Pediatrics and Neonatology (2013) 54, 228–234

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: http://www.pediatr-neonatol.com

REVIEW ARTICLE

The Preterm Lung and Airway: Past, Present, and Future

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Received Feb 4, 2012; received in revised form Jan 18, 2013; accepted Mar 1, 2013

Key Words
bronchopulmonary dysplasia;
neonatal lung injury;
neonatal respiratory therapy

The tremendous advancement that has occurred in neonatal intensive care over the last 40–50 years can be largely attributed to greater understanding of developmental pathobiology in the newborn lung. Nonetheless, this improved survival from respiratory distress syndrome has been associated with continuing longer-term morbidity in the form of bronchopulmonary dysplasia (BPD). As a result, neonatal lung injury is a renewed focus of scientific interest. The onset of such an injury may begin in the delivery room, and this has generated interest in minimizing oxygen therapy and aggressive ventilatory support during the transition from fetal to neonatal lung. Fortunately, antenatal steroid therapy and selective use of surfactant therapy are now widely practiced, although fine tuning of this therapy for selected populations is ongoing. Newer therapeutic approaches address many aspects of BPD, including the pro-inflammatory component that characterizes this disorder. Finally, there is a greater need to understand the epidemiology and pathogenesis of the longer-term respiratory morbidity, most notably asthma, that persists in the preterm survivors of neonatal intensive care.

1. Introduction

It is 45 years since Northway and colleagues first coined the term "bronchopulmonary dysplasia" (BPD) to describe a chronic form of neonatal lung injury associated with delivery of barotrauma to a group of preterm infants.[1] Over the ensuing decades, the spectrum of disease has changed and the emphasis has moved away from baro- or even volutrauma as fundamental to its etiology. Nonetheless, the etiology remains multifactorial, as summarized in Figure 1. Although the low gestation associated with an underdeveloped lung is the key ingredient of BPD, pathobiology is clearly aggravated by the presence of intrauterine growth restriction, supplemental oxygen exposure, pre- and postnatal pro-inflammatory mechanisms, and nutritional deficits compromising lung maturation and repair.[2,3] Early

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1875-9572/$36
http://dx.doi.org/10.1016/j.pedneo.2013.03.001

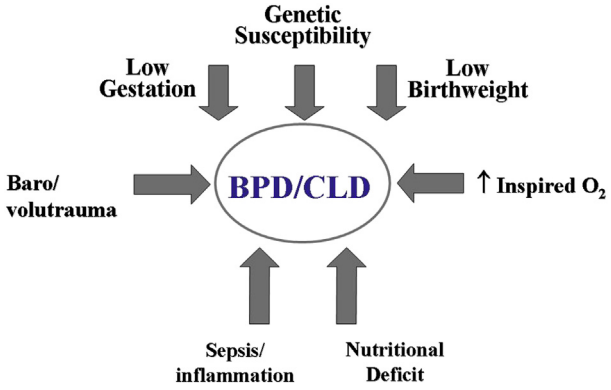

Figure 1 An overview of the major multifactorial factors contributing to the genesis of BPD or CLD of the neonate. BPD = bronchopulmonary dysplasia; CLD = chronic lung disease.

evidence also points to a genetic predisposition, the basis of which still needs to be unraveled.[4,5]

During embryogenesis, airway branching plays a central role in lung development. Nonetheless, over the last decade, the focus of research in BPD has been on impaired alveolar development resulting in larger, "simplified" alveolar structures.[6] This line of investigation has been complemented by novel studies demonstrating an important role for intrapulmonary vascular structures and downstream signaling via vascular endothelial growth factor (VEGF) on lung parenchymal development.[7] Available outcome data suggest a later reduction in pulmonary diffusing capacity, reflecting a decrease in gas transfer across the alveolar/capillary unit and possibly abnormal lung parenchyma in the low-birth-weight BPD survivors.[8] At the same time, there has been increasing recognition that the epidemiology of BPD has changed considerably, placing at risk extremely low-birth-weight infants exposed to no or minimal barotrauma and to relatively low levels of supplemental oxygen over the first days of life. Such infants may develop a respiratory deterioration as late as 1—2 weeks postnatally, and a pro-inflammatory process is often implicated in this downhill progression to BPD.[9]

The pathobiology of injury to the immature airway has taken somewhat of a backseat to unraveling the signaling pathways that regulate aberrant alveolar development. Although traumatic injury to structurally immature, compliant airway structures is well described as a result of ventilator-induced lung injury, this problem is probably diminished by decreased use of intermittent positive pressure ventilation. By contrast, asthma and wheezing disorders manifested by increased airway reactivity are the major longer term respiratory morbidity demonstrated by former preterm infants. Lung parenchymal structures and intrapulmonary airways are anatomically closely interrelated such that parenchymal damage may decrease the tethering between airways and lung parenchyma and compromise airway caliber.[10] This review will focus primarily on the pathophysiology of lung injury as it impacts on airway function, recognizing that such injury may begin as early as during the fetal to neonatal transition.

2. Optimizing the fetal to neonatal respiratory transition

2.1. Oxygen

There is considerable current interest in enhancing an effective fetal to neonatal respiratory transition while avoiding short- or potential longer-term injury with therapeutic interventions imposed on preterm infants. The use and abuse of supplemental oxygen immediately after delivery has attracted great interest.[11] We are most indebted to Saugstad and Vento for drawing attention to the hazards of supplemental oxygen at this vulnerable period in the immature infant. Hyperoxia at this time has been shown to delay the onset of spontaneous respiratory efforts and potentially leads to unnecessary subsequent interventions. More importantly, brief but excessive oxygen exposure may result in greater expression of reactive oxygen species and oxidant-induced impairment of metabolic function. This may be caused by exposure of the airway epithelium to excessive supplemental oxygen with potential adverse effects on airway-related signaling pathways. Systemic effects may also come into play as demonstrated by elevated markers of both oxidant and inflammatory stress in blood and urine of high versus low oxygen-exposed infants.[12] A provocative single-center study demonstrated that initially high versus low supplemental oxygen exposure after delivery may be associated with a greater need for ventilatory support and a higher subsequent incidence of BPD in the high oxygen group.[12] This has spawned a series of blinded multicenter studies to further evaluate both optimal practice (concentration of blended oxygen accompanied by pulse oximetry) and outcome (focused on BPD) with regard to initial oxygen administration for this high risk population.

2.2. Ventilation

In the preterm infant, we seek to rapidly establish an optimal functional residual capacity (FRC) in order to support gas exchange without provoking a stretch-induced injurious cascade of lung injury. Recent studies have employed a fetal lamb model briefly ventilated in the absence of supplemental oxygen while exteriorized, then returned to the uterus prior to delivery.[13] These data provide evidence for a pro-inflammatory cascade and bronchial epithelial disruption initiated by just a brief period of positive ventilation in the fetal model. te Pas and colleagues have also employed animal models to determine the ability of ventilatory techniques to open the lungs and establish an FRC.[14] They have documented that a longer sustained inflation at delivery is associated with more rapid establishment of an FRC. However, the resultant rapid lung aeration and improved oxygenation must be weighed against the potential for initiating lung or airway injury.

Finally, in our attempts to minimize the need for endotracheal intubation and intermittent positive pressure ventilation, continuous positive airway pressure (CPAP)-based strategies have been widely studied in well-designed multicenter trials.[15,16] It can be concluded from their studies that an initial CPAP-based strategy provides an