Pediatrics and Neonatology (2013) 54, 228–234

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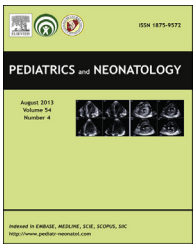

REVIEW ARTICLE

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

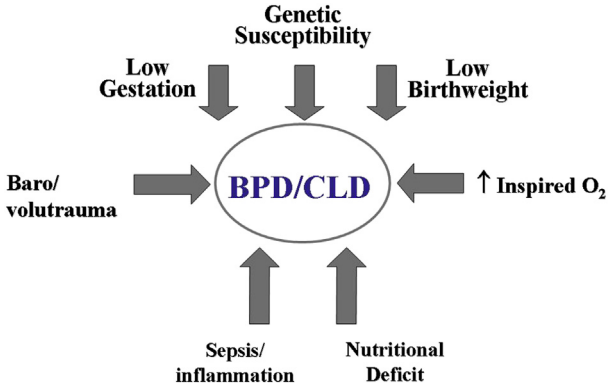

Figure 1 An overview of the major multifactorial factors contributing to the genesis of BPD or CLD of the neonate. BPD = bronchopulmonary dysplasia; CLD = chronic lung disease.

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

effective alternative to immediate intubation and surfactant administration for many infants in the 25—28 weeks' gestation range. Unfortunately, there is currently no simple bedside test or biomarker to determine which very preterm infants are likely to succeed with a CPAP-based strategy and clinical judgment must prevail as excessive delay in surfactant therapy may be suboptimal.

3. Antenatal steroid and surfactant therapy: What's new?

3.1. Antenatal steroids

Use of antenatal corticosteroids in women at risk of preterm delivery to facilitate fetal lung maturation is an established standard of care. Many clinical trials[17,18] conducted over the past four decades have demonstrated that a single course of antenatal corticosteroid treatment reduces the incidence of RDS by at least 50% (odds ratio 0.35; 95% CI 0.26, 0.46) and substantially reduces mortality (odds ratio 0.60; 95% CI 0.48, 0.76).[18] These beneficial effects are independent of postnatal surfactant therapy. There is still debate about the best product and this is unlikely to be resolved.

Multiple courses of antenatal corticosteroids are reserved for women who have continued the pregnancy after an initial course, administered in anticipation of imminent delivery, and who are now about to deliver prior to 34 weeks' gestation. There is some concern that multiple dosing would adversely affect fetal and neonatal growth; however, this is probably not a significant longer-term clinical problem if total dosing does not exceed two courses.[19]

Carlo et al reported that among infants born at 23—25 weeks' gestation, antenatal exposure to corticosteroids compared with non-exposure was associated with a lower rate of death or neurodevelopmental impairment at 18—22 months. This may extend the use of antenatal corticosteroids to 23 weeks, although even with antenatal corticosteroids, an adverse outcome, including death, was observed in 83% of the infants, compared with 90% in those not exposed to steroids.[20] Finally, there is interest in the role of antenatal steroids for the late preterm infant. This is consistent with recent data that airway expression of epithelial sodium channels correlates with cortisol in term infants, such that postnatal fluid resorption might be enhanced with exogenous steroid therapy and the incidence of transient tachypnea of the newborn decreased.[21]

3.2. Surfactant therapy

Much is now known about the surfactant proteins, their inheritance, functions, and gene structure. Surfactant proteins A and D are integral components of the host defense, whereas surfactant proteins B and C reduce surface tension. Surfactant protein B (SFTPB) deficiency disrupts cellular processes in Type 2 alveolar cells causing lethal respiratory failure. It is inherited as an autosomal recessive and is accompanied by misprocessing of surfactant protein C (SFTPC). More inherited disorders of surfactant metabolism have been recognized and include mutations in the genes encoding SFTPB, SFTPC, ATP binding cassette member A3 (ABCA3), and thyroid transcription factor (NKX2.1).[22,23]

