Control of Breathing and Apnea of Prematurity

Ruben E. Alvaro, MD*

*Departments of Pediatrics, Physiology, and Reproductive Medicine, University of Manitoba-Winnipeg, Manitoba, Canada

Education Gaps

1. The short- and long-term morbidities associated with apnea of prematurity continue to be a clinical concern.
2. Optimizing therapeutic approaches to apnea of prematurity depend on understanding the pathophysiologic mechanisms of the condition.

Abstract

Apnea of prematurity is a significant clinical problem manifested by an unstable respiratory pattern leading to bradycardia and hypoxemia. Most of these apneas are idiopathic and represent a physiologic manifestation of an immature control of breathing and adaptation to extrauterine life. In extremely preterm infants, this unstable breathing pattern superimposed on an immature lung that is injured by inflammation and infection may lead to frequent and profound episodes of intermittent hypoxemia. These cardiorespiratory events during early postnatal life may be associated with both short- and long-term morbidity. In this review the author discusses the most important pathophysiologic mechanisms responsible for periodic breathing and apnea in preterm infants, as well as the diagnostic assessment and therapeutic interventions that help to stabilize breathing in this unique population.

Objectives

After completing this article, readers should be able to:

1. Describe the pathophysiologic mechanisms underlying periodic breathing and apnea of prematurity.
2. Understand the role of the peripheral chemoreceptors and the carbon dioxide apneic threshold in the pathogenesis of apnea and periodic breathing.
3. Understand the negative effect of inflammation and infection on respiratory development, which contributes to worsening apnea and aggravation of intermittent hypoxemic events in extremely preterm infants.
4. Describe the most important therapeutic approaches to apnea of prematurity.

AUTHOR DISCLOSURE

Dr Alvaro has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂</td>
<td>carbon dioxide</td>
</tr>
<tr>
<td>CPAP</td>
<td>continuous positive airway pressure</td>
</tr>
<tr>
<td>FRC</td>
<td>functional residual capacity</td>
</tr>
<tr>
<td>LCR</td>
<td>laryngeal chemoreflex</td>
</tr>
<tr>
<td>NIPPV</td>
<td>nasal intermittent positive pressure ventilation</td>
</tr>
<tr>
<td>REM</td>
<td>rapid eye movement</td>
</tr>
<tr>
<td>SpO₂</td>
<td>pulse oximetry</td>
</tr>
</tbody>
</table>
INTRODUCTION

Apnea of prematurity is one of the most common diagnoses in neonatology and has become one of the most important clinical problems in the NICU. This type of apnea should not be considered a pathologic state but rather a physiologic manifestation of an unstable breathing pattern, which reflects the immaturity of the control of breathing and adaptation to extrauterine life.

The prevalence of apnea increases exponentially with decreasing gestational age and is present in almost 100% of infants with less than 29 weeks of gestation. (1)(2) From a physiologic point of view, it is not the apnea but its effect on oxygenation and heart rate that alter the well-being of the patient. Recent studies have shown an association between apnea and intermittent hypoxia with short- and long-term consequences such as retinopathy of prematurity, bronchopulmonary dysplasia, and neurologic disabilities. (3)(4)(5) This article will present a review of respiratory control with an emphasis on apnea of prematurity. The physiologic disorders of the control of breathing, which predispose infants to apnea, as well as the most relevant aspects of the treatment necessary for these patients will be identified.

