Published in final edited form as:

Respir Physiol Neurobiol. 2013 November 1; 189(2): . doi:10.1016/j.resp.2013.07.015.

Ventilatory Control in Infants, Children, and Adults with Bronchopulmonary Dysplasia

Melissa L. Bates, PhD^{1,5}, De-Ann M. Pillers, MD, PhD², Mari Palta, PhD⁴, Emily T. Farrell, PhD^{1,5}, and Marlowe W. Eldridge, MD, MSME^{1,3,5}

¹Department of Pediatrics, Division of Critical Care, University of Wisconsin, Madison, WI USA

²Department of Pediatrics, Division of Neonatology, University of Wisconsin, Madison, WI USA

³Departments of Biomedical Engineering and Kinesiology, University of Wisconsin, Madison, WI USA

⁴Population Health Sciences, University of Wisconsin, Madison, WI USA

⁵John Rankin Laboratory of Pulmonary Medicine, University of Wisconsin, Madison, WI USA

Abstract

Bronchopulmonary dysplasia (BPD), or chronic lung disease of prematurity, occurs in ~30% of preterm infants (15,000 per year) and is associated with a clinical history of mechanical ventilation and/or high inspired oxygen at birth. Here, we describe changes in ventilatory control that exist in patients with BPD, including alterations in chemoreceptor function, respiratory muscle function, and suprapontine control. Because dysfunction in ventilatory control frequently revealed when O₂ supply and CO₂ elimination are challenged, we provide this information in the context of four important metabolic stressors: stresses: exercise, sleep, hypoxia, and lung disease, with a primary focus on studies of human infants, children, and adults. As a secondary goal, we also identify three key areas of future research and describe the benefits and challenges of longitudinal human studies using well-defined patient cohorts.

Keywords

Bronchopulmonary dysplasia; premature infant; ventilatory control; peripheral chemoreceptors; carotid bodies; central chemoreceptors; exercise; hypoxia; sleep; lung disease

1. Introduction

The primary purpose of the respiratory system is to support metabolism, largely by facilitating the delivery of O₂ and removal of CO₂. To that end, peripheral and central neural centers provide chemical, mechanical, and sensory feedback to the central nervous system in order to mount an appropriate response to metabolic demands. Sensory, chemical, and mechanical feedback signals are integrated by respiratory centers in the brainstem, which then provide efferent signals to respiratory muscles. Derangements in these processes may

© 2013 Elsevier B.V. All rights reserved.

Address correspondence to: Melissa L. Bates, PhD, Department of Pediatrics, 600 Highland Avenue, H6/551 Clinical Sciences Center, Madison, WI 53792, mlbates@pediatrics.wisc.edu or 608-265-5095.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

result in an inappropriate ventilatory response to metabolic demand, with hypo- or hyperventilation as the potential outcomes.

Bronchopulmonary dysplasia (BPD) or chronic lung disease of prematurity occurs in ~30% of preterm infants (15,000 per year) and is associated with a clinical history of mechanical ventilation (Ruiz et al. 1981), lung infection and inflammation (Yoon et al. 1997; Lyon 2000; Kasper et al. 2011) and/or high inspired oxygen at birth (Thebaud and Abman 2007). While the study of ventilatory control in premature infants has been extensive, much less is known about how ventilatory control is further modified by BPD.

1.1 Overall purpose

The goal of this review is to describe alterations in ventilatory control with a specific focus on human infants, children, and adults with BPD. Because the dysfunction in ventilatory control may only become apparent when O₂ delivery and CO₂ elimination are challenged, we describe research investigating the effect of three important stresses: exercise, sleep, hypoxia. We also discuss important clinical impact of ventilatory control abnormalities in the treatment of the infant with BPD. We hope that this review will be valuable both the scientist and to the clinician treating this population, especially as they continue to age. As a secondary goal, we outline future research directions and hope that this review will inspire additional research and collaboration from our colleagues in the field of respiratory neurobiology.

2. The “old” and “new” BPD

Several clinical definitions of BPD have been used with the goal of relating clinical observations to functional outcomes like mortality, re-hospitalization and gas exchange capacity. Northway, et al. first described BPD in 1967, using radiographic evidence of lung damage as the primary criteria (Northway et al. 1967). The most severe findings were associated with an increased risk of mortality.

This “old” BPD first described by Northway, et al. was observed in older preterm infants that, because of the unavailability of surfactant, required aggressive mechanical ventilation and supplemental oxygenation. The barotrauma and oxygen toxicity resulted in inflammation and lung fibrosis as hallmark features.

There is no doubt that the pathophysiology of BPD has evolved considerably over the last 35 years. The use of surfactant and prenatal glucocorticoids, combined with milder ventilatory strategies, has essentially eliminated BPD in older preterm infants born within the last 20 years. Found primarily in less mature, very- (<1500 g) and extremely-low birth weight infants (<1000 g), the “new BPD” is thought to be a disease of arrested lung development, in contrast to the traumatic lung injury associated with the “old” BPD (Jobe 1999). The change in pathophysiology made Northway’s definition largely obsolete and it was, thus, revised to incorporate physiological endpoints that reflect the gas exchange impairments caused by impaired alveolarization. These definitions rely primarily on the need for prolonged oxygen use after birth, with either O₂ use at 28 days or 36 weeks post-menstrual age used as the primary diagnostic criterion (see (Bancalari et al. 2003) for an excellent discussion of this).

2.1 Current definitions of BPD

In 2000, a National Institute of Child Health and Human Development/National Heart, Lung, and Blood Institute Workshop proposed a severity-based definition of BPD, which mainly used oxygen supplementation as criteria for stratification (Jobe and Bancalari 2001). This was validated in 2005, relating the severity to the risk of re-hospitalization and future pulmonary medication use (Ehrenkranz et al. 2005), and defines BPD as:

- Mild - a need for supplemental O₂ for 28 days but not at 36 weeks' postmenstrual age (PMA) or at discharge,
- Moderate – a need for supplemental O₂ for 28 days plus treatment with <30% O₂ at 36 weeks PMA
- Severe – a need for supplemental O₂ for 28 days plus 30% O₂ and/or positive pressure at 36 weeks PMA.

Walsh, et al. have provided an alternative “physiological definition” of BPD in which the diagnosis is based on arterial oxygen saturation (SpO₂) at 36 weeks postmenstrual age (Walsh et al. 2004). These authors suggest a diagnosis of BPD when SpO₂ <96% in pressure-supported patients or patient receiving >30% O₂, without the need for additional challenge. In patients without pressure or O₂ support, or with SpO₂ >96% while breathing >30% O₂, BPD is defined as SpO₂<90% after a room air challenge.

Although there are certainly not sufficient data to begin to compare “old” versus “new” BPD, scientists and clinicians should be aware of the differences in both the pathophysiology and definition and take caution in over-generalizing findings from patients with “old” or “new” BPD to all patients with BPD. This applies also to this review, and the reader should look to the date of publication for further consideration of which BPD is likely represented in a particular study.

3. The ventilatory response to hypoxia

We begin with a discussion of studies examining the ventilatory response to hypoxia as a result of impaired chemoreceptor function. The increase in ventilation in response to hypoxia is largely the result of carotid body stimulation by low arterial PO₂. Birth is a critical transitional period in the development of normal cardiopulmonary control and, specifically, the carotid body (Teppema and Dahan 2010). In the fetus, hypoxia inhibits normal fetal breathing movements and, although the carotid bodies are active when PaO₂<25 mmHg, their ability to increase ventilation is overridden by suprapontine input (Dawes et al. 1983).

3.1 Post-natal development of normal carotid body function

In utero and at birth, the carotid bodies are less sensitive to hypoxia and neuronal output from the carotid body is not essential for the initiation of normal breathing (Blanco et al. 1984; Forster et al. 2000). Three key events occur post-natally in the development of the carotid body: 1) the activation threshold of the carotid body to PaO₂ increases to a level similar to that observed in the adult (from <25 mmHg PaO₂ to ~55 mmHg), 2) the ability of CO₂ to modulate responsiveness develops and 3) the carotid bodies increase in volume and mature in receptor and neurotransmitter expression. These changes allow the carotid bodies to assume an essential role in the generation of a normal ventilatory response (Blanco et al. 1984).

3.2 Alterations in normal carotid body function in the infant with BPD

The carotid chemoreceptors of preterm infants are physiologically unprepared to undergo the changes necessary for the transition to the ex utero environment, making these infants more prone to apneas, periodic breathing and respiratory decompensation. These infants may require continuous positive airway pressure (CPAP), supplemental oxygen, and unplanned intubation and re-intubation until ~36 weeks post-menstrual age (Clark et al. 2013).

