level of CO_2 , minute ventilation in babies who have apnea is lower. Because the pulmonary mechanics, respiratory frequency, and dead space volume are similar between the two groups, these data strongly suggest a central immaturity of respiratory neural output for the attenuated CO_2 response in preterm babies, particularly in those who have apnea. However, a cause-and-effect relationship between apnea of prematurity and the attenuated response to CO_2 has not been established clearly, and both simply might represent facets of a decreased respiratory drive.

The prominence of mixed apnea has led to comparative analysis of upper airway versus chest wall muscle responses to chemoreceptor stimulation. Upper airway muscles, such as the alae nasi, genioglossus, and posterior cricoarytenoid (laryngeal abductor), typically have their onset and peak of phasic activity prior to corresponding events in the diaphragm. This presumably serves to ensure upper airway patency at peak inspiratory flow. In response to hypercapnic exposure in piglets, there is a relatively linear increase in diaphragm activation. In contrast, genioglossus and alae nasi exhibit a higher threshold, and muscle activity increases at a significantly higher level of CO_2 . It is possible that during hypercapnia (and also during apnea), an initial increase in diaphragm, but not upper airway, activation causes pharyngeal or laryngeal structures to collapse and leads to the obstructed inspiratory efforts that characterize mixed apnea. Furthermore, cooling at chemosensitive sites causes decreased central chemosensitivity that preferentially inhibits neural output to upper airway muscles. In preterm infants, noninvasive measurements have demonstrated that diaphragm activity is low during obstructed inspiratory efforts. However, when apnea resolves, both dia-

phragm and upper airway activities are increased. Therefore, it appears that a decrease in diaphragm activity is common to both central and mixed apnea, and delayed upper airway muscle activation may prolong the episode.

Decreased central chemosensitivity also may contribute to apnea by modulation of inhibitory reflexes arising from laryngeal afferents. Laryngeal stimulation is a well-documented trigger for reflex apnea, which serves to protect the lungs from aspiration. This response is most prominent during the neonatal period, and while it is assumed to be an essential protective reflex, an exaggerated response has been implicated as a cause for apnea of prematurity. The mechanism responsible for the greater sensitivity of the respiratory system to the inhibitory effects of laryngeal stimulation early in development is not clear, although maturational changes in central chemosensitivity might contribute to postnatal alterations in the strength of this potent inhibitory reflex.

Responses to Hypoxia

A decrease in arterial PO_2 and oxygen saturation is the typical response to apnea in preterm infants, although the extent of that fall varies. Presumably the decrease in oxygenation is related directly to the duration of apnea and the initial level of PaO_2 . The decrease in oxygenation is reportedly greater in obstructive than in central apnea. The bradycardia that accompanies apnea and resultant desaturation has been attributed to hypoxic stimulation of the carotid body chemoreceptors, especially in the absence of lung inflation (Fig. 3). With more severe bradycardia, both systolic and diastolic blood pressures may fall, and this has been associated with a decline in cerebral blood flow velocity. Therefore, in infants who have inadequate cerebrovascular autoregulation, cerebral perfusion may decrease to very low levels during prolonged apnea and potentially could exacerbate hypoxic-ischemic brain injury in susceptible preterm infants.

The rise in PaO_2 (from the mid 20s) at birth effectively silences the peripheral chemoreceptors, the major source of afferents that leads to hypoxic stimulation of breathing. The precise timing of this resetting differs between species. The hypoxic ventilatory response after birth has been well characterized, especially in preterm infants. During exposure to hypoxia, neonates exhibit a biphasic ventilatory response that consists of an initial increase in ventilation that lasts 1 to 2 minutes, followed by a decline in breathing, often to below baseline ventilation. This late decline traditionally has been termed hypoxic ventilatory depression. The initial increase in ventilation is believed to be due to stimulation of peripheral chemoreceptors, primarily in the carotid body. In preterm human