DEFINITION

Apnea is the cessation of respiratory air flow. It is considered pathologic if it is prolonged (>20 seconds) or if it is associated with bradycardia, cyanosis, pallor, or hypotonia. (1)(2) However, what best defines apnea is not the duration of the respiratory pause but the physiologic consequences that result from that pause, such as the severity of bradycardia and hypoxemia. For example, very low-birthweight infants usually develop significant bradycardia and hypoxemia after respiratory pauses of less than 10 seconds in duration. The term “apnea of infancy” refers generally to pathologic apneas that begin in newborns of more than 37 weeks of gestational age. The term “apnea of prematurity” is reserved for apnea that occurs in preterm infants and which are usually resolved at 37 weeks of gestation. (2)

Periodic breathing is another form of central apnea characterized by ventilatory cycles of 10 to 15 seconds, with pauses of 5 to 10 seconds that are commonly observed in preterm infants and in adults traveling to high altitudes. Its physiopathogenic root could be the same as that of apnea, which would be a more advanced step in the basic disturbance that induces periodic breathing. The cyclic changes in respiratory rate and tidal volume observed during periodic breathing are partly due to the instability of the respiratory center, which in a more advanced degree would appear as apnea. (6) In support of this idea, several studies have shown that prolonged apneas (>20 seconds) associated with bradycardia and hypoxemia are not isolated events but are usually preceded by other short-lived apneas and by decreases in respiratory frequency and minute ventilation. (6)(7) The fact that the incidence of periodic breathing and apnea decreases with postnatal age, with the administration of methylxanthines and with an increase in oxygenation, supports this hypothesis. In patients with inadequate functional residual capacity (FRC), periodic breathing may be accompanied by significant oxygen desaturations which, if they persist, may result in the so-called intermittent chronic hypoxia.

CLASSIFICATION

Traditionally, apneas have been classified as central, obstructive, or mixed, depending on the presence of respiratory efforts and upper airway obstruction (Fig 1). These differences have become less clear with the evidence that central apneas can occur with airway obstruction (silent obstruction). Central apneas are characterized by lack of respiratory efforts, measured by the diaphragmatic activity or by chest or abdominal movements. Obstructive apneas are characterized by absent respiratory flow, measured usually at the nasal level, but with respiratory efforts present throughout the pause. These apneas are rare, usually short (<10 seconds) and occur generally before or after generalized body movements. Longer obstructive apneas are usually observed in newborn infants with Pierre-Robin syndrome (mandibular hypoplasia), in neonates with bronchopulmonary dysplasia, and in those with severe neurologic problems such as intracranial bleeding, hydrocephalus, and severe asphyxia. Mixed apneas are the most common type and are characterized by a central and obstructive component. These apneas may go undetected with thoracic impedance monitors and be detected only by the presence of bradycardia or hypoxemia. Because most mixed apneas begin with a central component and are followed by airway obstruction, their frequency progressively increases with the duration of apnea (Fig 2). (7)

PATHOGENESIS

Most premature infants have the basic tools to breathe spontaneously and with relative continuity. However, significant disadvantages, such as the immaturity of respiratory control, inability to maintain adequate FRC due to the high distensibility of the rib cage, propensity to airway obstruction, and difficulties in coordinating respiration with suction and swallowing, predispose premature infants to breathe irregularly, periodically, and with frequent apneas.
Periodic breathing and apnea are clearly a disorder of the control of breathing but the precise mechanisms are not very clear. In premature infants, the negative feedback system that controls respiration is affected by the anatomic and physiologic immaturity that affects many levels of the respiratory control system including the central and peripheral chemoreceptors. The most important factors that contribute to this type of breathing are the following.

**Immaturity of the Respiratory Control**

**The Role of the Decreased Activity of the Central Respiratory Chemoreceptors.** These receptors, mostly responsible for the hypercapnic ventilatory response, are considered the most important chemoreceptors that modulate breathing and promote regular and continuous respiration. The activity of these chemoreceptors is measured by the ventilatory response to carbon dioxide (CO₂). This response to CO₂ is expressed as the change in minute ventilation with the changes in alveolar CO₂. Preterm infants have a decreased response to CO₂ and therefore increased ventilation is not triggered until higher levels of CO₂ are achieved. This response increases with gestational age and postnatal age likely related to the maturation of the central nervous system.\(^{(6)(7)(8)(9)}\) One of the most fascinating findings in preterm infants compared to adults is the opposite response to CO₂ with different concentrations of oxygen. In adults, the lower the concentration of inspired oxygen, the greater is the response to CO₂. On the contrary, in preterm infants, the lower the concentration of inspired oxygen, the more depressed or flat is the response to CO₂ (Fig 3). It is very likely that this paradoxical response is related to the known depressant effect of hypoxia on the central chemoreceptors observed only in premature infants as described later in this article.\(^{(6)(7)(8)(9)(10)}\)

