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Hypoxic Episodes in Bronchopulmonary Dysplasia

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Abstract

Hypoxic episodes are troublesome components of bronchopulmonary dysplasia in preterm infants. Immature respiratory control appears to be the major contributor, typically superimposed upon abnormal respiratory function. As a result, relatively short respiratory pauses may precipitate desaturation and accompanying bradycardia. As this population is predisposed to pulmonary hypertension, it is likely that pulmonary vasoconstriction may also play a role in hypoxic episodes. The natural history of intermittent hypoxic episodes has been well characterized in the preterm population at risk for BPD. However, the consequences of these episodes are less clear. Proposed associations of intermittent hypoxia include retinopathy of prematurity, sleep disordered breathing, and neurodevelopmental delay. Future study should address whether these associations are causal relationships.

Keywords

neonatal respiratory control; apnea of prematurity; desaturation episodes in preterm infants

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Introduction

Hypoxic episodes remain a major source of frustration for care providers of preterm infants in the Neonatal Intensive Care Unit [NICU]. While optimizing oxygen saturation remains a challenge, fortunately the newest generation of pulse oximeters has enabled us to document the incidence of episodic desaturation in this population. These episodes persist beyond the first weeks and even months of postnatal life and, therefore, are temporally related to the development of bronchopulmonary dysplasia [BPD] in a high proportion of extremely low birth weight infants. Unfortunately, there are limited data on how development of BPD modifies respiratory control, airway function and the pulmonary vascular contribution to hypoxic episodes during postnatal maturation. While the primary etiology of intermittent hypoxic episodes in preterm infants is immature respiratory control¹, abnormal lung function present in developing BPD clearly aggravates vulnerability to desaturation.

Role of Immature Respiratory Control in BPD

The multiple contributors to apnea of prematurity and resultant desaturation are summarized in Figure 1. They comprise upregulation of brainstem mediated inhibitory pathways, altered peripheral chemosensitivity, decreased central chemosensitivity, enhanced inhibition from upper airway afferents, and an unstable upper airway². Apnea is clearly more likely to elicit desaturation with the low functional residual capacity [and other abnormalities of lung function] that characterizes BPD [Fig. 1].

a. Data from Animal Models

Large animal models of BPD have proven to be a challenge and very expensive due to the need for longer term survival. Studies have, therefore, focused primarily on hyperoxia exposed neonatal rodents who exhibit lung injury somewhat analogous to the BPD seen in preterm infants. Unfortunately, few studies have focused on vulnerability of respiratory control in the face of neonatal lung injury in such a model. Ratner has demonstrated that intermittent hypoxia [to which infants with BPD are clearly predisposed] superimposed open hyperoxic lung injury aggravates both alveolar arrest and neurological handicap in neonatal mice³⁻⁴. More recent studies in neonatal rats have documented that an early period of sustained postnatal hypoxia followed by subsequent chronic intermittent hypoxia causes a markedly attenuated ventilator response to acute hypoxic exposure⁵. The conditions precipitating this vulnerability of respiratory control may be analogous to the oxygenation status of preterm infants exposed to low baseline levels of oxygen as described later.

Inflammation and oxidant stress are both interrelated components of the pulmonary and central nervous system [CNS] morbidities to which preterm infants are predisposed, especially those with BPD. Available data support the concept that inflammatory mechanisms contribute to instability of neonatal respiratory control. Clinically, apnea increases in frequency and severity during acute infections in premature infants. Although inflammatory cytokines probably do not readily cross the blood brain barrier, systemic infection does upregulate inflammatory cytokines at the blood brain barrier, resulting in activation of prostaglandin signaling and resultant inhibition of respiratory neural output⁶. Chorioamnionitis is a major precipitant of preterm birth, definitively associated with

neonatal brain injury in the form of periventricular leukomalacia [PVL] and probably BPD. It is possible that antenatal or postnatal exposure of the lung to a proinflammatory stimulus may activate brain circuits via vagally-mediated processes. LPS [0.1 mg/kg] instilled into the trachea of newborn rat pups at day of life 10–12 increases inflammatory cytokine gene expression in the medulla oblongata and attenuates both the immediate and late hypoxic ventilator response when animals were tested within three hours of LPS treatment⁷ [Fig. 2]. This brainstem response to intrapulmonary LPS was diminished after vagotomy, suggesting a lung-to-brainstem communication via vagal afferents. It is, therefore, tempting to speculate that the intrapulmonary inflammation that is an integral part of BPD contributes to impaired respiratory control. It is of interest that caffeine, which is used to prevent BPD, appears to be associated with improved lung function and decreased proinflammatory cytokine expression in rat pups exposed to lipopolysaccharide-induced amnionitis⁸.

