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Vulnerability of the developing airway

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ABSTRACT

Longer term respiratory morbidity is a frequent concern for former preterm infants. Increased airway reactivity and wheezing disorders are extremely common in this population, both in infants who meet diagnostic criteria for bronchopulmonary dysplasia [BPD], and in the absence of this diagnosis. It is, therefore, imperative to gain a better understanding of normal and abnormal postnatal development of the immature airway. Airway hyperreactivity may be secondary to abnormal bronchoalveolar attachments in the face of parenchymal lung injury, or secondary to an imbalance between constrictor and dilator neural pathways. Finally, the airway itself may undergo functional and/or structural changes, including increased airway smooth muscle mass, and changes in airway extracellular matrix which may, in turn, modulate downstream signaling pathways to hyperoxia or pressure exposed vulnerable airways.

1. Introduction

It has been five decades since Northway et al (Northway et al., 1967) 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. Airway dysfunction was a major complication in the follow-up of this cohort. Over the ensuing decades the spectrum of disease has changed, however, the etiology remains multifactorial (Reyburn et al., 2012). While the low gestation associated with an underdeveloped lung is the key driver of chronic lung injury, pathobiology is clearly aggravated by the presence of intrauterine growth restriction, supplemental oxygen exposure, pre- and postnatal proinflammatory mechanisms, and nutritional deficits compromising lung maturation and repair (Trembath and Laughon, 2012). Meanwhile, there has been a widespread shift from invasive mechanical ventilation to non-invasive [CPAP, nasal mask] ventilation over the last decade. Unfortunately, this has not been associated with a clear decrease in school age respiratory morbidity as measured by airway function (Doyle et al., 2017). This raises the question: why do former preterm/term infants wheeze?

2. Airway hyperreactivity in former preterm infants

The pathobiology of injury to the immature airway has taken somewhat of a backseat to unraveling the signaling pathways that regulate aberrant alveolar development. While 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. On the other hand, asthma and wheezing disorders manifested by airway hyperreactivity are the major longer-term respiratory morbidities demonstrated by former preterm infants.

In the United States approximately one in 10 children will receive a diagnosis of asthma (Been et al., 2014). In premature infants the rate may be as high as one in three. Large international birth cohorts have similarly revealed elevated asthma risk in premature infants compared with their term peers. These studies have found that the most premature infants have the most risk, but even moderately premature infants have a significantly increased risk for asthma. McEvoy observed a 33% higher respiratory resistance in late preterm versus term controls at 40 weeks' postmenstrual age at comparable weights (McEvoy et al., 2013).

The asthma phenotype in preterm infants may differ from the allergic asthma seen in their term peers. The airway hyperreactivity observed in former preterm neonates is strongly associated with a history of prolonged supplemental oxygen exposure and/or exposure to some form of positive pressure compared with the airway hyperreactivity observed in term controls which, instead, is associated with a history of genetic inheritance, allergy, and airway inflammation. Hack and colleagues have reported that formerly extremely preterm low-birthweight children at eight years of age were likelier than their normal-birth-weight controls to require medication for asthma [23% versus 8%,

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respectively] (Hack et al., 2011). The rates of asthma medication use did not change between the ages of 8 and 14 years among the extremely low-birth-weight cohort [23% at both ages], but did increase among former normal-birth-weight controls from 8% to 17%. This increase in the use of asthma medication in the control group appears to be consistent with the increase in allergic asthma that is seen in teenagers. Overall, these data suggest stability in wheezing prevalence among extremely low-birth-weight children as they age, with increased incidence of allergic asthma among their teenage peers. In follow-up studies of children and adults born prematurely, there continues to be evidence of impaired pulmonary function, manifesting signs of obstructive pulmonary disease with decreased predicted forced expiratory volume in one second (Caskey et al., 2016).