The ventilatory response to hypoxia is expressed as the percentage change in minute ventilation with the change in the arterial or alveolar PO₂. This response is also unique in preterm infants and is characterized by a classic biphasic curve with an immediate increase in ventilation lasting 1 to 2 minutes followed by a decrease in ventilation below baseline levels at 5 minutes of hypoxia, often transforming the breathing pattern into apneas.

![Figure 1. Examples of types of apnea diagnosed with the traditional method. Apnea is termed central when respiratory efforts are absent, obstructive when respiratory efforts are present continuously, and mixed when elements of both are seen. ECG=electrocardiography.](http://neoreviews.aappublications.org/)
into irregular and periodic. (7) The immediate increase in ventilation is similar to the one observed in adults and is attributed to the stimulation of peripheral chemoreceptors by hypoxemia. The mechanism responsible for the late ventilatory depression is still unclear, but it is likely related to central release of inhibitory neuromodulators in response to hypoxia. (11) Very low-birthweight infants show only a sustained decrease in ventilation in response to inhaled low oxygen (Fig 4). Although the exact relationship between the respiratory depression with hypoxia and neonatal apnea is not fully understood, it is likely a significant factor in the occurrence of periodic breathing and delayed recovery after apnea.

The Role of the Increased Activity of the Peripheral Chemoreceptors. The most important peripheral chemoreceptors that modulate breathing are located in the carotid bodies at the bifurcation of the common carotid arteries. These chemoreceptors respond to rapid decreases in arterial PO$_2$ and pH and increases in arterial PCO$_2$ and are mostly responsible for transient changes of these variables. The relationship between the arterial PO$_2$ and the firing rate of the peripheral chemoreceptors is nonlinear with very little response until the arterial PO$_2$ is reduced below 100 mm Hg when the rate increases exponentially. Hypoxia promotes respiratory instability by moving the response of these chemoreceptors to the steep part of the curve where small changes in arterial PO$_2$ and PCO$_2$ produce large changes in ventilation, leading to unstable respiration. (7)(8)(9) Al-Matary et al showed that the activity of peripheral chemoreceptors is much higher in the newborn than in the adult and in neonates who breathe periodically compared with those who breathe continuously. (12) This increase in the activity of peripheral chemoreceptors is because arterial PO$_2$ is lower in this group of newborns. These findings support the hypothesis that the drive to breathe early in life depends on increased peripheral chemoreceptor activity, and that this heightened peripheral chemoreceptor activity may play a role in disturbing the respiratory control system, leading to periodic breathing and apnea. The fact that small increases in oxygenation significantly decrease periodic breathing and apnea supports the notion that hypoxemia is a crucial factor in the mechanism responsible for apnea of prematurity.

The Role of the PCO$_2$ Apneic Threshold. The PCO$_2$ apneic threshold is the minimal PCO$_2$ level required to sustain breathing. When the CO$_2$ decreases below this minimal level, breathing stops. This notion of a CO$_2$ apneic threshold is crucial to our understanding of periodic breathing and apnea in humans. Recent publications have suggested that the closer the eupneic PCO$_2$ is to the threshold PCO$_2$, the more prone the patient is to instability of breathing. (13) Khan et al showed that the average CO$_2$ apneic threshold in preterm infants is only 1.5 mm Hg lower than the actual or baseline PCO$_2$, whereas in adults it is ~5 mm Hg lower. (14) This narrow difference between eupneic and apneic PCO$_2$ in neonates is likely related to a low baseline PCO$_2$ because of a decrease in metabolism triggered by hypoxemia. Thus, the great variability in tidal volume with major oscillations in PCO$_2$ under normal circumstances, together with the closeness of the CO$_2$ apneic threshold to the baseline CO$_2$, likely contributes to the high prevalence of periodic breathing in infants compared with adults (Fig 5) (6)(7)(8)(9).