The development of normal carotid body morphometry, and a normal ventilatory response, is critically dependent on the perinatal environment. Calder, et al. first described the ventilatory response to hypoxia in a group of three month old infants born at ~27 weeks, with and without BPD, using alternating breaths of 21% and 16% O₂ (Calder et al. 1994). In contrast to the premature infants that did not need mechanical ventilation or supplemental oxygen, the infants with BPD failed to increase ventilation in response to a hypoxic challenge. Katz-Salamon and colleagues followed this work by examining how short hyperoxic exposures, which inhibit carotid sinus nerve output and depress ventilation, affect the ventilatory response (Katz-Salamon et al. 1995; Katz-Salamon et al. 1996). They found a lack of hyperoxic ventilatory depression in infants with BPD. Taken together, this suggests that BPD is associated with impairments in carotid body function such that both the contribution of carotid body signaling to baseline ventilation and to the response to hypoxia is diminished.

Katz-Salamon, et al. also found an association between the severity of BPD and alterations in ventilatory drive, such that the infants with the most severe disease experienced the smallest change in ventilation in response to hyperoxia (Katz-Salamon et al. 1995). BPD severity and the degree of hyperoxia-induced ventilatory depression were both related to the time spent mechanically ventilated, suggesting that the perinatal ventilatory support links the BPD severity with impairments in ventilatory drive.

3.3 Rodent models of perinatal hyperoxia and hypoxia and their relationship to BPD

Subsequent research in rodents has improved our understanding of the mechanisms by which perinatal hyperoxia impacts carotid body function, demonstrating that supplemental oxygen at birth profoundly blunts future carotid body development. An excellent, detailed review of this work was recently published (Bavis et al. 2013) for those interested in an in-depth discussion of this field. Briefly, hyperoxia at birth blunts the ventilatory response to hypoxia in feline and rodent models, similarly to that seen in infants with BPD (Hanson et al. 1989; Ling et al. 1996). Deficits in normal carotid body function that result from perinatal hyperoxia are caused by a combination of impaired O₂ sensitivity (Hanson et al. 1989; Donnelly et al. 2005; Donnelly et al. 2009; Bavis et al. 2011), carotid body hypoplasia and decreased total afferent neuron number (Bisgard et al. 2003; Chavez-Valdez et al. 2012; Bavis et al. 2013). Perinatal hyperoxia also reduces neurotrophin expression and increases caspase-3 levels in the nucleus tractus solitarii (nTS), the critical site for the integration of chemosensory input. Neurons in the nTS exhibit a proapoptotic phenotype, potentially impairing the normal formation of this neural circuit (Chavez-Valdez et al. 2012). The ventilatory response to CO₂ is unchanged in this model (Ling et al. 1996).

Given our limited ability to access and manipulate the carotid bodies in humans for the purpose of research, it is unknown whether these physiological alterations in carotid body morphometry and signaling are present in humans with BPD. It is, however, of important clinical consequence that these ventilatory control impairments appear to be permanent in adult rats with BPD (Ling et al. 1997). Katz-Salamon studied the ventilatory response to hyperoxia in a cohort of preterm infants with BPD (Katz-Salamon et al. 1996). These authors found that while hyperoxia failed to depress ventilation soon after birth, the response recovered over the subsequent several months, suggesting recovery of chemoreceptor function. It is important to note that the magnitude of the response was not compared to term infants, nor were these infants followed beyond infancy. Indeed, our recent preliminary data from 20–22 year old adults with BPD, exposed to five minute periods of eucapnic hypoxia and hyperoxia, suggest that these impairments may also be permanent in humans (Beshish et al. 2012) (See Figure 1).

Although rodent models of BPD provide a physiologically plausible explanation for observations in humans, the physiologic contributors to the disrupted ventilatory response in the human are probably more complex. Infants with BPD rarely experience sustained normal or above normal PaO_2 , but are more likely to experience cycles of high, normal, and low PaO_2 as they experience apneas and adjustments to their ventilatory support, overlaid with their lung disease. In contrast to the effects of hyperoxic exposure, postnatal intermittent hypoxia sensitizes the carotid chemoreceptor to hypoxia, leading to hyperventilation, a fall in PaCO_2 , and an increase in apnea number and breathing instability (Khan et al. 2005; Pawar et al. 2008; MacFarlane et al. 2013). In this way, chronic, intermittent hypoxia may be self-perpetuating in the BPD infant.

3.4 Clinical consequences of an impaired hypoxic ventilatory drive

Chemoreceptor hypersensitivity may manifest itself clinically in the BPD patient, contributing to feeding difficulties that are not observed in preterm infants without BPD. Craig et al. found that babies with severe BPD had a lower tolerance for breathing pause during sucking and swallowing than term infants. The shorter than normal breath pauses in the BPD infants were followed by a period of irregular hyperventilation (Craig et al. 1999). In some preterm infants, these periods of hyperventilation are followed by an apnea (Gryboski 1969). While some conclude that this hyperventilation is the result of lower SpO_2 during the swallowing phase (Mizuno et al. 2007), others speculate that ventilatory control dysfunction is an important contributor (Gewolb et al. 2001). Indeed, ventilatory control dysfunction, occurring in combination with gas exchange inefficiency, muscle immaturity and an increased work of breathing, may pose an important barrier to the transition from gavage to nipple feeding in the parenteral nutrition-dependent BPD infant (McCain et al. 2012).

The inability to generate a hypoxic ventilatory response is also associated with an increased risk of acute mountain sickness after ascent to altitude (Nespoulet et al. 2012). In a 2001 consensus statement on children at altitude, the International Society for Mountain Medicine noted cases of mountain sickness and high altitude pulmonary edema in children previously diagnosed with BPD (Pollard et al. 2001). Whether a poor ventilatory response contributes to mountain sickness in individuals with BPD remains an area for future exploration.

3.5 The response to hypercapnia

In comparison to the hypoxic ventilatory drive, the ventilatory response to hypercapnia is less well understood. Infants with BPD may retain CO_2 , transiently suppressing central chemoreceptor function. This is discussed in more detail in Section 6. In rodent models, perinatal hyperoxia does not impact the long-term ventilatory response to hypercapnia (Ling et al. 1996). The ventilatory response to CO_2 has not been systematically studied in children and adults with BPD but, given the known interactions between carotid body function and the ventilatory response to CO_2 (Chenuel et al. 2004) and the fact that carotid body function is altered in individuals with BPD, this is an important future area of study.

4. Sleep

Ventilation is the one of the few physiological processes under both voluntary and involuntary control. During sleep, the voluntary control is suppressed, leaving a complex, multi-layered neural network that incorporates feedback from the peripheral and central chemoreceptors, airway sensory neurons, and metaboreceptors to modulate ventilation. Ventilation during sleep is highly sleep state and age dependent (Berthon-Jones and Sullivan 1982; Rosen 2000; Parslow et al. 2003) but, in general, alveolar ventilation, airway tone and caliber, and the sensitivity of the chemoreceptors to hypoxia and hypercapnia are reduced,

increasing the vulnerability to hypoxemia (McKay et al. 2010). Although alveolar PO_2 (PAO_2) falls as a result of the decreased alveolar ventilation, this typically poses only a minor challenge to oxygen delivery in healthy individuals. Recall that the oxygen-hemoglobin dissociation curve is non-linear and hemoglobin remains near maximally saturated at PaO_2 60 mmHg (West 2008). In healthy humans, the PaO_2 and PAO_2 remain sufficiently high to ensure that they remain on the plateau portion of the oxygen-hemoglobin dissociation curve. Individuals with lung diseases like BPD that challenge oxygen diffusion, resulting in a widening of the alveolar-arterial PO_2 difference, are more vulnerable to hypoxemia and oxygen delivery limitation.

Many of the initial studies investigating the hypoxic and hyperoxic ventilatory responses in infants with BPD were motivated by a desire to understand why these infants are at increased risk of sudden death after discharge from the NICU (Thompson et al. 2006). Specifically, it has been speculated that this risk of sudden death may be related to impairments in ventilatory control that leave infants with BPD particularly vulnerable to disordered breathing during sleep, contributing to a higher risk of sudden infant death syndrome (SIDS) (Hunt et al. 1981; Werthammer et al. 1982; Garg et al. 1988; Calder et al. 1994; Katz-Salamon et al. 1996). During sleep, infants with BPD experience more central and obstructive apneas than age-matched infants without BPD (Sekar and Duke 1991; Fajardo et al. 1993), and the apneas occur more frequently in the prone position than supine (Hibbs et al. 2008). Infants with BPD also tend to maintain a higher minute ventilation to support their oxygenation demands compared to term infants. This minute ventilation is achieved preferentially by increasing respiratory rate, which minimizes the work of breathing in the face of increased lung stiffness (Latzin et al. 2009).