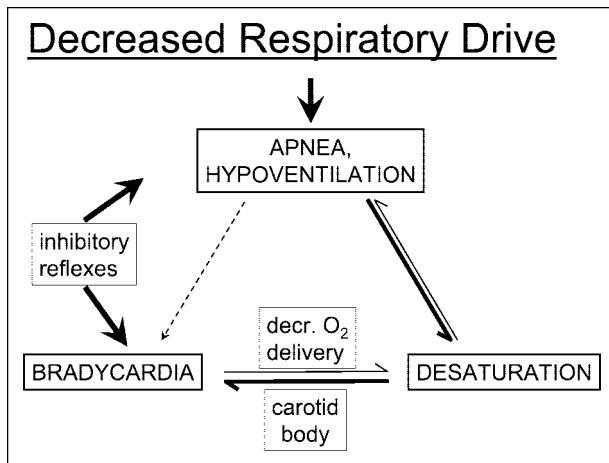


Figure 3. Proposed physiologic mechanisms whereby apnea induces reflex bradycardia. This may be due to hypoxemia in the absence of lung inflation or via stimulation of upper airway inhibitory afferents. Reprinted with permission from Martin RJ, Fanaroff AA. Neonatal apnea, bradycardia or desaturation: does it matter? *J Pediatr.* 1998;132:758.

infants, the late decrease in ventilation is due to a decrease in respiratory frequency, with the tidal volume remaining relatively sustained. The origin of the late depression is not well understood, but it may persist for several weeks postnatally in preterm infants. In the fetal environment where levels of PO_2 are in the 20s and gas exchange occurs at the placenta, hypoxic respiratory depression may be physiologic because continuous breathing is not necessary. However, when pulmonary ventilation must be continuous postnatally, this response may present a problem.

Several theories have been postulated to explain hypoxic ventilatory depression, including a decrease in $Paco_2$ following the initial hyperventilation and accompanying decrease in cerebral blood flow, a decrease in metabolism, and hypoxia-mediated central depression of ventilation. Exposure to a combination of CO_2 and hypoxia does not prevent the late respiratory depression, suggesting that a decrease in $Paco_2$ is not the origin of this hypoxic depression. Multiple neurotransmitters have been implicated as mediators for hypoxic depression, including adenosine, endorphins, and GABA. The use of blockers for these neurotransmitters, such as methylxanthines for adenosine, naloxone for endorphins, and bicuculline for GABA, successfully prevents the late hypoxic depression and causes a sustained ventilatory response. Furthermore, the depressive response to hypoxia is diminished by experimental lesions in the upper brainstem

and midbrain of fetal lambs, which implicates the presence of descending inhibitory tracts that contribute to hypoxic ventilatory depression. Consistent with these findings is the observation that a progressive decrease in inspired oxygen concentration causes a significant flattening of CO_2 responsiveness in preterm infants.

Hypoxic ventilatory depression has been implicated as underlying apnea of prematurity. However, hypoxia does not appear to precede episodes of apnea and, in most occasions, the infants have a normal PaO_2 prior to the occurrence of apnea. Although supplemental oxygen can prevent periodic breathing, it has no role for treating apnea of prematurity in the absence of baseline hypoxemia. Furthermore, hypoxic ventilatory depression persists in healthy preterm infants at the time of hospital discharge (around 33 to 36 weeks' postconceptional age), at a time where there may not be clinically significant apnea. Although the role of the biphasic ventilatory response to hypoxia in the genesis of neonatal apnea is unclear, once hypoxia occurs, it appears to aggravate apnea and result in delayed recovery of the infant.

Responses to Stimulation of Upper Airway Afferents

Stimulation of the laryngeal mucosa, either chemically (by water, ammonium chloride, or acidic solutions) or mechanically, causes inhibition of breathing and apnea in humans and animals. This reflex-induced apnea is mediated through the superior laryngeal nerve. Bilateral sectioning of the superior laryngeal nerve abolishes laryngeal stimulation-induced apnea. The reflex apnea has been shown to be associated with contraction of the thyroarytenoid muscle, causing closure of the glottis and swallowing movements, which signify active stimulation of expiratory-related brainstem centers.