Pulmonary Mechanics

The FRC is important to maintain oxygenation and decrease the degree of oxygen desaturation during brief periods of apnea. Preterm infants are particularly prone to an inadequate expiratory lung volume because of their highly compliant chest wall, which lead to closure of the distal airway, potentially leading to intrapulmonary shunting. (15) To compensate for this disadvantage, preterm infants use compensatory mechanisms such as expiratory braking, shortening of expiratory time, and sighing to try to maintain lung volume. These mechanisms are mediated through the inflation and deflation vagal reflexes (Hering-Breuer reflexes).

Activation of intercostal muscles contributes to chest wall stability and maintenance of FRC. However, these muscles are tonically inhibited during rapid eye movement (REM) sleep which is problematic because premature infants spend more than 50% in this sleep state. (6)(11) The disappearance of tone in the intercostal muscles has been suggested as a major factor responsible for the increased...
chest distortion and chest wall collapse seen on inspiration during REM sleep in infants, which leads to decreased FRC.

**Upper Airway and Pulmonary Reflexes**

The laryngeal chemoreflexes (LCRs) comprise a group of reflexes triggered by the contact between liquids and receptors of the laryngeal mucosa. Stimulation of the laryngeal mucosa in premature infants, either chemically or mechanically, can lead to apnea, bradycardia, and oxygen desaturation. This reflex-induced apnea is mediated through superior laryngeal nerve afferents. Immature LCRs, characterized by an exaggerated inhibitory cardiorespiratory response, are mainly observed in preterm infants or in conditions in which upper airway inflammation is present.

![Figure 4](https://example.com/figure4.png)

**Figure 4.** Changes in ventilatory variables in response to 15% oxygen in preterm infants of less than or equal to 1,500 g. Left, sustained decrease in ventilation occurred in both sleep states, mainly due to a decrease in frequency. Right, percentages of change show that ventilation decreased significantly more during REM sleep than in quiet sleep as a result of a lack of increase in tidal volume. Values are mean ± SEM; *, P ≤ .05 compared with controls; †, P ≤ .05 between sleep states. (Reprinted with permission from Alvaro R, Alvarez J, Kwiatkowski K, Cates D, Rigatto H. Small preterm infants (less than or equal to 1500 g) have only a sustained decrease in ventilation in response to hypoxia. Pediatr Res. 1992;32:403–406.)
With maturation, the duration and severity of apneas secondary to LCRs decrease. This is in part related to decreased stimulation of the LCR because of improved coordination of upper airway muscles and the increase in the excitatory respiratory-related neurons within the respiratory network that counterbalance the inhibitory afferent input from the LCR.

Inflation of the lungs is associated with a decrease in inspiratory time and prolongation of expiratory time mediated through stimulation of vagal receptors (Hering-Breuer inflation reflex). This reflex is much more active in the newborn period than in adult life when small increases in lung volume can cause apnea. (6)(7)(9)(11) Reduction in lung volume can activate the Hering-Breuer deflation reflex. This reflex shortens expiration and prolongs inspiration. This reflex is less active in premature infants and can cause inhibition of breathing and short apneas when stimulated.

Spontaneous distortion of the thoracic cage, which occurs most commonly in premature infants during REM sleep, may trigger diaphragmatic inhibition through the intercostal inhibitory reflex and may contribute to the onset of periodic breathing and apnea. (6)(7)(9)(11) The immaturity of other reflexes, such as those associated with obstruction of the airway (gamma system), aspiration of endotracheal tube (irritant reflexes), and pulmonary congestion from a significant left to right shunt through the ductus arteriosus (J receptors), could also contribute to some type of apnea in preterm infants.