Recognition of prematurity as an independent risk factor for childhood and long-term wheezing, even among the late preterm infant and those infants who do not have a diagnosis of BPD, should prompt the clinician to make families aware of the future risk and avoid exogenous exposure to cigarettes. Future investigation of the pathophysiology and clinical indicators of airway disease among former preterm infants will, hopefully, lead to targeted interventions and long-term management strategies in this high-risk population.

3. Role of the lung parenchyma

During embryogenesis airway branching plays a central role in lung development. Nonetheless, over the last decade the focus of research in BPD and chronic lung injury has been on impaired alveolar development resulting in larger 'simplified' alveolar structures (Jobe and Bancalari, 2001). 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 on lung parenchymal development (Kunig et al., 2005). 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 survivors of BPD (Balinotti et al., 2010).

Data of alveolar structure and function are challenging to obtain, therefore, the focus of follow-up studies has been airway function which is readily available. This raises the question whether adverse airway function is contributed to by abnormal alveoli. Mansell et al. found that airway-parenchymal coupling played an important role in the way immature airways react to changes in transpulmonary pressure (Mansell et al., 1985). Lung parenchymal structures and intrapulmonary airways are anatomically closely interrelated such that parenchymal damage may decrease the tethering between airways and lung parenchyma and comprise airway caliber (Colin et al., 2010). In support of this concept O'Reilly has shown that hyperoxia exposed neonatal rats have a long-lasting decrease in alveolar-airway attachments, potentially decreasing airway caliber and predisposing to airway hyperreactivity (O'Reilly et al., 2014). Unfortunately, there are limited data on how parenchymal injury impacts airway function.

4. Neuroepithelial contribution to airway smooth muscle function

Elegant immunohistochemical studies of developing human and porcine fetal airways have been performed from as early as the first trimester (Sparrow and Lamb, 2003). These have revealed the development of an airway smooth muscle layer by the end of the human embryonic period, extending from the trachea to terminal lung sacs, as well as an extensive nerve plexus comprising nerve trunks and ganglia, investing the airways and innervating smooth muscle.

This layer of airway smooth muscle is functional in the first trimester as evidenced by phasic spontaneous narrowing and relaxation of airways with back and forth movement of lung fluid (Sward-Comunelli et al., 1997). Phasic or tonic activity in airway smooth muscle might stimulate lung growth by providing positive intraluminal pressure. These data are consistent with human autopsy findings that airway smooth muscle is present at 23 weeks' gestation at all levels of the conducting airways and is increased in amount during the earliest signs of developing chronic lung disease, as early as 10 days after birth.

Despite clear evidence of an intact airway smooth muscle layer early in gestation, the effect of postnatal maturation on airway contractile responses is somewhat controversial. Physiologic studies using isolated tracheal smooth muscle strips from several species have demonstrated decreased, vagally mediated, cholinergic responsiveness in early postnatal life (Haxhiu-Poskurica et al., 1993; Panitch et al., 1985a). These in vitro studies are complicated by the need to carefully normalize the airway constriction response for smooth muscle mass and myosin content. Another study with piglets found a significant decrease in bronchial compliance between 1 and 4 weeks of age (McFawn and Mitchell, 1997). Additionally, bronchial segments from deceased human infants in the same report had twice the compliance when compared to older children (4 to 11 years). The weight of evidence currently appears to point to an anatomically intact airway smooth muscle layer superimposed on highly compliant airway structures in early postnatal life.