b. Data from Human Infants

The transition from fetal to neonatal life is accompanied by a dramatic increase in PaO_2 from around 25 to at least 80 torr within 5–10 minutes of birth. This postnatal onset of continuous breathing is probably primarily the result of arousal and thermal, rather than chemical, stimuli. The abrupt increase in PaO_2 is widely believed to inhibit O_2 sensitive peripheral chemoreceptors in the early postnatal period. While CO_2 is the major chemical driver of breathing, ventilatory responses to hypoxia have been extensively studied and well characterized in human infants and newborn animal models⁹. A transient increase in ventilation in response to hypoxia of 1–2 minutes' duration, and mediated via oxygen-sensitive peripheral chemoreceptors, is followed by a decline in ventilation that may even fall below baseline ventilation, and is presumably centrally mediated. This pattern persists in preterm infants into the second postnatal month¹⁰.

While absent peripheral chemosensitivity may inhibit breathing, upregulated peripheral chemoreceptors may also destabilize breathing [Fig. 3]. Two studies of human preterm infants have shown a direct relationship between apnea frequency and increased peripheral chemosensitivity to hypoxia^{11–12}. The mechanisms underlying this relationship are unclear, although if baseline PaCO_2 and the CO_2 threshold for apnea are close, fluctuations in ventilation associated with increased oxygen sensitive peripheral chemosensitivity may readily lower PaCO_2 to below the apnea threshold¹³.

Two groups of investigators have studied peripheral chemosensitivity in preterm infants of advanced postnatal age who have developed bronchopulmonary dysplasia [BPD] or chronic neonatal lung disease^{14–15}. Such infants with BPD may be exposed to a combination of acute or more chronic hypoxia, although these may coexist. In both studies BPD was associated with decreased peripheral chemosensitivity, possibly associated with a declining rate of intermittent hypoxia [IH] episodes [Fig. 3]. From these studies it would appear that increased peripheral chemosensitivity may predispose to respiratory pauses while decreased peripheral chemosensitivity may delay recovery from apnea-induced hypoxia episodes. The latter observation in infants with BPD, i.e., delayed recovery from hypoxia, may contribute to the reported association between BPD and sudden infant death syndrome [SIDS]¹⁶.

Consequences of Intermittent Hypoxic Episodes

Many diseases of the neonatal period, including bronchopulmonary dysplasia (BPD), retinopathy of prematurity [ROP], necrotizing enterocolitis [NEC], and periventricular leukomalacia [PVL], are related to free radical damage, although the specific contribution of oxidative stress has yet to be elucidated. In rodents, intermittent hypoxemia [IH] has been shown to elicit an oxidative stress response that occurs during the re-oxygenation period¹⁷. This may, in turn, serve as a proinflammatory stimulus creating a vicious cycle as proposed in Figure 4. In the preterm infant, the incidence of IH during the first few months of life changes dramatically with increasing postnatal age. During the first week of life there are relatively few IH events, followed by an increase over weeks 2–4 with a subsequent plateau or decrease thereafter¹⁸ [Fig. 3]. As a result of these alterations in oxygenation, the preterm infant may be exposed to increasing levels of reactive oxygen species [ROS] during early postnatal life. Consequently, the effect of oxidative stress on morbidity and how to reduce this exposure continues to be of great interest to neonatal care.

Neonatal intermittent hypoxemic exposure may disrupt maturation of the central nervous system [CNS] at a critical time of development, resulting in neurodevelopmental sequelae. In rodents, intermittent hypoxia exposure during the first weeks of life inhibits myelin formation in the corpus callosum¹⁹ and evokes hyper-locomotive behavior and impaired working memory²⁰. Although direct effects of IH on neurodevelopmental impairment have yet to be determined in infants, related evidence, including prematurity, caffeine exposure, and apnea reporting, suggest a relationship. Former preterm infants exhibit increased deficits in cognitive ability and academic achievement at 8 to 10 years of age²¹. The risk factor of prematurity may be a marker of the high incidence of cardiorespiratory events during early postnatal maturation. Caffeine therapy for apnea of prematurity reduced the rate of cerebral palsy and cognitive delay at 18 months of age²², although the effect of caffeine was no longer significant at the 5 year assessment²³. There was, however, a reduction in developmental coordination disorder in the caffeine treated group²⁴. While apnea was not documented in the Schmidt trials, caffeine has been shown to be effective for reducing both apnea²⁵ and intermittent hypoxemia²⁶. Apnea of prematurity during hospitalization, as recorded by nursing staff, has been associated with both abnormal neurodevelopment at 3 years of age²⁷ and early school age outcomes²⁸. However, it is well known that nursing documentation grossly underestimates the number of cardiorespiratory events. More extensive documentation by home memory monitoring in the Collaborative Home Infant Monitoring Evaluation (CHIME) study demonstrate an association between five or more cardiorespiratory events during the first few months of life and poor motor outcome at 7 years of age²⁹. Since intermittent hypoxemia and bradycardia are considered the detrimental components of apnea of prematurity, these studies suggest a relationship between oxygenation and brain injury.