**Sleep State**

We now know that sleep modulates breathing and predisposes patients to apnea. We also know that most apneas occur during REM sleep, which is usually accompanied by irregular breathing in terms of the frequency and amplitude of the tidal volume. (6)(11) The effects of sleep on breathing in preterm infants are many. REM sleep increases the incidence of periodic breathing and apnea, decreases the ventilatory response to CO₂, enhances the late decrease in ventilation with hypoxia, increases the rate of sighs, increases chest distortion leading to muscle fatigue and increased oxygen consumption, inhibits pulmonary reflexes, and decreases upper airway tone and postinspiratory activity of the diaphragm leading to partial lung collapse during expiration. (6) These changes will no doubt affect newborns much more because they spend 80% of time sleeping compared with adults who spend only 30% of time sleeping, with a higher percentage of this sleep in the REM state.

**Infection and Inflammation**

Recent evidence suggests that infection and inflammation may play a crucial role in the pathogenesis of apnea of prematurity. (1)(5) The progressive inflammation observed in the lungs of preterm infants secondary to intra- and extrauterine infection and the oxidative stress caused by oxygen exposure and mechanical ventilation leads to respiratory morbidity. This negative effect of infection and
inflammation on respiratory development would contribute to a worsening apnea of prematurity and aggravation of the intermittent chronic hypoxic episodes observed during periodic breathing and apnea. This local and systemic inflammation, in turn, could have short- and long-term effects by increasing the expression of inflammatory mediators in the central and peripheral nervous system, modifying the structure and function of chemoreceptors. This effect on the already immature respiratory neural control system may destabilize breathing and cause apnea and chronic intermittent hypoxic events. This intermittent hypoxia and its recovery to normoxia or hyperoxia may also increase oxidative stress and predispose the infant to a proinflammatory cascade that may further inhibit central respiratory neural output and aggravate the problem. These chronic intermittent hypoxic events not only increase respiratory instability, but also alter growth and cardiovascular regulation, and increase the risk for retinopathy of prematurity and neurologic disability. (1)(3)(4)(5)(16)(17)(18)

**DIAGNOSIS**

The high incidence of apneas in preterm infants makes cardiorespiratory monitoring mandatory in children younger than 35 weeks of gestation and in all high-risk infants. Most neonatal units use a combination of respiratory impedance, heart rate, and pulse oximeter monitors. Although respiratory impedance monitors do not detect obstructive apneas, heart rate and oxygenation monitors generally detect bradycardia and decreased oxygenation associated with such apneas. For the accurate diagnosis of airway obstruction, more sophisticated monitoring such as pneumotacography, nasal thermistors, plethysmography, and CO2 expiratory pressure monitors are needed but rarely used in daily practice. The sudden increase in the number or severity of apneas in preterm or term infants should be investigated to rule out other clinical problems associated with apneas. Continuous pulse oximetry (SpO2) measured by new generation high-resolution pulse oximeters with target oxygen ranges is a very important monitoring tool to assess the degree of intermittent hypoxic events associated with periodic breathing and apnea. Frequent assessment of SpO2 measurements, including the percentage of time infants spend within their desired target oxygen saturation range and the number of prolonged hypoxic events could be an important and valuable strategy to adapt and reflect the intensity of therapeutic interventions and improve neonatal outcomes.

**TREATMENT**

**General**

The integral management of apneas in preterm infants involves the diagnosis and correction of secondary causes before making a conclusive diagnosis of apnea of prematurity. The decision to start medical treatment should be based not only on the frequency and duration of events but also on the severity of the apnea measured by the degree of bradycardia, hypoxemia, and the intensity of the stimulation necessary to end the apnea. In general, the lower the gestational age, the more aggressive the treatment should be.