Many factors may contribute to the increased airway reactivity seen after neonatal hyperoxic exposure [Fig. 1]. One likely contributor is enhancement of the cholinergic pathway leading to airway constriction. Epithelial injury with loss of airway relaxant factors may also contribute to the hyperoxia-induced increase in airway constriction. This is supported by data from tracheal strips in preterm sheep in which epithelium removal was associated with greater cholinergic responsiveness (Panitch et al., 1985b). Additionally, epithelial injury will lead to reduced barrier function in addition to mediator release. A similar phenomenon is observed in rat pups, in which the response of lung resistance induced by vagal stimulation was increased after non-specific blockade of nitric oxide (NO) synthase in normoxic animals (Iben et al., 1985). However, after hyperoxic exposure NO synthase blockade no longer affected the contractile response induced by vagal stimulation. These findings indicate that NO, released by stimulation of vagal preganglionic fibers, modulates bronchopulmonary constriction responses to endogenously released acetylcholine in rat pups. This effect appears to be lost after prolonged hyperoxic exposure and may contribute to airway hyperreactivity under these conditions. Impairment of the prostaglandin/cyclic adenosine monophosphate signaling pathway may also contribute to hyperoxia-induced airway hyperreactivity (Mhanna et al., 2004). Data suggest that hyperoxic conditioning during early postnatal life impairs relaxation by impairing dephosphorylation of the 20-κDa regulatory light chain of myosin (Smith et al., 2007).

An alternate line of investigation has been to characterize the enhancement of contractile function in the airway. Neurotrophins belong to a protein family essential for vertebrate nervous system development. They are also expressed in epithelial smooth muscle and immune components of the lung (Yao et al., 2005). The neurotrophin family includes brain derived neurotrophic factor [BDNF], nerve growth

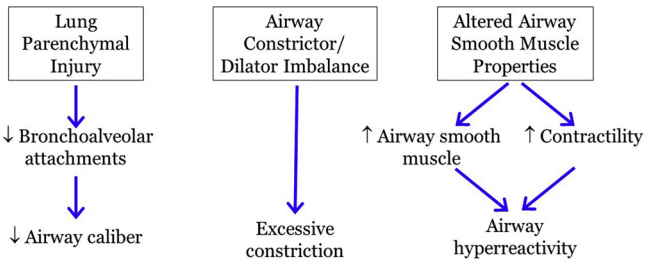

Fig. 1. Factors related to hyperoxia exposure in preterm infants and possible underlying mechanisms resulting in future respiratory morbidity including juvenile airway hyperreactivity. The relative contribution of decreased airway caliber and increased airway constriction to small airway hyperreactivity need further studies.

factor, neurotrophin 3, and neurotrophin 4. They share common structural features and act through their corresponding high-affinity tyrosine receptor kinase subtypes. The rapid excitatory activity of BDNF is via activation of tyrosine receptor kinase B. BDNF appears to stabilize excitatory [e.g., cholinergic] postsynaptic receptors, and/or enhance quantal excitatory neurotransmitter release, probably via postsynaptic Ca^{2+} signaling. During development, regulation of the lower airway appears to be influenced by neurotrophins. Data show the presence of neurotrophins and their corresponding receptor on airway smooth muscle cells in developing rat pups and upregulation of the BDNF system after hyperoxic exposure (Prakash et al., 2006; Martin et al., 2016). The precise role of BDNF in upregulating contractile responses of immature airways and respiratory structures remains to be determined.

5. Interventions impacting airway smooth muscle function

a Role of Hyperoxia

Preterm infants who are < 32 weeks are at a higher risk for developing BPD as they need longer time on oxygen and ventilation. While late preterm infants do not typically require that much oxygen or ventilation support, they are still at risk for long-term airway hyperreactivity and asthma (Colin et al., 2010; Doyle et al., 1996). The question, however, remains whether this is secondary solely to the immaturity of the airways or if supplemental oxygen treatment plays an important role.

Reactive oxygen species (ROS) related damage to airway epithelium and secondary disruption of cellular function has long been postulated as a direct result of hyperoxia. This theory has driven the change in practice in most NICUs towards using more modest oxygen supplementation. Recent evidence suggests that hyperoxia significantly affects the developing airway and may result in long-term morbidity in the form of wheezing and asthma (Jobe and Kallapur, 2010).