There appears to be a maturational change in reflex-induced apnea. Chemical stimulation of the larynx in newborn piglets causes respiratory arrest, which is not seen in older piglets. Preterm infants have an exaggerated inhibitory reflex, and they develop prolonged apnea in response to instillation of saline in the oropharynx. The precise mechanisms underlying the maturational change in reflex-induced apnea are not known, but they do not seem to be related to either changes in laryngeal receptors, changes in central synaptic connections, or maturation of the carotid body. It has been shown that hypercapnia increases and hypocapnia decreases the threshold for superior laryngeal nerve stimulation-induced apnea. Cooling of the ventromedullary surface, a technique used to decrease central chemosensitivity by inhibiting synaptic transmission at this site, decreases the threshold

for laryngeal stimulation-induced apnea. Theophylline, which stimulates respiratory neural output, blocks laryngeal-induced apnea. It seems, therefore, that the exaggerated reflex-induced apnea seen in newborn infants and animals is related to decreased central neural output or a dominance of inhibitory pathways. Furthermore, blocking GABA_A receptors results in complete abolition of superior laryngeal nerve stimulation-induced apnea in piglets. Nonetheless, the role of laryngeal reflex-induced apnea as an underlying mechanism for apnea of prematurity is uncertain.

Conclusion

A clear understanding of the rationale for therapy of neonatal apnea (as described in the accompanying article in this issue) is greatly enhanced by an appreciation of the underlying pathophysiologic mechanisms. It is now well recognized that upper airway patency is essential for maintaining ventilatory stability in preterm infants. Nonetheless, the major problem in these infants appears to be in their ability to translate sensory afferent input into a sustained excitatory ventilatory response. Current studies focusing on changes in the neurochemical bal-

ance of respiratory-related neurons and resultant signaling pathways should offer greater insight into the mechanisms underlying this troublesome clinical problem.

Suggested Reading

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NeoReviews Quiz

1. Neonatal apnea is defined as cessation of respiration for 15 seconds or longer, typically accompanied by desaturation and bradycardia. Of the following, the *most* accurate statement regarding neonatal apnea is that:
 - A. Central apnea is the most common type of neonatal apnea.
 - B. Neonatal apnea is positively related to gestational age.
 - C. Onset of apnea is accelerated in the presence of lung disease.
 - D. Swallowing movements typically are observed during neonatal apnea.
 - E. The site of obstruction in obstructive apnea is mostly the larynx.
2. Ventilatory maturation begins in fetal life in preparation for spontaneous and sustained respiration after birth. Of the following, the *most* accurate statement regarding ventilatory maturation is that:
 - A. Carotid body chemoreceptors are essential for intrauterine breathing.
 - B. Chemosensitive neural elements for control of respiration are located on the ventrolateral surface of the medulla.
 - C. Deficiency of the neuronal network is the cause of decreased carbon dioxide response during early maturation.
 - D. Neurally mediated respiratory output is independent of protein kinase C activity in the immature animal.
 - E. Preterm infants respond to carbon dioxide by increasing respiratory frequency rather than tidal volume.
3. Preterm neonates exhibit a biphasic ventilatory response to hypoxia. The first phase consists of an increase in ventilation, which is followed by the second phase of ventilatory depression. The latter is influenced by inhibitory neurotransmitters, which can be blocked by specific drugs. Of the following, the neurotransmitter blocker bicuculline is *most* effective against:
 - A. Adenosine.
 - B. Dopamine.
 - C. Endorphin.
 - D. Gamma-aminobutyric acid.
 - E. Prostaglandin.
4. Which of the following features of neonatal respiratory control is *most* likely to contribute to apnea of prematurity?
 - A. Unchanged ventilatory response to CO₂.
 - B. Hypoxic respiratory depression.
 - C. Diminished laryngeal inhibitory reflexes.
 - D. Increased protein kinase C activity in the central nervous system.
 - E. Enhanced diaphragm activity.
5. Which of the following features is *most* characteristic of mixed apnea?
 - A. Usually preceded by gastroesophageal reflux.
 - B. Usually associated with neck flexion.
 - C. Most commonly observed during assisted ventilation.
 - D. Not relieved by xanthine therapy.
 - E. Typically associated with obstruction of inspiratory efforts at the pharyngeal or laryngeal airway.
6. Which of the following statements concerning immature ventilatory responses to CO₂ is correct?
 - A. Fetal breathing is not responsive to hypercapnia.
 - B. Hypoxia depresses neonatal hypercapnic responses.
 - C. Hyperoxia depresses neonatal hypercapnic responses.
 - D. Central chemosensitive cells are absent in the fetus.
 - E. Peripheral chemoreceptors are the dominant site for neonatal hypercapnic response.

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