In very low-birthweight infants, the temperature should be maintained at the minimum level of the neutral thermal environment (97.7°F–98.2°F [36.5°C–36.8°C]). Although the ideal position to reduce apneas is somewhat controversial, in this author’s institution, the prone position is recommended, with the head-elevated tilt position about 30 to 45 degrees in a nestlike environment. This would improve lung function by stabilizing the chest wall and respiration, facilitating thermoregulation, reducing gastroesophageal reflux, and stabilizing the autonomic nervous system. (1)(2)(9)(10)(11)(18)(19) Although no studies have been conducted to evaluate the benefits or damage of increased inhaled oxygen concentration, it is important to keep these premature infants well oxygenated, avoiding hyperoxemia. At this author’s institution, oxygen saturation is maintained between 88% and 92%. Higher range (90%–94%) may be considered in infants of more than 32 weeks’ postmenstrual age with frequent episodes of intermittent desaturation.

**Medical**

**Methylxanthines.** Since the first report in by Kuzemko and Paala in 1973, several studies have confirmed the efficacy of methylxanthines in decreasing the frequency of apneas and the use of mechanical ventilation in preterm infants. (20) The main mechanism of action of methylxanthines is through a competitive antagonism of adenosine, a potent inhibitor of respiration. Methylxanthines increase ventilation, improve CO2 sensitivity, decrease hypoxic depression, and increase diaphragmatic activity. (1)(2)(9)(10)(11)(17)(19)(21) The undesirable effects of xanthines include tachycardia, cardiac arrhythmias, feeding intolerance, increased basal metabolism and oxygen consumption, irritability, and much less frequently, convulsions.

The most commonly used xanthines are theophylline and caffeine. Although the efficacy is similar, caffeine citrate is preferred because of its longer half-life, greater therapeutic margin, fewer undesirable effects, fewer daily doses, and a lack of need for plasma level control. The largest study of
caffeine in preterm infants of less than 1,250 g showed that caffeine not only decreases the incidence of bronchopulmonary dysplasia, but also increases survival without neurologic disability. (22)(23) This study used a loading dose of 20 mg/kg of caffeine citrate followed by maintenance doses of 5 to 10 mg/kg per day. Caffeine can be administered intravenously or orally and the dosage is similar for both. In the case of theophylline, the loading dose is 5 to 6 mg/kg per day, with a maintenance dose of about 2 to 4 mg/kg per day divided every 8 to 12 hours depending on the gestational age. Although the optimal time to start caffeine in patients at risk for apnea is not known, it is recommended to start as soon as possible in patients of less than 28 weeks’ gestational age especially if they are receiving mechanical ventilation. Because of the prolonged half-life, the patient should be observed for a period of no less than 5 to 7 days after cessation of caffeine and before discharge. A recent randomized controlled study showed that the use of caffeine in small preterm infants after 34 weeks’ postconceptional age decreases the frequency and intensity of intermittent hypoxic episodes. (24)

Nasal Continuous Positive Airway Pressure. Nasal continuous positive airway pressure (CPAP) used in conjunction with xanthines has been shown to be very effective in reducing the frequency and severity of apnea of prematurity. The most important effects are related to improvement in lung volume and FRC and consequently in oxygenation. Nasal CPAP mainly decreases mixed and obstructive apneas by keeping the airway open and stabilizing the thoracic cage. (1)(2)(9)(10)(17)(19)(21) Low pressures of 4 to 6 cm H$_2$O are generally effective in suppressing apneas. Pressures greater than 6 cm H$_2$O are more effective only in cases of residual pulmonary disease or in cases of laryngotracheomalacia. In young preterm infants, high levels of pressure may increase work of breathing and lead to muscle fatigue.