Inherited disorders of surfactant metabolism present as acute, severe respiratory dysfunction in the neonatal period (SFTPB, ABCA3, NKX2.1) or as chronic respiratory insufficiency in later infancy and childhood, which is of variable onset, severity, and course (SFTPC, ABCA3, NKX2.1). SFTPC deficiency has a dominant inheritance causing respiratory distress syndrome, chronic lung disease of infancy, and adult respiratory distress syndrome.[23] Diagnosis is established with sequencing of the relevant genes, and supported by lung biopsy with electron microscopy. The treatment options for SFTPB and ABCA3 deficiency (recessive disorders) if they present with intractable respiratory failure in the neonatal period are limited to lung transplantation or compassionate care.

For almost a quarter of a century, we have been administering various surfactants to neonates. It has been established that the surfactant pool in preterm infants is very small, hence relatively large doses (100—200 mg/kg) are needed. Antenatal corticosteroids enhance the clinical response to surfactant. Remarkably, in the SUPPORT Trial, only 67% of infants in the CPAP limb required surfactant.[24] Much of the debate today concerns the various surfactants and their route of administration. Singh et al, in a meta-analysis, reported that there were significant reductions in deaths and the need for re-dosing with high-dose poractant alfa (200 mL/kg), but not low-dose poractant alfa (100 mg/kg) compared with beractant.[25] Göpel et al successfully administered surfactant via a thin catheter in spontaneously breathing preterm infants receiving CPAP. There were no complications, and the need for mechanical ventilation was reduced.[26] This technique is also being currently studied by Dargaville et al, and it needs to be further evaluated as we strive to avoid intubation, with the attendant risks of sedation, barotrauma, and volutrauma.[27]

The emphasis for many years has been on prophylactic administration of surfactant. The dogma was that the earlier the prophylactic surfactant was administered, the better the outcome for infants below 29 weeks' gestation. Recent findings have challenged these concepts by consistently demonstrating that prophylactic surfactant is not superior to nasal CPAP (nCPAP) and early selective surfactant in decreasing the need for mechanical ventilation or the incidence of main morbidities of prematurity in spontaneously breathing, very preterm infants. Dunn et al, from the Vermont—Oxford Network, randomized preterm neonates to either nCPAP or prophylactic surfactant with rapid extubation to CPAP.[28] The clinical outcomes were similar (mortality, bronchopulmonary dysplasia, and other complications of prematurity). They concluded that an approach that uses early CPAP leads to a reduction in the number of infants who are intubated and given surfactant without evidence of harm. The NICHD SUPPORT Trial led by Finer and the Italian trial headed by Sandri came to a similar conclusion. The trend, therefore, is to commence nCPAP in infants who are breathing spontaneously and selectively administer surfactant if and when they require intubation and mechanical ventilation with the objective of rapidly extubating back to nCPAP.[24,29]

4. Impact of therapeutic approaches on lung and airway function

4.1. Inhibition of inflammatory mechanisms

Proinflammatory mechanisms have been widely implicated in the pathogenesis of BPD.[30] This is supported by the observation that postnatal steroid therapy enhances the ability to extubate many infants with developing lung injury, although potential benefit must be weighed against the adverse neurodevelopmental side effects of such therapy. Longer-term outcome studies have focused on neurodevelopmental rather than respiratory follow-up of postnatal steroid therapy; however, if extubation is enhanced, one would expect that longer-term airway function would be improved. There is still controversy regarding optimal dosing and timing of postnatal steroid therapy, and whether reduction in its use has been associated with an increase in the incidence or severity of BPD in NICU survivors.[31] Future clinical data may provide greater detail on specific cytokine-mediated pathways in neonatal lung injury, thus providing a safer, more selective, approach to therapy.