Pediatric sleep disordered breathing is an increasingly recognized disorder associated with behavioral morbidity. Former preterm infants have a higher prevalence of sleep disordered breathing³⁰ at 8–10 years of age which may be a manifestation of respiratory remodeling during early maturation. In rodents, early postnatal intermittent hypoxia exposure is associated with a higher spontaneous apnea frequency during recovery in room air,

enhanced acute ventilatory response to hypoxia³¹ and increased carotid body excitation³². Similarly, in preterm infants apnea frequency is positively correlated with the ventilatory response to acute hypoxic exposure¹¹. These findings suggest that IH exposure may markedly increase carotid body excitation resulting in destabilization of respiration.

Although the optimal oxygen saturation target remains unknown, oxygen saturation levels of >95% are generally avoided in infants requiring supplemental oxygen. To assess whether oxygen supplementation can be further decreased without detrimental consequences, recent collaborative multicenter trials randomized >5000 extremely preterm infants to a low [85–89%] versus high [91–95%] oxygen saturation target to compare the effect of oxygen saturation targeting on the rate of death or ROP. The outcomes varied among the multinational trials with the Surfactant, Positive Pressure, and Pulse Oximetry Randomization Trial³³ and Benefits of Oxygen Saturation Targeting [BOOST II] Trial³⁴ finding a lower incidence of severe ROP but an unexpected increase in mortality in the low target group. In a sub-cohort of infants enrolled in SUPPORT, the low target was also associated with an increase in IH events³⁵. During the trials the investigators were met with the underappreciated challenge of keeping the infants within the randomized target range, resulting in numerous fluctuations in oxygen saturation and the actual achieved median oxygen saturation quite often outside of the expected target range. Therefore, both actual achieved baseline oxygen saturation levels and intermittent hypoxemia may have played a role on the increase in mortality, but their potential contribution has yet to be determined.

Trials in both animal and infant models indicate that the development of ROP may be based on the pattern and timing of intermittent hypoxemia [IH] events. Retinopathy of prematurity is triggered by multiple factors, including levels of oxygenation encompassing two phases of development. The first phase includes hyperoxia-induced suppression of normal retinal vascularization predominantly by inhibition of vascular endothelial growth factor [VEGF]. The second phase comprises retinal vascular over-proliferation via hypoxia-induced elevation of VEGF and other growth factors³⁶. Rodent models have shown that various derivations of intermittent hypoxia/hyperoxia cycling can also cause neovascularization^{37–38} with clustered, compared to equally dispersed, IH over the same period yielding increased abnormal vascular morphology³⁸. Similar findings have been seen in neonates with distinct patterns and timing of IH associated with severe ROP requiring laser therapy, including a higher incidence of IH, longer duration and short time period [1–20 mins] between IH events³⁹. Interestingly, the time period between IH events reported by Di Fiore et al. corresponds with the ROS response during the re-oxygenation period described in rodents¹⁷.

Intermittent hypoxemia events have implications on growth trajectory and cardiovascular control. In rodent models, IH exposure during early postnatal life restricts both body⁴⁰ and brain growth¹⁹, however, these effects were reversed after a few weeks of recovery. IH effects on cardiovascular control are more complex and longer lasting. Changes in arterial blood pressure are dependent on the timing of the IH events with a clustered pattern associated with lower blood pressure than equaling dispersed events⁴⁰ with no recovery in either IH paradigm after 7 weeks of exposure. Interestingly, there is an association between extreme prematurity, increased blood pressure in adolescence and functional vascular

changes, although it is speculative whether intermittent hypoxic episodes in early life might be contributory⁴¹.