4.1 Sleep and the hypoxic ventilatory response

While this is certainly not intended to be a comprehensive review of the vast literature related to the development of normal ventilatory-sleep interactions (Gaultier and Gallego 2005), we can identify several likely contributors to abnormal ventilation during sleep in infants with BPD. Impairments in chemoreceptor function may result in an inappropriate response to hypoxemia during sleep. Garg, et al. studied the arousal response to hypoxia ($FIO_2=0.15-0.11$) during sleep in twelve infants with BPD at 40 weeks post-menstrual age (Garg et al. 1988). One infant failed to arouse in response to hypoxia. Eight infants experienced prolonged apnea with bradycardia and four infants required assisted bag and mask ventilation to reinitiate breathing. All infants required vigorous stimulation and supplemental O_2 to restore normal respiration. This study was limited in that minute ventilation and end tidal gases were not measured during the exposure, thereby limiting the ability to determine the cause of the apneas. It is possible that, as discussed previously, the peripheral chemoreceptors may be hypersensitive, triggering hyperventilation in response to hypoxia, followed by a fall in $PaCO_2$ resulting in an apnea.

4.2 The arousal and autoresuscitation responses in infants with BPD

During sleep, the ultimate line of defense against hypoxemia is arousal (Shannon 1980). The suprapontine regions of the brain responsible for arousal receive multiple mechanical, metabolic, and sensory inputs and hypercapnia and elevated inspiratory effort are potent stimuli of these regions. One might expect, given 1) the fact that perinatal intermittent hypoxia impairs arousal in the rat (Darnall et al. 2010; Darnall et al. 2012) and 2) that the arousal centers are located diffusely in the brain (Berry and Gleeson 1997) and infants with BPD may have congenital, hypoxia, or sepsis-induced brain lesions (Peterson et al. 2000; Inder et al. 2005; Wilkinson et al. 2007; Bednarek et al. 2008), that the arousal response might be impaired in infants with BPD. Indeed, magnetic resonance imaging studies demonstrate a high incidence of brain lesions in premature infants, including periventricular

abnormalities with reductions in white matter volume and ventriculomegaly. Infants <26 weeks gestational age demonstrate global cerebral atrophy with reduced white and gray matter volume and immature cortical folding and gyral patterning (Battin et al. 1998; Ajayi-Obe et al. 2000; Inder et al. 2003). It is possible that these lesions impact ventilatory control and arousal during sleep (Kanda et al. 2003; Zhang et al. 2013), although this has not been systematically evaluated in infants with BPD.

That said, polysomnographic studies demonstrate that infants with BPD arouse normally in response to an apnea (Garg et al. 1988; Harris and Sullivan 1995; Bhat et al. 2006), although the restoration of normal breathing may not be associated with the arousal. In fact, infants with BPD spend more time in active sleep compared to infants without BPD, where the latency to arousal in response to hypoxia is shorter than during quiet sleep (Horne et al. 2005). As a result, infants with BPD experience more sleep fragmentation than other preterm or term-born infants (Harris and Sullivan 1995). While we cannot rule out that some infants with BPD may have specific lesions that impair the arousal response, the arousal response itself does not appear to be altered in the population in general.

In most term infants, very severe hypoxia is associated with an attempt to auto-resuscitate (Sridhar et al. 2003). That is to say, the infant will gasp in an attempt to increase lung oxygen delivery. If successful, this may lead to an improvement in heart rate and a restoration of normal breathing. In home monitor recordings of three infants with BPD, apnea was followed by bradycardia and death, yet there is no evidence of auto-resuscitation (Meny et al. 1994; Sridhar et al. 2003). The failure of these infants with BPD in particular, to auto-resuscitate suggests impairments in the medullary neurons responsible for this response (Paton et al. 2006).

4.3 Sleep architecture and ventilatory control

Sleep architecture, itself, directly influences ventilation. The homeostatic setpoints for PaCO_2 and PaO_2 are largely sleep- state dependent. Thus, injury to the cortical centers that dictate sleep state, thereby altering sleep architecture, will certainly impact ventilation. Infants with BPD experience more sleep disturbances and spend more time in active sleep than term-born infants (Harris and Sullivan 1995). This is important because apneas are most prevalent during active sleep in the preterm infant. Even a brief apnea can result in brief periods of hypoxemia in the healthy infant (Ng and Chan 2013). In 12-hour, overnight recordings of 67 full term infants (29–54 days gestational age), 81% of infants experienced episodes associated with an apnea in which SpO_2 fell to 80% or lower (Stebbins et al. 1991). In infants with BPD, this hypoxemia may be further exacerbated by both alveolar diffusion limitation and increased frequency and duration of apneas (Zinman et al. 1992).

4.4 Ventilatory control during sleep beyond infancy

Of important clinical consequence, early life alterations in ventilatory control during sleep may last beyond infancy. Having been born preterm is a risk factor for sleep disordered breathing during mid-childhood (Rosen et al. 2003), although whether BPD further increases that risk is unclear (Hibbs et al. 2008; Sharma et al. 2011). There have been no studies investigating sleep apnea in adults with a history of BPD, but given that sleep apnea increases the risk of age-related diseases (Kasai et al. 2012), understanding how BPD impacts the development of sleep apnea is vital. Indeed, this is a fruitful area for future clinical and translational research,

5. Exercise

During exercise, the demand for oxygen increases substantially, resulting in an increase in minute ventilation from 6 L/min at rest to >100 L/min in athletes performing maximal

exercise. While there is some suggestion that BPD is associated with a tendency toward a more sedentary lifestyle (Kajantie et al. 2010), it is not clear whether these individuals are exercise-limited. The majority of exercise testing has been conducted in children aged 5–14 years, with a single study in 19-year-olds. These studies show either that children with BPD have no difference in their exercise capacity compared to their term-born peers (Kriemler et al. 2005; Karila et al. 2008; Zavorsky et al. 2009; Clemm et al. 2012; Novais et al. 2012), or that they demonstrate exercise limitation (Vrijlandt et al. 2006; Abreu et al. 2007; Smith et al. 2008).

But, how might ventilatory control during exercise be different in individuals with BPD? Mitchell and Babb describe exercise hyperpnea as a “layered”, network-type response with feed-forward, feed-back, and adaptive components that give the ventilatory control system substantial potential for plasticity (Mitchell and Babb 2006). The exact nature of exercise-induced hyperpnea remains a topic of debate, with contradictory findings frequently appearing in the literature (Forster 2000; Poon 2007; Poon et al. 2007). In that spirit, whether the ventilatory response to exercise is altered in individuals with BPD is unclear, with both hypo- and hyperventilation having been experimentally observed.

5.1 Observations of hypoventilation during exercise

A study of 20 children (7–14 years old) found that, despite having similar exercise capacity as term-born controls, 60% of the children with BPD hypoventilated during exercise, resulting in hypoxemia and hypercapnia (Karila et al. 2008). The EPICure study group also found hypoventilation in a cohort of children born extremely preterm (<25 weeks gestational age, 71% BPD incidence), with decreased tidal volume at peak exercise compared to controls (Bolton et al. 2012). Similarly, Lovering, et al. studied a 27-year-old man with BPD and found that PaCO_2 failed to decline with maximal exercise, suggesting a diminished hyperpneic response (see Figure 2) (Lovering et al. 2007). This individual had a history of high altitude pulmonary edema and markedly reduced spirometric function.

Although no studies have addressed the specific mechanisms by which the development of BPD might be associated with hypoventilation during exercise, we can speculate as to how this might occur. We know that carotid chemoreceptor function is depressed in infants with BPD and that this may be permanent. The ventilatory response to exercise has been previously examined in a small population of individuals with complete, bilateral carotid body resection as treatment for persistent asthma (Lugliani et al. 1971; Wasserman et al. 1975). Like the BPD populations reported here, with potentially depressed carotid body function, individuals with completely denervated carotid bodies experience hypoventilation during exercise, evidenced by a decreased $\dot{V}_E/\text{CO}_2$, increased PaCO_2 and hypoxemia compared to non-asthmatics with intact carotid bodies.