Recent technologic advances have allowed the synchronized or nonsynchronized use of nasal intermittent positive pressure ventilation (NIPPV), and nasal CPAP with variable flow. NIPPV would decrease the closure of the upper airway and stimulate the respiratory center through an intermittent increase in pressure at the pharyngeal level. (2)(17)(19) Several randomized trials are under way to test the effectiveness and safety of these new techniques for the treatment of apnea of prematurity. The use of high-flow nasal cannula therapy is increasingly used as a convenient, more portable alternative to CPAP delivery devices. Some questions remain about the safety and efficacy of devices that provide relatively unregulated high flow as a means of CPAP delivery.

Mechanical Ventilation. When severe apnea persists despite the aforementioned treatments, intubation and mechanical ventilation are the last resort. Minimal ventilation parameters should be used, which allow spontaneous breathing and minimize the risk for lung damage. At this author’s institution, the use of assisted control volume guaranteed ventilators is preferred, which have short inspiratory times and a level of positive end-expiratory pressure according to pulmonary pathology. The duration of mechanical ventilation depends on the cause of the apneas but in general it is for short periods.

Treatments not Recommended or not Properly Studied
Although gastroesophageal reflux is able to produce apnea through stimulation of laryngeal chemoreceptors, several studies have clearly demonstrated that treatment for gastroesophageal reflux with antacids or gastrointestinal motile stimulants are not only ineffective for the treatment of apnea of prematurity but also could be associated with important undesirable effects such as necrotizing enterocolitis, sepsis, and death. (1)(2)(17)(19) Several studies have shown that doxapram, used in continuous intravenous infusion, may decrease the incidence of refractory apneas to xanthines and the need for intubation. Their action would be mediated through the stimulation of central and peripheral chemoreceptors. Because of the limited number of studies and the level of evidence, coupled with its important side effects such as seizures, arterial hypertension, arrhythmias, gastrointestinal disorders, and a possible worse neurologic development in the long term, doxapram is not currently recommended for the treatment of apnea of prematurity. Mechanosensory stimulation using acoustic mattresses may reduce the incidence of apnea and oxygen desaturation. More studies are needed to corroborate its use at the clinical level. The effect of blood transfusions on apnea of prematurity is controversial. Although recent studies have shown an improvement in the number of apneas after transfusion, the effect is minimal and transient. Currently, there is no information to suggest that blood transfusion offers long-term benefits (1)(2)(17)(19)

SUMMARY
Apnea is one of the most important clinical problems in NICU, especially nowadays when smaller preterm infants survive and undergo extubation early with the use of surfactant. Most apneas are idiopathic and represent a physiologic manifestation of an unstable breathing pattern that reflects the immaturity of the control of breathing and adaptation to extrauterine life that improves with gestational age. The low level of oxygenation in preterm infants leads to inhibition of central chemoreceptor activity, increased activity of peripheral chemoreceptors, and a narrow difference between the
eupneic and apneic CO₂ that predisposes infants to periodic breathing and apnea. Chronic episodes of intermittent hypoxia associated with these apneas and periodic breathing may further increase the expression of inflammatory mediators in the central nervous system. This effect produces increased respiratory instability and also altered growth and cardiovascular regulation, and increases the risks of retinopathy of prematurity and neurologic disability. Medical treatment with respiratory stimulants and the use of nasal CPAP are generally effective and should always be combined with an optimal general supportive treatment.

**References**

1. A 26-week gestational age infant is now 3 weeks old in the NICU and is having occasional episodes of apnea and bradycardia. Immaturity of respiratory control plays an important role in the pathogenesis of apnea of prematurity. Which of the following statements regarding control of breathing in preterm infants is true?
   A. Unlike in adults, hypoxia results in an immediate decrease in ventilation characterized by irregular and periodic breathing.
   B. Peripheral respiratory chemoreceptors are considered the most important chemoreceptors that modulate breathing and promote regular and continuous respiration.
   C. The lower the concentration of inspired oxygen, the greater is the response to carbon dioxide (CO₂).
   D. Preterm infants have a decreased response to CO₂ and therefore increased ventilation is not triggered until the levels of CO₂ are higher.
   E. Peripheral chemoreceptors respond to rapid increases in arterial Po₂ and pH and decreases in arterial Pco₂.