Role of the Immature Airway

Hypoxic episodes in infants with BPD are often attributed to airway closure either during assisted ventilation or spontaneous breathing. The exact pathophysiologic etiology of such events and the underlying biologic mechanisms may be difficult to elucidate. The two likely candidates are airway collapse or bronchospasm [Fig. 5]

The high compliance and resultant deformability of the trachea in the preterm period appears to be a consequence of decreased airway smooth muscle contractility and diminished cartilaginous support⁴². The obvious result is that lower airways are vulnerable to the injurious effects of positive pressure ventilation. Greater understanding of the detrimental effects of positive pressure ventilation at high inflating pressures has decreased the risk of deformation injury in the immature airway. Lung parenchymal injury is a well recognized complication of neonatal intensive care and is characterized by the development of enlarged, simplified alveolar structures in infants with BPD. This may result in decreased tethering of intraparenchymal airways and the accompanying decrease in airway lumen would increase baseline airway resistance⁴³. A related observation is that lung parenchymal injury elicited by hyperoxic exposure is associated with fewer bronchiolar-alveolar attachments in a rodent model of neonatal lung injury⁴⁴. A resultant increase in baseline lung resistance would likely enhance vulnerability to hypoxic episodes.

Data in rat pups indicate that enhancement of airway reactivity occurs even after short-term mechanical ventilation⁴⁵. In newborn animal models hyperoxic exposure has also been associated with development of airway hyperreactivity⁴⁶. Although hyperoxic exposure may increase smooth muscle area, this effect is variable and does not, of itself, explain the development of hyperoxia-induced airway hyperresponsiveness, suggesting a functional component for increased airway reactivity⁴⁷.

Many factors may contribute to the increased airway reactivity that is seen after neonatal hyperoxic exposure. Studies have focused on neonatal rodent models exposed to only moderate [e.g., 40–60%] hyperoxic exposure as this more closely simulates the clinical condition. Recent data demonstrate that 40% oxygen exposure elicited a greater increase in airway reactivity than 70% oxygen exposure, associated with greater airway smooth muscle thickness⁴⁸. This might be attributed to a dominant proliferative effect of 40% oxygen on airway smooth muscle versus a predominantly apoptotic effect at the high oxygen level^{49–50}. Epithelial injury with loss of airway relaxant factors may also contribute to the hyperoxia-induced increase in airway contractile responses.

It is often difficult to identify specific precipitants of apparent bronchospasm with resultant hypoxia in infants with BPD. Afferent fibers from the upper or lower airway, which precipitate apnea as a protective reflex, may also induce bronchospasm. Earlier studies in infants with BPD have documented a significant increase in lung resistance induced by an abrupt reduction in inspired oxygen⁵¹. Conversely, exposure to supplemental oxygen in infants with BPD and increased baseline resistance caused relief of bronchoconstriction⁵².

Studies in newborn dogs have demonstrated that hypercapnia is more likely than hypoxia to elicit bronchoconstriction⁵³. They, therefore, speculated that central chemoreceptors are more effective than peripheral chemoreceptors in altering contractile airway smooth muscle responses. These data support the concept that respiratory depression with superimposed chronic lung disease and resultant hypoxia/hyperoxia may contribute to bronchospasm and establish a vicious cycle of impaired gas exchange. Susceptibility to airway closure may be further aggravated by increased work of breathing and resultant asynchrony of chest wall movements in infants with BPD^{54–55}. Such asynchrony of chest wall motion is aggravated in the supine position. McEvoy has documented that prone positioning decreases hypoxic episodes in infants with BPD, although this must be weighed against avoidance of that position prior to discharge⁵⁶.

Role of Pulmonary Vasoconstriction

The contribution of pulmonary vasoconstriction to hypoxic spells in bronchopulmonary dysplasia has been recognized from the earliest descriptions of the disease. Vascular remodeling with intimal hyperplasia leads to abnormal vasoreactivity, as evidenced by the marked vasoconstrictor response seen in even modest episodes of hypoxia^{57–58}. Infants with BPD who were assessed at cardiac catheterization were found to have marked elevations of pulmonary arterial pressure in response to mild hypoxia, regardless of the severity of BPD⁵⁹. Thus, maintaining normoxic conditions, as measured by oxygen saturation of 92–94%, is the mainstay of therapy. However, Lakshminursimha found that exposure to both brief [30 min] or prolonged [24 hrs] of 100% oxygen increased pulmonary artery reactivity⁶⁰. Subsequent work demonstrated that this effect was mediated by depletion of antioxidant enzymes⁶¹. Thus, neonatologists must guard against hyperoxia while avoiding hypoxia.