We cannot rule out that the hypoventilation observed in adults and children born preterm may be related to mechanical dysfunction and not chemoreceptor function. Infants with BPD have less compliant lungs and, thus, the work of breathing is increased. The imposition of this additional inspiratory work of breathing challenges the respiratory muscles and causes them to fatigue more quickly than the respiratory muscles of term infants. Thus, infants with BPD are unable to maintain minute ventilation (Deoras et al. 1992; Greenspan et al. 1992). It is possible that this poor compliance remains after infancy, leading to an increased work of breathing and lower peak minute ventilation, during exercise. The inability of infants with BPD to maintain minute ventilation may still have a neural control component; inspiratory loading results in asynchrony between the abdominal muscles, intercostal muscles, and diaphragm that limits their ability to coordinate respiration and maintain minute ventilation (Deoras et al. 1992).

5.1 Observations of hyperventilation during exercise

In contrast to the finding that children with BPD hypoventilate during exercise, a study of 19 children (8–9 years old, <29 weeks gestational age, 53% BPD incidence) found hyperventilation and hypocapnia during submaximal exercise (Novais et al. 2012). Notably, these children tended to have more severe respiratory disease in infancy than the participants demonstrating exercise hypoventilation in the aforementioned studies. Finding that maximal inspiratory pressure was impaired, these authors speculate that children with BPD may be more susceptible to inspiratory muscle fatigue and that they have adapted by hyperventilating in situations associated with high respiratory muscle work. If the authors' speculation is correct, this adaptation would indicate long-term plasticity in response to inspiratory load, potentially involving the pre-motor cortex (Raux et al. 2007). In healthy individuals subjected to temporary periods of high inspiratory load stress (Revelette and Wiley 1987), asthmatics (Davenport et al. 2012), the elderly (Allen et al. 2009) and endurance athletes (Paulus et al. 2012), the ability to sense inspiratory load is attenuated. It is notable that these four studies were completed in populations where the inspiratory stress was imposed after infancy. It is possible that the long-term adaptation to a high work of breathing is different when the stress is imposed in infancy.

Although the medulla and pons are the major sites of respiratory rhythm generation, we also appreciate a role for suprapontine areas of the brain in modulating ventilation in response to internal and external cues (Horn and Waldrop 1998). For example, group III and IV muscle afferents are stimulated by metabolic byproducts, vasoactive mediators, muscle stretch, and temperature (Hertel et al. 1976; Mense and Stahnke 1983; Haouzi et al. 1999; Kaufman et al. 2002) and increase ventilation in response to stimuli. In humans, the hyperpneic response to exercise is associated with increased activity in the superomedial and superolateral primary motor cortices, suggesting motor cortex involvement in the ventilatory response (Fink et al. 1995; Thornton et al. 2001). While we again note that the precise mechanisms governing the ventilatory response to exercise are unclear (Haouzi 2006), animal and human studies strongly support a role for higher brain centers in the initiation and maintenance of exercise hyperpnea (Waldrop et al. 2010). As we note in our discussion of sleep (see Section 4.2), individuals with BPD may have cortical and subcortical brain lesions. It is possible that these may also contribute to the inconsistent exercise hyperpneic response observed in humans with BPD. This is, however, speculative and additional work in this area is needed.

6. Ventilatory control and the treatment of the infant with BPD

Both the lung disease associated with BPD, and conditions which lead to premature delivery, can adversely impact ventilatory control. The BPD infant, with a diminished alveolar and vascular cross-sectional area available for gas exchange, may retain CO₂. Diuretic use and high fat feeding can exacerbate CO₂ retention (de Meer and Heymans 1989) and chronic CO₂ retention can blunt or reset central chemoreceptor responsiveness. Impairments in CO₂ chemoreceptors sensitivity leaves the already compromised peripheral chemoreceptors as the primary feedback mechanism maintaining the drive to breathe (Allen et al. 2003). Hyperoxia suppresses peripheral chemoreceptor function, thereby withdrawing some of the drive to breathe. Because of their reliance on peripheral chemoreceptors, infants with BPD are sensitive to hyperoxia-induced apnea.

6.1 The importance of prematurity-related comorbidities in infants with BPD

The degree of prematurity may directly influence the drive to breathe independent of the development of BPD. For example, preterm infants demonstrate a prolonged reliance on the Hering-Breuer reflex, which allows the infant to protect lung volume until the mechanics of the chest wall and lung have stabilized (Stocks et al. 1996). In the preterm infant, breathing

instability and poor responsiveness to CO₂ may occur in the supine position, which favors thoracic-abdominal asynchrony (Hand et al. 2007). This is alleviated by transition to the prone position.

Because BPD rarely occurs as an isolated condition, there may be additional factors that modulate ventilatory control in this population. Maternal use of nicotine, alcohol, cocaine and opiates impacts the drive to breathe (Cayetanot et al. 2009). Exposure to these agents may have occurred in utero, although their contributions to ventilatory control dysfunction in infants with BPD has not been systematically studied. BPD also may exist in combination with other comorbidities that impact the control of breathing (Bos et al. 1993; Zhao et al. 2011). Alternatively, we do not know how ventilatory control abnormalities that develop in infancy may impact the response to future respiratory comorbidities.

7. Future research directions

We believe that ventilatory control in the context of BPD is not only a potentially fruitful area for physiological research, but that the findings from these studies have the potential to have a real and meaningful impact on the care of human patients. Future research in this area should aim to answer the following three basic questions:

1. How do clinically-relevant perinatal treatments influence the development of the ventilatory drive in patients with BPD?
2. What are the physiological mechanisms by which ventilatory control is impaired in individuals with BPD?
3. What are the long-term consequences of altered ventilatory control for patients with BPD?

7.1 Mechanistic studies and the use of animal models

In this review, we outline several potential mechanisms by which ventilatory control may be altered, but it is important to point out that this is an area where mechanistic data in humans are severely lacking. Using animal models, we can probe the physiological consequences of individual (or a small number of) stressors and use the resultant data to inform our understanding. However, these experiments may miss the complexity of the human patient's experience. That is to say, these stressors when applied in isolation in an animal model may induce physiological changes that are different from those that occur in human patients who rarely encounter stressors in isolation. For example, there are a number of rodents studies cited in this manuscript that have contributed importantly to our understanding of ventilatory control by investigating the impact of perinatal hyperoxia or intermittent hypoxia on ventilatory control. Yet, the infant with BPD experiences both hyperoxia and intermittent hypoxia in a background of permissive hypercapnia. For that reason it is critical that investigators use these compelling findings from animal studies to generate hypotheses testable in humans.

Many studies are uniquely suited for conduct in human research participants. For example, in Section 4.2 we discuss brain lesions in the premature infant with BPD that may contribute to ventilatory control abnormalities during sleep and exercise. Studies investigating the role that these lesions play in ventilatory control abnormalities would be useful both in improving our mechanistic understanding and in identifying subpopulations that may be at higher risk for ventilatory control abnormalities. In Section 3.5 we highlight the need for future study of the hypercapnic ventilatory drive. This is another question well-suited to study in human research participants.

7.2 Proposal for the support of future longitudinal cohort studies

We propose that investigators should strongly consider a focus on humans with BPD in the future. To that end, longitudinal cohorts, like the Newborn Lung Project (NLP) cohorts, will be extremely valuable. The NLP cohorts (birth years 1988–1991 and 2003–2004) encompass all very low birth weight infants born at seven regional Wisconsin and Iowa neonatal intensive care units (NICUs). The major advantages of these cohorts are the availability of medical records in order to retrospectively analyze the relationship between perinatal events and outcomes and the ability to follow the cohort participants as they age. Studies using this cohort have already been immensely informative (Palta et al. 1990; Palta et al. 1991; Palta et al. 1994; Weinstein et al. 1994; Palta et al. 1996; Evans et al. 1998; Palta et al. 1998; Palta et al. 1998; Palta et al. 2000; Palta et al. 2001; Hagen et al. 2006; Palta et al. 2007). We expect that the study of these participants will aid in our understanding of ventilatory control in humans with BPD and hope to see the support of similar cohorts in the future.

We must also ask what happens to these babies after their NICU stay, especially after they reach adulthood. Over the last 10 years, we have come to appreciate the concept of developmental origins of disease such that experiences within the perinatal period can influence the development of disease later in life. Despite this, perinatal history is frequently lost from the medical record in the transfer from the pediatrician to the general family practitioner. While there has been much focus on long-term pulmonary function, lung growth and neuromuscular sequelae in individuals with BPD (Gough et al. 2012), less is known about the challenges to ventilatory control that these individuals may face after they reach adulthood. Certainly very little is known beyond ~20 years of age. However, as these individuals continue to age, it is possible that they will experience a greater disease burden specifically related to alterations in their ventilatory control, including an increased risk of periodic breathing, sleep disordered breathing, and altitude sickness. Discerning the disease risk associated with BPD is an area in which a longitudinally-followed cohort would be exceptionally valuable.