2. A 24-week gestational age infant is now 2 weeks old and receiving maintenance nasal cannula oxygen. He has intermittent episodes of apnea and bradycardia. These episodes typically resolve spontaneously, but occasionally require stimulation or increased oxygen. It is recognized that upper airway and pulmonary reflexes play an important role in the pathophysiology of apnea of prematurity. Which of the following mechanisms is inhibited during rapid eye movement (REM) sleep and may contribute to chest wall collapse during REM sleep in preterm infants?
   A. Expiratory braking.
   B. Shortening of expiratory time.
   C. Activation of intercostal muscles.
   D. Decrease in effective time constant.

3. A 26-week gestational age male infant has been transitioned to respiratory support by nasal cannula oxygen. He has intermittent episodes of apnea and bradycardia. These episodes typically resolve spontaneously, but occasionally require stimulation or increased oxygen. Which of the following statements regarding these reflexes is correct?
   A. Immature LCRs are characterized by a lack of inhibitory cardiorespiratory responses.
   B. The Hering-Breuer inflation reflex is a unique feature of preterm physiology and is triggered by apnea and bradycardia, leading to lung collapse.
   C. The lower the concentration of inspired oxygen, the greater is the response to carbon dioxide (CO₂).
   D. Reduction in lung volume can activate the Hering-Breuer deflation reflex, which shortens expiration and prolongs inspiration. This reflex is less active in premature infants.
   E. Distortion of the thoracic cage, which occurs most commonly in premature infants during awake activity, triggers cycles of tachypnea and apnea through the intercostal inhibitory reflex.

4. An infant born at 25 weeks’ gestational age is now at a corrected age of 28 weeks, and is in the NICU receiving continuous monitoring. She is noted to have apneic episodes, particularly during sleep. Sleep has been shown to modulate breathing and predispose premature infants to apnea, with most apnea events occurring during REM sleep. Which of the following statements regarding the effects of REM sleep on apnea is correct?
A. REM sleep is associated with a heightened state of pulmonary reflexes.
B. REM sleep decreases the incidence of periodic breathing.
C. REM sleep decreases the ventilatory response to $CO_2$.
D. REM sleep increases upper airway tone and postinspiratory activity of the diaphragm.
E. REM sleep inhibits the late decrease in ventilation with hypoxia.

5. An infant born at 24 weeks' gestational age has been receiving mechanical ventilation since admission to the NICU, and is now 1 week old and ready to transition to noninvasive ventilation. You are considering strategies to manage apnea of prematurity. Which of the following statements regarding management of apnea of prematurity for preterm infants is correct?

A. Methylxanthines decrease apnea frequency through a competitive antagonism of nitric oxide synthase.
B. Theophylline has similar efficacy as caffeine, but is less commonly used because of its narrower therapeutic margin and its need for plasma level control.
C. Nasal continuous positive airway pressure is often used in apnea of prematurity, but has not been shown to reduce the frequency or severity of apneas in infants born before 28 weeks' gestational age.
D. Meta-analyses have shown that antacid and promotility agents are effective for the treatment of apnea of prematurity, with low risk of short- and long-term adverse events, and with excellent cost-benefit value.
E. Regardless of hematocrit value, blood transfusions are effective in decreasing frequency of apnea in the short-term and improving neurodevelopmental outcomes at 2 years of age.
Control of Breathing and Apnea of Prematurity
Ruben E. Alvaro

*NeoReviews* 2018;19:e224
DOI: 10.1542/neo.19-4-e224

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://neoreviews.aappublications.org/content/19/4/e224