A second mechanism of vascular impairment has been recognized more recently. Very preterm infants with BPD may have decreased angiogenesis, and this may be a contribution factor to the development of pulmonary hypertension. Reduced vascular growth limits the vascular surface area, and further increases pulmonary vascular resistance, especially when cardiac output is increased, such as with exercise or stress. In animal models, Abman's group has demonstrated in a series of elegant experiments that impaired angiogenesis can lead to impaired alveolarization^{62–66}. Thus, a primary contributor to the development of BPD is abnormal vascular development. Mourani and colleagues prospectively studied 277 preterm infants with echocardiograms at 7 days of age and correlated evidence of pulmonary hypertension with the severity of BPD at 36 weeks PMA. Infants who ultimately had severe BPD were more likely to have early pulmonary hypertension on the 7 day echo⁶⁷. These findings suggest that early pulmonary vascular disease contributes to the susceptibility for BPD [see Chapter 10, Vascular Abnormalities].

In conclusion, hypoxic episodes are significant challenges in the shorter and longer term management of former preterm infants. As the etiology may be multifactorial, including immature respiratory control and both airway and vascular related etiologies, an integrated approach to understanding the Pathobiology of these events is essential in this high risk population.

Summary Approach to Management

There is currently no “quick fix” for eliminating the recurrent hypoxic episodes that occur so frequently in infants who are developing, or have established, BPD. Table 1 summarizes potential etiologies and approaches that may prove effective, although it is important to recognize that recurrent hypoxic episodes may have multifactorial overlapping etiologies in this high-risk population.

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Key Points

- intermittent hypoxic episodes frequently accompany BPD
- immature respiratory control superimposed upon abnormal pulmonary function is a major contributor to intermittent hypoxia in BPD
- pulmonary hypertension may aggravate predisposition to intermittent hypoxia

Figure 1.

Multiple factors contribute to both immature respiratory control and poor respiratory function, are potentially aggravated by BPD, and enhance vulnerability for development of intermittent hypoxic episodes.

Figure 2.

Pre- or postnatal exposure of the respiratory system to endotoxin may elicit a proinflammatory cytokine response in the brainstem via stimulation of vagal afferents. This, in turn, may inhibit respiratory neural output [Adapted from Balan KV, Kc P, Hoxha Z, et al. Vagal afferents modulate cytokine-mediated respiratory control at the neonatal medulla oblongata. *Respir Physiol Neurobiol* 2011; 178:458–64; with permission]. Such vulnerability of respiratory control is likely aggravated by the inflammatory processes that are associated with BPD.

Figure 3.

A proposed relationship between O₂ sensitive peripheral chemosensitivity [PCS] and the natural history of intermittent hypoxia [IH] in a cohort of preterm infants studied over the first 8 weeks of life [data from Di Fiore JM, Bloom JN, Orge F, et al. A higher incidence of intermittent hypoxemic episodes is associated with severe retinopathy of prematurity. *J Pediatr* 2010; 157:69–73]. The fetal to neonatal transition is associated with decreased PCS and a low incidence of IH. Subsequently there is an increased incidence of IH associated with increased PCS, while later maturation is accompanied by a declining incidence of IH and decreased PCS in the presence of bronchopulmonary dysplasia [BPD]. [Adapted from Martin 2012: Nurse CA et al [eds]: *Advances in Experimental Medicine and Biology*; with permission.

Figure 4.

A proposed vicious cycle whereby immature respiratory control precipitates recurrent intermittent hypoxia/re-oxygenation, which in turn, serves as a proinflammatory stimulus and further depresses respiratory neural output.

Contributors to Abnormal Airway Function

Figure 5.

Interacting contributors from the airways and lung parenchyma that are proposed to modulate airway function in the face of neonatal lung injury, and contribute to airway-related hypoxic episodes. *Adapted from* Martin RJ. Regulation of lower airway function, Chapter 67, In Fetal and Neonatal Physiology Eds Polin, Abman, Bentz and Rowitch 5th edition (In press), Elsevier (Saunders), Philadelphia PA; with permission.

Table 1

Approach to Intermittent Hypoxic Episodes

<u>Clinical Presentation/Etiology</u>	<u>Diagnostic Approach & Therapy</u>
Apneic/bradycardic episodes [spontaneous breathing]	CPAP ± caffeine
Bradycardic episodes [intubated]	Consider extubation Caffeine & CPAP
Pulmonary hypertension	Confirm via echocardiogram Consider iNO
Bronchospasm	Poor air entry Consider bronchodilator