7.3 Methodological considerations for future human cohort studies

The challenge to future investigators lies in determining what events during the perinatal period are the most important in determining respiratory outcomes. In many of the studies cited here, infants were drawn from single hospital populations. To illustrate the potential limitation of this type of approach, we analyzed between-hospital variability in the average number of hours preterm infants from the 1988–1991 NLP cohort were mechanically ventilated, and the percent of preterm infants ventilated (See Figure 3). These data represent infants that were admitted to the NICU for at least 3 days (n=675). We found substantial between-site and within-site variability in the duration of ventilation. We also found substantial variability in the percentage of infants intubated at each center, ranging from 45–83%. We would predict that respiratory outcomes from infants born at Center 2, with a low incidence of intubation, a limited duration of ventilation, and low variability in ventilator time might be different from those obtained from babies born at Center 7, where the incidence of intubation was higher and the variability in ventilator time was greater. Given the high degree of inter-center variability, if the goal of a study were to look at differences in a particular treatment variable, drawing a population from a single center might be the best approach. However, extrapolating data from a single center to the entire population of individuals with BPD might not be appropriate. It is important to recognize that different approaches may be required for physiological versus epidemiological studies.

Extrapolating results forward and backward in time also presents a challenge to future investigators. Consider again our own Newborn Lung Project cohort. This population was

born during an incredibly dynamic period of time in perinatal therapy when glucocorticoids and surfactant were becoming the standard of care. During this three- year period, 21% of infants were exposed to antenatal steroids, 24% received surfactant, and 9% received postnatal steroids (Palta et al. 1998). Due to changes in the clinical approach to management of these infants over the past 20 years, the ability to extrapolate data from this population to future populations of infants may be limited. The use of supplemental oxygen has also changed, beginning with a preference for hyperoxia and moving toward a period of permissive hypoxemia in an attempt to limit BPD and retinopathy of prematurity (STOP-ROP 2000). Some physicians are now favoring a return to hyperoxia, after finding that permissive hypoxemia is associated with an increased risk of mortality (Network et al. 2010).

8. Conclusions

Humans with BPD demonstrate alterations in ventilatory control in response to important physiological stressors, including hypoxia, sleep, exercise, and lung disease. Future studies should be aimed not only at understanding the mechanistic changes in ventilatory control that occur in individuals with BPD, but also in understanding the long-term disease burdens that adult populations might face as a result of impairments in ventilatory control.

Acknowledgments

Drs. Bates and Eldridge received support from the National Institutes of Health for the completion of this work (5R01HL086897 and 5T32HL007654). The authors are indebted to Erica L. White and Dr. Mihaela Teodorescu for their assistance in the preparation of this manuscript.

References

- Abreu LR, Costa-Rangel RCA, et al. Cardiorespiratory capacity assessment on children with bronchopulmonary dysplasia. *Revista Brasileira De Fisioterapia*. 2007; 11(2):105–111.
- Ajayi-Obe M, Saeed N, et al. Reduced development of cerebral cortex in extremely preterm infants. *Lancet*. 2000; 356(9236):1162–1163. [PubMed: 11030298]
- Allen J, Zwerdling R, et al. Statement on the care of the child with chronic lung disease of infancy and childhood. *Am J Respir Crit Care Med*. 2003; 168(3):356–396. [PubMed: 12888611]
- Allen SC, Vassallo M, et al. The threshold for sensing airflow resistance during tidal breathing rises in old age: implications for elderly patients with obstructive airways diseases. *Age Ageing*. 2009; 38(5):548–552. [PubMed: 19589812]
- Bancalari E, Claure N, et al. Bronchopulmonary dysplasia: changes in pathogenesis, epidemiology and definition. *Semin Neonatol*. 2003; 8(1):63–71. [PubMed: 12667831]
- Battin MR, Maalouf EF, et al. Magnetic resonance imaging of the brain in very preterm infants: visualization of the germinal matrix, early myelination, and cortical folding. *Pediatrics*. 1998; 101(6):957–962. [PubMed: 9606219]
- Bavis RW, Fallon SC, et al. Chronic hyperoxia and the development of the carotid body. *Respir Physiol Neurobiol*. 2013; 185(1):94–104. [PubMed: 22640932]
- Bavis RW, Kim I, et al. Recovery of carotid body O₂ sensitivity following chronic postnatal hyperoxia in rats. *Respir Physiol Neurobiol*. 2011; 177(1):47–55. [PubMed: 21420511]
- Bednarek N, Akhavi A, et al. Outcome of cerebellar injury in very low birth-weight infants: 6 case reports. *J Child Neurol*. 2008; 23(8):906–911. [PubMed: 18660474]
- Berry RB, Gleeson K. Respiratory arousal from sleep: mechanisms and significance. *Sleep*. 1997; 20(8):654–675. [PubMed: 9351134]
- Berthon-Jones M, Sullivan CE. Ventilatory and arousal responses to hypoxia in sleeping humans. *Am Rev Respir Dis*. 1982; 125(6):632–639. [PubMed: 6807150]
- Beshish A, Bates ML, et al. Blunted hypoxic ventilatory drive in adult humans with a history of premature birth. *Faseb Journal*. 2012:26.

- Bhat RY, Hannam S, et al. Effect of prone and supine position on sleep, apneas, and arousal in preterm infants. *Pediatrics*. 2006; 118(1):101–107. [PubMed: 16818554]
- Bisgard GW, Olson EB, et al. Adult carotid chemoafferent responses to hypoxia after 1, 2, and 4 wk of postnatal hyperoxia. *J Appl Physiol*. 2003; 95(3):946–952. [PubMed: 12909596]
- Blanco CE, Dawes GS, et al. The response to hypoxia of arterial chemoreceptors in fetal sheep and new-born lambs. *J Physiol*. 1984; 351:25–37. [PubMed: 6747866]
- Bolton CE, Stocks J, et al. The EPICure study: association between hemodynamics and lung function at 11 years after extremely preterm birth. *J Pediatr*. 2012; 161(4):595–601 e592. [PubMed: 22575246]
- Bos AP, Hussain SM, et al. Radiographic evidence of bronchopulmonary dysplasia in high-risk congenital diaphragmatic hernia survivors. *Pediatr Pulmonol*. 1993; 15(4):231–234. [PubMed: 8469576]
- Calder NA, Williams BA, et al. ABSENCE OF VENTILATORY RESPONSES TO ALTERNATING BREATHS OF MILD HYPOXIA AND AIR IN INFANTS WHO HAVE HAD BRONCHOPULMONARY DYSPLASIA - IMPLICATIONS FOR THE RISK OF SUDDEN INFANT DEATH. *Pediatr Res*. 1994; 35(6):677–681. [PubMed: 7936817]
- Cayetant F, Larnicol N, et al. Antenatal environmental stress and maturation of the breathing control, experimental data. *Respir Physiol Neurobiol*. 2009; 168(1–2):92–100. [PubMed: 19427414]
- Chavez-Valdez R, Mason A, et al. Effect of hyperoxic exposure during early development on neurotrophin expression in the carotid body and nucleus tractus solitarius. *J Appl Physiol*. 2012; 112(10):1762–1772. [PubMed: 22422797]
- Chenuel BJ, Smith CA, et al. Ventilatory instability induced by selective carotid body inhibition in the sleeping dog. *Adv Exp Med Biol*. 2004; 551:197–201. [PubMed: 15602964]
- Clark MT, Vergales BD, et al. Predictive Monitoring for respiratory decompensation leading to urgent unplanned intubation in the neonatal intensive care unit. *Pediatr Res*. 2013; 73(1):104–110. [PubMed: 23138402]
- Clemm H, Roksund O, et al. Aerobic Capacity and Exercise Performance in Young People Born Extremely Preterm. *Pediatrics*. 2012; 129(1):E97–E105. [PubMed: 22201154]
- Craig CM, Lee DN, et al. Modulations in breathing patterns during intermittent feeding in term infants and preterm infants with bronchopulmonary dysplasia. *Dev Med Child Neurol*. 1999; 41(9):616–624. [PubMed: 10503920]
- Darnall RA, McWilliams S, et al. Reversible blunting of arousal from sleep in response to intermittent hypoxia in the developing rat. *J Appl Physiol*. 2010; 109(6):1686–1696. [PubMed: 20930126]
- Darnall RA, Schneider RW, et al. Arousal from sleep in response to intermittent hypoxia in rat pups is modulated by medullary raphe GABAergic mechanisms. *Am J Physiol Regul Integr Comp Physiol*. 2012; 302(5):R551–560. [PubMed: 22160541]
- Davenport K, Huang C, et al. Relationship between Respiratory Load Perception and Perception of Nonrespiratory Sensory Modalities in Subjects with Life-Threatening Asthma. *Pulm Med*. 2012; 7.
- Dawes GS, Gardner WN, et al. Breathing in fetal lambs: the effect of brain stem section. *J Physiol*. 1983; 335:535–553. [PubMed: 6875894]
- de Meer K, Heymans HS. Diet and CO₂-production in pediatric chronic pulmonary disease. *J Pediatr Gastroenterol Nutr*. 1989; 9(1):133–134. [PubMed: 2506322]
- Deoras KS, Greenspan JS, et al. EFFECTS OF INSPIRATORY RESISTIVE LOADING ON CHEST-WALL MOTION AND VENTILATION - DIFFERENCES BETWEEN PRETERM AND FULL-TERM INFANTS. *Pediatr Res*. 1992; 32(5):589–594. [PubMed: 1480462]
- Donnelly DF, Bavis RW, et al. Time course of alterations in pre- and post-synaptic chemoreceptor function during developmental hyperoxia. *Respir Physiol Neurobiol*. 2009; 168(3):189–197. [PubMed: 19465165]
- Donnelly DF, Kim I, et al. Perinatal hyperoxia for 14 days increases nerve conduction time and the acute unitary response to hypoxia of rat carotid body chemoreceptors. *J Appl Physiol*. 2005; 99(1):114–119. [PubMed: 15731397]
- Ehrenkranz RA, Walsh MC, et al. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. *Pediatrics*. 2005; 116(6):1353–1360. [PubMed: 16322158]

