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Review

Ventilatory control in infants, children, and adults with bronchopulmonary dysplasia☆

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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 O_2 supply and CO_2 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.

1. Introduction

The primary purpose of the respiratory system is to support metabolism, largely by facilitating the delivery of O_2 and removal of CO_2. 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 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 O_2 delivery and CO_2 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

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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 O_2 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 O_2 for ≥28 days but not at 36 weeks' postmenstrual age (PMA) or at discharge.
- Moderate – a need for supplemental O_2 for ≥28 days plus treatment with <30% O_2 at 36 weeks PMA.
- Severe – a need for supplemental O_2 for ≥28 days plus ≥30% O_2 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 (SpO_2) at 36 weeks postmenstrual age (Walsh et al., 2004). These authors suggest a diagnosis of BPD when SpO_2 <96% in pressure-supported patients or patient receiving >30% O_2, without the need for additional challenge. In patients without pressure or O_2 support, or with SpO_2 >96% while breathing >30% O_2, BPD is defined as SpO_2 <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 PO_2. 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 PaO_2 < 25 mm Hg, 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 PaO_2 increases to a level similar to that observed in the adult (from <25 mm Hg PaO_2 to ~55 mm Hg), (2) the ability of CO_2 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% O_2 (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, 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

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