Airway remodeling secondary to hyperoxia also alters airway structure and function. Airway remodeling may include increased airway smooth muscle mass or increased extracellular matrix (ECM) deposition around the airways. Wang et al. studied the effects of different levels of hyperoxia on the developing mouse airway and found that mild hyperoxia (40%) had a more detrimental effect on methacholine-induced airway reactivity and lung compliance compared to severe hyperoxia (70%) (Wang et al., 2014). Mild hyperoxia caused a significant dose-dependent increase in airway resistance and a simultaneous decrease in lung compliance in response to methacholine. The same was true for airway smooth muscle mass around the airway which was increased in the mild hyperoxia compared to severe hyperoxia groups. An earlier study by the same group demonstrated dose related effects of hyperoxia on human fetal airway smooth muscle cells (fASM) where increased proliferation was seen at oxygen levels < 60% while increased apoptosis was seen at oxygen > 60%. These studies have shed some light on how developing airways respond to different levels of hyperoxia (Hartman et al., 2012).

Changes in ECM deposition secondary to hyperoxia have been studied in the last two decades. Juul et al. showed in 1995 that hyperoxia (first 10 days of life) alone resulted in increased proteoglycans and hyaluronan (HA) deposition in the lung (Juul et al., 1995). During the same period, the amount of lung HA in the control rats decreased. Histochemical assessment showed that the HA accumulated in the alveolar walls and in the perivascular areas of pulmonary vessels. The study also indicated that these changes in the ECM interfere with normal airway development, thus placing the preterm infants at particular risk. A newer study looked at the effect of hyperoxia on fASM cells and concluded that moderate hyperoxia causes remodeling through alteration in the ECM of developing airways (Vogel et al., 2017). Their findings included increased collagen deposition in the ECM along with an altered balance of several ECM molecules such as Matrix metalloproteinase 9 (MMP9), Tissue inhibitor of metalloproteinase 1 (TIMP1) and Caveolin 1 (CAV1), which have been associated with neonatal pulmonary diseases. Interestingly, many of these aberrant changes in airway structure and function are common to reactive airway disease and asthma (Liang et al., 2011).

Overall, these studies point towards a complicated mechanistic pathway through which hyperoxia exerts its effect on developing airways. Unfortunately, simply withholding or limiting supplemental oxygen in the newborn is not the solution. The NeOProM group has shown in their metanalysis that targeting even modest hypoxemia is associated with higher risk for mortality (Askie et al., 2018), hence the problem with oxygen is yet to be solved. However, recent studies are uncovering possible underlying mechanisms which may become potential targets for future therapy.

b Role of Hypoxia

Severe desaturation episodes are hallmarks of preterm infants with BPD or infants who are developing BPD. These recurrent hypoxic episodes can be detrimental to the developing airway. Several studies have explored the effects of chronic hypoxia on the developing lung. Blanco et al. in 1991 showed that chronic hypoxia alters normal lung development in rats and leads to fewer and smaller number of alveoli with a decreased effective surface area for gas exchange (Blanco et al., 1991). Another study with chronic hypoxia found that it disrupts calcium signaling in airway smooth muscle cells and is also associated with airway hyperresponsiveness (Belouchi et al., 1999). They suggested that the airway hyperresponsiveness may be secondary to changes in calcium signaling. Severe chronic hypoxia has also been shown to cause airway remodeling in the form of increased airway smooth muscle cell proliferation (Cogo et al., 1985). The role of maternal hypoxia-induced intrauterine growth restriction on juvenile airway hyperreactivity has been studied as well (Wang et al., 2018). Seven days of hypoxic exposure during pregnancy in a murine model caused juvenile airway hyperresponsiveness (2 wks after birth) in male pups. An interesting gender difference was also uncovered in that the female pups developed airway hyperresponsiveness at adulthood (8 wks after birth) while, in males, there was a reversal in airway hyperresponsiveness.