- Evans M, Palta M, et al. Associations between family history of asthma, bronchopulmonary dysplasia, and childhood asthma in very low birth weight children. *Am J Epidemiol.* 1998; 148(5):460–466. [PubMed: 9737558]
- Fajardo C, Alvarez J, et al. The incidence of obstructive apneas in preterm infants with and without bronchopulmonary dysplasia. *Early Hum Dev.* 1993; 32(2–3):197–206. [PubMed: 8486121]
- Fink GR, Adams L, et al. Hyperpnoea during and immediately after exercise in man: evidence of motor cortical involvement. *J Physiol.* 1995; 489(Pt 3):663–675. [PubMed: 8788932]
- Forster HV. Exercise hyperpnea: where do we go from here? *Exerc Sport Sci Rev.* 2000; 28(3):133–137. [PubMed: 10916706]
- Forster HV, Pan LG, et al. Important role of carotid chemoreceptor afferents in control of breathing of adult and neonatal mammals. *Respir Physiol.* 2000; 119(2–3):199–208. [PubMed: 10722863]
- Garg M, Kurzner SI, et al. Hypoxic arousal responses in infants with bronchopulmonary dysplasia. *Pediatrics.* 1988; 82(1):59–63. [PubMed: 3380600]
- Gaultier C, Gallego J. Development of respiratory control: evolving concepts and perspectives. *Respir Physiol Neurobiol.* 2005; 149(1–3):3–15. [PubMed: 15941676]
- Gewolb IH, Bosma JF, et al. Abnormal developmental patterns of suck and swallow rhythms during feeding in preterm infants with bronchopulmonary dysplasia. *Dev Med Child Neurol.* 2001; 43(7):454–459. [PubMed: 11463175]
- Gough A, Spence D, et al. General and respiratory health outcomes in adult survivors of bronchopulmonary dysplasia: a systematic review. *Chest.* 2012; 141(6):1554–1567. [PubMed: 22116801]
- Greenspan JS, Wolfson MR, et al. INCREASED RESPIRATORY DRIVE AND LIMITED ADAPTATION TO LOADED BREATHING IN BRONCHOPULMONARY DYSPLASIA. *Pediatr Res.* 1992; 32(3):356–359. [PubMed: 1408475]
- Gryboski JD. Suck and swallow in the premature infant. *Pediatrics.* 1969; 43(1):96–102. [PubMed: 5764074]
- Hagen EW, Palta M, et al. School achievement in a regional cohort of children born very low birthweight. *J Dev Behav Pediatr.* 2006; 27(2):112–120. [PubMed: 16682874]
- Hand IL, Noble L, et al. The effects of positioning on the Hering-Breuer reflex in the preterm infant. *Pediatr Pulmonol.* 2007; 42(1):37–40. [PubMed: 17123323]
- Hanson, M.; Eden, G., et al. Peripheral chemoreceptors and other oxygen sensors in the fetus and newborn. In: Lahiri, S.; Forster, R.; Davises, R.; AIP, editors. *Chemoreceptors and reflexes in breathing: Cellular and molecular aspects.* New York: Oxford University Press; 1989. p. 113–120.
- Haouzi P. Theories on the nature of the coupling between ventilation and gas exchange during exercise. *Respir Physiol Neurobiol.* 2006; 151(2–3):267–279. [PubMed: 16412707]
- Haouzi P, Hill JM, et al. Responses of group III and IV muscle afferents to distension of the peripheral vascular bed. *J Appl Physiol.* 1999; 87(2):545–553. [PubMed: 10444611]
- Harris MA, Sullivan CE. Sleep pattern and supplementary oxygen requirements in infants with chronic neonatal lung disease. *Lancet.* 1995; 345(8953):831–832. [PubMed: 7898231]
- Hertel HC, Howaldt B, et al. Responses of group IV and group III muscle afferents to thermal stimuli. *Brain Res.* 1976; 113(1):201–205. [PubMed: 133748]
- Hibbs AM, Johnson NL, et al. Prenatal and neonatal risk factors for sleep disordered breathing in school-aged children born preterm. *J Pediatr.* 2008; 153(2):176–182. [PubMed: 18534222]
- Horn EM, Waldrop TG. Suprapontine control of respiration. *Respir Physiol.* 1998; 114(3):201–211. [PubMed: 9926985]
- Horne RS, Parslow PM, et al. Postnatal development of ventilatory and arousal responses to hypoxia in human infants. *Respir Physiol Neurobiol.* 2005; 149(1–3):257–271. [PubMed: 15876558]
- Hunt CE, McCulloch K, et al. Diminished hypoxic ventilatory responses in near-miss sudden infant death syndrome. *J Appl Physiol.* 1981; 50(6):1313–1317. [PubMed: 7263394]
- Inder TE, Warfield SK, et al. Abnormal cerebral structure is present at term in premature infants. *Pediatrics.* 2005; 115(2):286–294. [PubMed: 15687434]