4.2. Targeting lung elastase

Given the functional interdependence of lung parenchyma and intrapulmonary airways, it is important to consider experimental approaches that minimize elastin degradation in the genesis of neonatal lung injury. Earlier studies in preterm infants have demonstrated imbalance in elastase/anti-elastase ratios associated with neonatal lung injury.[32,33] Recent data in mechanically ventilated neonatal mice have shown that intratracheal administration of a specific lung protease inhibitor protected against neonatal lung injury induced by a combination of mechanical ventilation and high oxygen exposure.[34] This may be a mechanism for the slight decrease in BPD observed in preterm infants treated with a prolonged course of vitamin A.[35,36]

4.3. Caffeine therapy

Use of xanthines (theophylline and caffeine) has been widespread for treating apnea since the 1970s. The most widely accepted mechanism of action is inhibition of adenosine receptors and resultant increase in respiratory neural output. However, xanthines also inhibit phosphodiesterase and the resultant increase in cyclic AMP may cause bronchodilatation (Figure 2). Of relevance is the large multicenter trial performed in the last decade that demonstrated a decrease in the need for supplemental oxygen and mechanical ventilation in caffeine versus placebo-treated preterm infants.[37] Neurodevelopmental outcome at 18–21 months seems to benefit from caffeine therapy, and data on longer-term benefit on airway and respiratory function are pending.[38]

Intermittent hypoxic episodes are almost universal in preterm infants and a likely source of oxidant stress.[39] A vicious cycle of oxidant stress and pro-inflammatory mechanisms may contribute to lung and airway injury in this population. Therefore, antioxidant therapy might represent a novel therapeutic approach. Only one clinical trial has addressed this strategy in preterm infants.[40] The researchers administered intratracheal recombinant human superoxide dismutase repeatedly for up to 1 month and did not impact the incidence of BPD. However, there was a significant decrease in wheezing disorders and the need for bronchodilator therapy in the treated group at 1 year of age. Despite this encouraging result, further clinical trials are not ongoing, in part because of limited pharmaceutical interest.

4.4. Inhaled nitric oxide and airway function

Animal models of BPD have demonstrated remarkable improvement in lung function when exposed to a several week course of inhaled nitric oxide (NO).[41] These and other data led to great enthusiasm for this therapy as a way to decrease BPD. However, a series of large, well-designed, multicenter, clinical trials failed to demonstrate a consistent benefit from inhaled NO; a consensus statement concluded that, despite biological plausibility, available data do not support its use to prevent or treat BPD.[42] Unfortunately, there was great heterogeneity in the various trials making metanalysis a problem. One study employing a prolonged course of initially high-dose NO did demonstrate a significant increase in survival without BPD in NO-treated infants.[43] Interestingly, the 1-year outcome

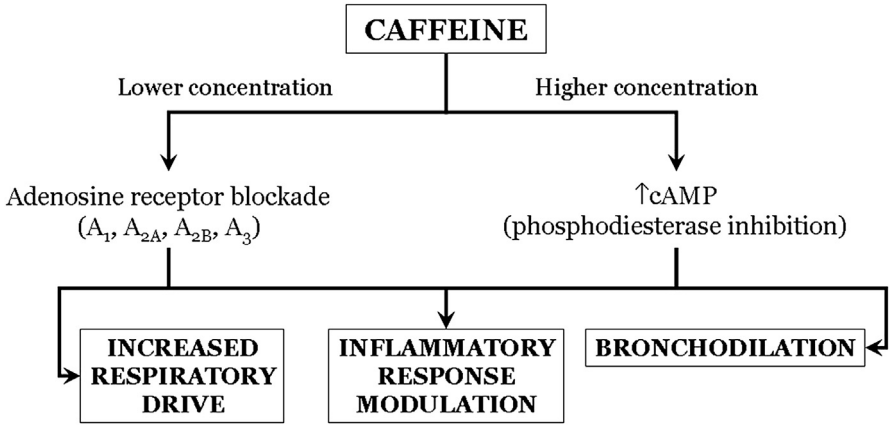

Figure 2 Proposed beneficial effects of xanthine therapy in preterm infants at risk for BPD. BPD = bronchopulmonary dysplasia.