- Inder TE, Wells SJ, et al. Defining the nature of the cerebral abnormalities in the premature infant: a qualitative magnetic resonance imaging study. *J Pediatr*. 2003; 143(2):171–179. [PubMed: 12970628]
- Jobe AH, Bancalari E. Bronchopulmonary Dysplasia. *American Journal of Respiratory and Critical Care Medicine*. 2001; 163(7):1723–1729. [PubMed: 11401896]
- Jobe AJ. The new BPD: an arrest of lung development. *Pediatr Res*. 1999; 46(6):641–643. [PubMed: 10590017]
- Kajantie E, Strang-Karlsson S, et al. Adults Born at Very Low Birth Weight Exercise Less than Their Peers Born at Term. *Journal of Pediatrics*. 2010; 157(4):610–U130. [PubMed: 20493499]
- Kanda A, Matsui T, et al. Periventricular white matter lesions and sleep alteration in older people. *J Am Geriatr Soc*. 2003; 51(3):432–433. [PubMed: 12588595]
- Karila C, Saulnier JP, et al. Exercise alveolar hypoventilation in long-term survivors of bronchopulmonary dysplasia. *Rev Mal Respir*. 2008; 25(3):303–312. [PubMed: 18449096]
- Kasai T, Floras JS, et al. Sleep Apnea and Cardiovascular Disease A Bidirectional Relationship. *Circulation*. 2012; 126(12):1495–1510. [PubMed: 22988046]
- Kasper DC, Mechtler TP, et al. In utero exposure to *Ureaplasma* spp. is associated with increased rate of bronchopulmonary dysplasia and intraventricular hemorrhage in preterm infants. *J Perinat Med*. 2011; 39(3):331–336. [PubMed: 21526978]
- Katz-Salamon M, Eriksson M, et al. Development of peripheral chemoreceptor function in infants with chronic lung disease and initially lacking hyperoxic response. *Arch Dis Child*. 1996; 75(1):F4–F9.
- Katz-Salamon M, Jonsson B, et al. Blunted peripheral chemoreceptor response to hyperoxia in a group of infants with bronchopulmonary dysplasia. *Pediatr Pulmonol*. 1995; 20(2):101–106. [PubMed: 8570299]
- Kaufman MP, Hayes SG, et al. Discharge properties of group III and IV muscle afferents. *Adv Exp Med Biol*. 2002; 508:25–32. [PubMed: 12171119]
- Khan A, Qurashi M, et al. Measurement of the CO₂ apneic threshold in newborn infants: possible relevance for periodic breathing and apnea. *J Appl Physiol*. 2005; 98(4):1171–1176. [PubMed: 15772056]
- Kriemler S, Keller H, et al. Aerobic and lung performance in premature children with and without chronic lung disease of prematurity. *Clinical Journal of Sport Medicine*. 2005; 15(5):349–355. [PubMed: 16162994]
- Latzin P, Roth S, et al. Lung volume, breathing pattern and ventilation inhomogeneity in preterm and term infants. *PLoS One*. 2009; 4(2):e4635. [PubMed: 19247491]
- Ling L, Olson EB Jr, et al. Attenuation of the hypoxic ventilatory response in adult rats following one month of perinatal hyperoxia. *J Physiol*. 1996; 495(Pt 2):561–571. [PubMed: 8887766]
- Ling L, Olson EB Jr, et al. Phrenic responses to isocapnic hypoxia in adult rats following perinatal hyperoxia. *Respir Physiol*. 1997; 109(2):107–116. [PubMed: 9299642]
- Lovering AT, Romer LM, et al. Excessive gas exchange impairment during exercise in a subject with a history of bronchopulmonary dysplasia and high altitude pulmonary edema. *High Alt Med Biol*. 2007; 8(1):62–67. [PubMed: 17394419]
- Lugliani R, Whipp BJ, et al. Effect of bilateral carotid-body resection on ventilatory control at rest and during exercise in man. *N Engl J Med*. 1971; 285(20):1105–1111. [PubMed: 5095735]
- Lyon A. Chronic lung disease of prematurity. The role of intra-uterine infection. *Eur J Pediatr*. 2000; 159(11):798–802. [PubMed: 11079191]
- MacFarlane PM, Ribeiro AP, et al. Carotid chemoreceptor development and neonatal apnea. *Respir Physiol Neurobiol*. 2013; 185(1):170–176. [PubMed: 22842008]
- McCain GC, Del Moral T, et al. Transition From Gavage to Nipple Feeding for Preterm Infants With Bronchopulmonary Dysplasia. *Nurs Res*. 2012; 61(6):380–387. [PubMed: 22960584]
- McKay LC, Atalla A, et al. Physiology and neural control of breathing during sleep. *Sleep Apnoea, European Respiratory Society Journals Ltd*. 2010; 50:1–16.
- Mense S, Stahnke M. Responses in muscle afferent fibres of slow conduction velocity to contractions and ischaemia in the cat. *J Physiol*. 1983; 342:383–397. [PubMed: 6631740]

- Meny RG, Carroll JL, et al. CARDIORESPIRATORY RECORDINGS FROM INFANTS DYING SUDDENLY AND UNEXPECTEDLY AT HOME. *Pediatrics*. 1994; 93(1):44–49. [PubMed: 8265322]
- Mitchell GS, Babb TG. Layers of exercise hyperpnea: Modulation and plasticity. *Respir Physiol Neurobiol*. 2006; 151(2–3):251–266. [PubMed: 16530024]
- Mizuno K, Nishida Y, et al. Infants with bronchopulmonary dysplasia suckle with weak pressures to maintain breathing during feeding. *Pediatrics*. 2007; 120(4):e1035–E1042. [PubMed: 17893188]
- Nespoulet H, Wuyam B, et al. Altitude illness is related to low hypoxic chemoresponse and low oxygenation during sleep. *European Respiratory Journal*. 2012; 40(3):673–680. [PubMed: 22523356]
- Network, SSGotEKSNR.; Carlo, WA., et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med*. 2010; 362(21):1959–1969. [PubMed: 20472937]
- Ng DK, Chan CH. A review of normal values of infant sleep polysomnography. *Pediatr Neonatol*. 2013; 54(2):82–87. [PubMed: 23590951]
- Northway WH, Rosan RC, et al. PULMONARY DISEASE FOLLOWING RESPIRATOR THERAPY OF HYALINE-MEMBRANE DISEASE - BRONCHOPULMONARY DYSPLASIA. *New England Journal of Medicine*. 1967; 276(7):357. [PubMed: 5334613]
- Novais ARB, Matecki S, et al. Hyperventilation during Exercise in Very Low Birth Weight School-Age Children may Implicate Inspiratory Muscle Weakness. *Journal of Pediatrics*. 2012; 160(3):415–U101. [PubMed: 22050873]
- Palta M, Gabbert D, et al. Development and validation of an index for scoring baseline respiratory disease in the very low birth weight neonate. Severity Index Development and Validation Panels and Newborn Lung Project. *Pediatrics*. 1990; 86(5):714–721. [PubMed: 2235225]
- Palta M, Gabbert D, et al. Multivariate assessment of traditional risk factors for chronic lung disease in very low birth weight neonates. The Newborn Lung Project. *J Pediatr*. 1991; 119(2):285–292. [PubMed: 1861218]
- Palta M, Sadek-Badawi M, et al. Functional assessment of a multicenter very low-birth-weight cohort at age 5 years. Newborn Lung Project. *Arch Pediatr Adolesc Med*. 2000; 154(1):23–30. [PubMed: 10632246]
- Palta M, Sadek-Badawi M, et al. Pulmonary testing using peak flow meters of very low birth weight children born in the perisurfactant era and school controls at age 10 years. *Pediatr Pulmonol*. 2007; 42(9):819–828. [PubMed: 17659600]
- Palta M, Sadek-Badawi M, et al. Respiratory symptoms at age 8 years in a cohort of very low birth weight children. *Am J Epidemiol*. 2001; 154(6):521–529. [PubMed: 11549557]
- Palta M, Sadek M, et al. Evaluation of criteria for chronic lung disease in surviving very low birth weight infants. Newborn Lung Project. *J Pediatr*. 1998; 132(1):57–63. [PubMed: 9470001]
- Palta M, Sadek M, et al. The relation of maternal complications to outcomes in very low birthweight infants in an era of changing neonatal care. *Am J Perinatol*. 1996; 13(2):109–114. [PubMed: 8672182]
- Palta M, Sadek M, et al. Association of tocolytic therapy with antenatal steroid administration and infant outcomes. Newborn Lung Project. *Am J Perinatol*. 1998; 15(2):87–92. [PubMed: 9514131]
- Palta M, Weinstein MR, et al. A population study. Mortality and morbidity after availability of surfactant therapy. Newborn Lung Project. *Arch Pediatr Adolesc Med*. 1994; 148(12):1295–1301. [PubMed: 7951809]
- Parslow PM, Harding R, et al. Ventilatory responses preceding hypoxia-induced arousal in infants: effects of sleep-state. *Respir Physiol Neurobiol*. 2003; 136(2–3):235–247. [PubMed: 12853014]
- Paton JFR, Abdala APL, et al. Respiratory rhythm generation during gasping depends on persistent sodium current. *Nature Neuroscience*. 2006; 9(3):311–313.
- Paulus MP, Flagan T, et al. Subjecting elite athletes to inspiratory breathing load reveals behavioral and neural signatures of optimal performers in extreme environments. *PLoS One*. 2012; 7(1):e29394. [PubMed: 22276111]
- Pawar A, Peng YJ, et al. Comparative analysis of neonatal and adult rat carotid body responses to chronic intermittent hypoxia. *J Appl Physiol*. 2008; 104(5):1287–1294. [PubMed: 18187605]

- Peterson BS, Vohr B, et al. Regional brain volume abnormalities and long-term cognitive outcome in preterm infants. *Jama-Journal of the American Medical Association*. 2000; 284(15):1939–1947.
- Pollard AJ, Niermeyer S, et al. Children at high altitude: An international consensus statement by an ad hoc committee of the International Society for Mountain Medicine, March 12, 2001. *High Alt Med Biol*. 2001; 2(3):389–403. [PubMed: 11682018]
- Poon CS. Response to commentaries on homeostasis of exercise hyperpnea and optimal sensorimotor integration: the internal model paradigm. *Respir Physiol Neurobiol*. 2007; 159(2):139–140. [PubMed: 17766195]
- Poon CS, Tin C, et al. Homeostasis of exercise hyperpnea and optimal sensorimotor integration: the internal model paradigm. *Respir Physiol Neurobiol*. 2007; 159(1):1–13. discussion 14–20. [PubMed: 17416554]
- Raux M, Straus C, et al. Electroencephalographic evidence for pre-motor cortex activation during inspiratory loading in humans. *J Physiol*. 2007; 578(Pt 2):569–578. [PubMed: 17110415]
- Revelette WR, Wiley RL. Plasticity of the mechanism subserving inspiratory load perception. *J Appl Physiol*. 1987; 62(5):1901–1906. [PubMed: 3597264]
- Rosen, CL. Maturation of breathing during sleep. Infants through adolescents. *Sleep and Breathing in Children*. In: Loughlin, GM.; Carroll, JL.; Carcus, CL., editors. A Developmental Approach. New York: Marcel Dekker; 2000. p. 181–205.
- Rosen CL, Larkin EK, et al. Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: association with race and prematurity. *J Pediatr*. 2003; 142(4):383–389. [PubMed: 12712055]
- Ruiz MP, LeFever JA, et al. Early development of infants of birth weight less than 1,000 grams with reference to mechanical ventilation in newborn period. *Pediatrics*. 1981; 68(3):330–335. [PubMed: 6168997]
- Sekar KC, Duke JC. Sleep apnea and hypoxemia in recently weaned premature infants with and without bronchopulmonary dysplasia. *Pediatr Pulmonol*. 1991; 10(2):112–116. [PubMed: 2030919]
- Shannon DC. Pathophysiologic mechanisms causing sleep apnea and hypoventilation in infants. *Sleep*. 1980; 3(3–4):343–349. [PubMed: 6784222]
- Sharma PB, Baroody F, et al. Obstructive sleep apnea in the formerly preterm infant: an overlooked diagnosis. *Front Neurol*. 2011; 2:73. [PubMed: 22144976]
- Smith LJ, van Asperen PP, et al. Reduced exercise capacity in children born very preterm. *Pediatrics*. 2008; 122(2):E287–E293. [PubMed: 18676514]
- Sridhar R, Thach BT, et al. Characterization of successful and failed autoresuscitation in human infants, including those dying of SIDS. *Pediatr Pulmonol*. 2003; 36(2):113–122. [PubMed: 12833490]
- Stebbens VA, Poets CF, et al. Oxygen saturation and breathing patterns in infancy. 1: Full term infants in the second month of life. *Arch Dis Child*. 1991; 66(5):569–573. [PubMed: 2039243]
- Stocks J, Dezateux C, et al. Delayed maturation of Hering-Breuer inflation reflex activity in preterm infants. *Am J Respir Crit Care Med*. 1996; 154(5):1411–1417. [PubMed: 8912757]
- STOP-ROP . Supplemental Therapeutic Oxygen for Prethreshold Retinopathy Of Prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes. *Pediatrics*. 2000; 105(2):295–310. [PubMed: 10654946]
- Teppema LJ, Dahan A. The ventilatory response to hypoxia in mammals: mechanisms, measurement, and analysis. *Physiol Rev*. 2010; 90(2):675–754. [PubMed: 20393196]
- Thebaud B, Abman SH. Bronchopulmonary dysplasia: where have all the vessels gone? Roles of angiogenic growth factors in chronic lung disease. *Am J Respir Crit Care Med*. 2007; 175(10):978–985. [PubMed: 17272782]
- Thompson JM, Mitchell EA, et al. Are the risk factors for SIDS different for preterm and term infants? *Arch Dis Child*. 2006; 91(2):107–111. [PubMed: 15871984]
- Thornton JM, Guz A, et al. Identification of higher brain centres that may encode the cardiorespiratory response to exercise in humans. *J Physiol*. 2001; 533(Pt 3):823–836. [PubMed: 11410638]
- Vrijlandt E, Gerritsen J, et al. Lung function and exercise capacity in young adults born prematurely. *Am J Respir Crit Care Med*. 2006; 173(8):890–896. [PubMed: 16456146]

- Waldrop, TG.; Eldridge, FL., et al. Comprehensive Physiology. John Wiley & Sons, Inc; 2010. Central Neural Control of Respiration and Circulation During Exercise.
- Walsh MC, Yao Q, et al. Impact of a physiologic definition on bronchopulmonary dysplasia rates. *Pediatrics*. 2004; 114(5):1305–1311. [PubMed: 15520112]
- Wasserman K, Whipp BJ, et al. Effect of carotid body resection on ventilatory and acid-base control during exercise. *J Appl Physiol*. 1975; 39(3):354–358. [PubMed: 240799]
- Weinstein MR, Peters ME, et al. A new radiographic scoring system for bronchopulmonary dysplasia. Newborn Lung Project. *Pediatr Pulmonol*. 1994; 18(5):284–289. [PubMed: 7898966]
- Werthammer J, Brown ER, et al. Sudden infant death syndrome in infants with bronchopulmonary dysplasia. *Pediatrics*. 1982; 69(3):301–304. [PubMed: 7199705]
- West, JB. Respiratory Physiology: The Essentials. 8. Philadelphia: Wolters Kluwer; 2008.
- Wilkinson AR, Brosi DM, et al. Functional impairment of the brainstem in infants with bronchopulmonary dysplasia. *Pediatrics*. 2007; 120(2):362–371. [PubMed: 17671063]
- Yoon BH, Jun JK, et al. Amniotic fluid inflammatory cytokines (interleukin-6, interleukin-1beta, and tumor necrosis factor-alpha), neonatal brain white matter lesions, and cerebral palsy. *Am J Obstet Gynecol*. 1997; 177(1):19–26. [PubMed: 9240577]
- Zavorsky GS, Kryder JR, et al. Exercise capacity of children with pediatric lung disease. *Clinical and Investigative Medicine*. 2009; 32(6):E302–E309. [PubMed: 20003836]
- Zhang Q, Wang D, et al. Altered resting-state brain activity in obstructive sleep apnea. *Sleep*. 2013; 36(5):651–659B. [PubMed: 23633747]
- Zhao J, Gonzalez F, et al. Apnea of prematurity: from cause to treatment. *Eur J Pediatr*. 2011; 170(9):1097–1105. [PubMed: 21301866]
- Zinman R, Blanchard PW, et al. Oxygen saturation during sleep in patients with bronchopulmonary dysplasia. *Biol Neonate*. 1992; 61(2):69–75. [PubMed: 1567933]

HIGHLIGHTS

- Individuals with bronchopulmonary dysplasia may experience impairments in ventilatory control
- These impairments extend beyond infancy, with ventilatory control abnormalities noted in childhood and adulthood
- Ventilatory control abnormalities become apparent when metabolic supply and demand are challenged (eg; hypoxia, sleep, and exercise)
- Ventilatory control in bronchopulmonary dysplasia is an important area for future investigation, but investigators should take care to understand the limitations of particular human populations.

Figure 1.

Change in minute ventilation during a five minute eucapnic, 12% O₂ challenge in a 20 year old woman with BPD (Beshish et al. 2012). This individual was clinically unremarkable, with normal spirometric function and exercise capacity. In the comparable term-born participant, minute ventilation increases within the first 30 seconds of hypoxic gas breathing, increasing 65% by the end of five minutes. In the participant with BPD, minute ventilation fails to increase.

Figure 2.

Change in arterial CO₂ (PaCO₂) in a 27 year old man with BPD performing incremental exercise to volitional exhaustion. Note that in a comparable term-born participant, PaCO₂ falls with high intensity exercise as is characteristic of the typical hyperpneic response. In the participant with BPD, PaCO₂ remains constant, indicating the lack of a hyperpneic response. This individual had previously experienced high altitude pulmonary edema and had compromised spirometric function (see (Lovering et al. 2007) for the complete case report).

Figure 3.

Mechanical ventilator duration (ventilator hours $\pm$ SD) and intubation frequency of very- and extremely-low birth weight infants at seven NICUs in Wisconsin and Iowa between 1988 and 1991 (n=675 infants). Note the high variability in both parameters. Given this high degree of inter-center variability, we might expect similarly high variability in response from individuals born at different centers. Understanding and quantifying this variability is important in future clinical studies.