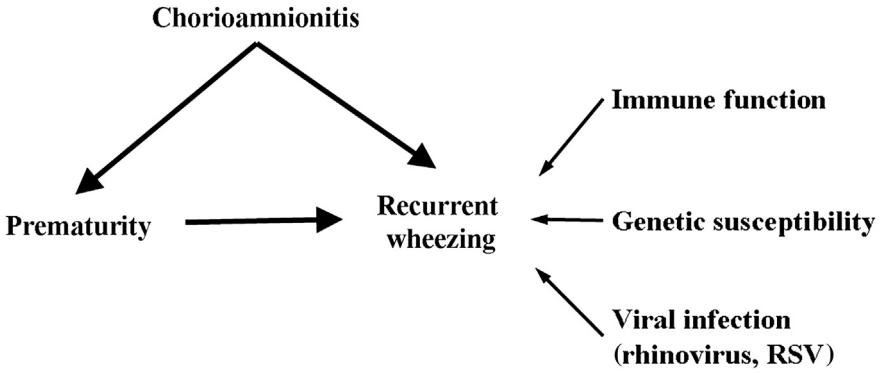

Figure 3 Risk factors for recurrent wheezing in former preterm infants. RSV = respiratory syncytial virus.

of that cohort demonstrated significantly decreased use of bronchodilator therapy in the NO-treated infants, with a number needed to treat of 6.3.[44] Again, these data demonstrate the potentially important role of airway function in assessing neonatal outcomes.

5. Respiratory function in former preterm infants

It was recognized from the earliest cohort of BPD patients that late pulmonary sequelae may persist into adolescence and young adulthood.[45] As already indicated, the epidemiology of BPD has changed significantly over the ensuing decades. Nonetheless, pulmonary sequelae of preterm birth remain a clinical problem of considerable magnitude.

The major focus of this problem is wheezing disorders and asthma in former preterm infants. Numerous studies from a variety of international preterm cohorts have identified an increased need for bronchodilator therapy, or higher airway resistance, and/or airway reactivity.[46] Hack et al documented a three-fold higher asthma rate in a school age cohort of extremely low-birth-weight infants born in the 1990s when compared with sociodemographically matched term controls.[47] Interestingly, when the same preterm cohort was studied in adolescence, their asthma rate had not changed, whereas the asthma rate had significantly increased in the term controls.[48] It is tempting to speculate from these data that the "asthma phenotype" may differ somewhat between former preterm and term infants. One possible explanation is that allergic manifestations may actually be lower in former preterm infants.[49] As shown in Figure 3, both antenatal factors, such as chorioamnionitis and intrauterine growth restriction, as well as postnatal factors related to genetic predisposition, immune mechanisms, and environment exposures may impact on later wheezing disorders.[50]

It is clearly apparent that the incidence of asthma in former preterm infants is enhanced in survivors with BPD. In the United Kingdom cohort of extremely low-birth-weight infants that constituted the EPICure Study, impaired lung function persisted into middle childhood, especially among those with BPD.[51] Approximately 25% of these infants had a positive bronchodilator response, indicative of increased airway reactivity, which was not necessarily recognized and, therefore, may have benefitted from appropriate treatment. Compromise in airflow, as measured by pulmonary function testing, may persist into late adolescence as a consequence of BPD.[46]

Beyond measurements of airway function, there are only limited data on lung parenchymal growth in the very low-birth-weight survivors of BPD. Recent data from a cohort up to 18 months of age indicate normal alveolar volumes corrected for body length, but reduced pulmonary diffusing capacity for alveolar volume, indicative of improved alveolar development.[8] Given the high rate of survival in this population, morphometric data from infants with BPD are not readily available, and we are dependent on respiratory function and imaging studies to follow these patients. It will be of great interest to continue this documentation as the survivors of preterm birth with and without BPD reach early and mid-adulthood.

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