An optimal real-life BPD scenario would incorporate both supplemental oxygen exposure with intermingled hypoxic episodes (i.e., intermittent hypoxia). Recent animal and infant models have incorporated this aspect in their experiments. Mankouski et al. exposed rat pups to 60% oxygen for two weeks followed by recovery in intermittent hypoxia (10% oxygen for 10 min every 6 h) or room air for an additional two weeks, and found that the rats recovered in intermittent hypoxia had abnormal lung development at four weeks (Mankouski et al., 2017). In contrast, the rats recovered in room air had normal lung structure. The abnormal lung changes in the intermittent hyperoxia group persisted into adulthood (10–12 wks). A different study exposed mouse pups to 50% oxygen with intermittent hypoxic episodes (10% oxygen) every 10 min for a total of seven days (Dylag et al., 2017). At three weeks of age, mice in the intermittent hypoxia and hyperoxia group had abnormalities in lung function. The animals in this group demonstrated increased airway resistance with methacholine challenge and had decreased compliance when compared to the mice in room air. Interestingly, alveolarization and airway smooth muscle mass was not affected, which is contradictory to many other pure hyperoxia BPD models and underlines the importance of conducting more studies with similar models of intermittent hypoxia and hyperoxia. While chronic intermittent hypoxia in the postnatal period alone has not been consistently shown to cause airway hyperresponsiveness, it does make reactive airway disease worse as was seen in a recent study with an allergic asthma model in rats (Broytman et al., 2015). This worsening was associated with ECM degradation and excess

collagen deposition in the airway. A recent retrospective study in infants < 28 weeks' gestational age found that intermittent hypoxic episodes in the early postnatal period were associated with increased use of asthma medications in the toddler age group (Di Fiore et al., 2019). Additional studies have found that development of BPD was associated with an increased amount of intermittent hypoxic events (Raffay et al., 2019; Fairchild et al., 2019).

Finding the 'sweet spot' for oxygen therapy in preterm infants remains a challenge to this day. Newer studies with interesting translational models will help to uncover the complex pathways and possibly guide oxygen therapy in the future.

c Role of Ventilation

In the last decade we have moved away from invasive ventilation towards using various modes of non-invasive ventilation such as: continuous positive airway pressure (CPAP), nasal intermittent mandatory ventilation (NIMV), and high-flow nasal cannula to name a few. CPAP can be effective immediately after birth in establishing a favorable functional residual capacity (FRC) while avoiding the detrimental effects of barotrauma caused by positive pressure ventilation (PPV), especially in preterm infants who are 25 weeks or above (SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network et al., 2010). Doyle et al. in 2017 showed that despite the steady decrease in invasive ventilation over the years and increasing use of non-invasive ventilation, oxygen dependence at 36 weeks' postmenstrual age has remained unchanged (Doyle et al., 2017). During their long term follow-up, the study group further uncovered that certain parameters of lung function related to peak flow (FEV_1) at eight years of age had worsened in the recent cohort (i.e., the cohort which received more non-invasive ventilation) compared to previous years. While we speculate upon the underlying mechanisms behind these findings, some intriguing animal models of non-invasive ventilation have been developed in the recent years. A mouse model was used to investigate the long-term effect of CPAP on airway hyperresponsiveness and found that CPAP treatment was associated with a long-term (3 wks postnatal) increase in airway reactivity in mouse pups (Mayer et al., 2015). When compared with the human-scale this would translate to the toddler age group when children tend to get diagnosed with reactive airway disease. Furthermore, the effects of CPAP were more profound on smaller airways compared to larger airways.

As described earlier, the airway smooth muscle layer is present around the developing preterm airways from an early gestational age (Sward-Comunelli et al., 1997). Eventually the larger airways get reinforced by cartilaginous layer which offers stability. The airway smooth muscle layer serves as an important driver during lung development by controlling fluid movement inside the airway much like the peristaltic movement of the gut. The resultant tone in this muscle layer may also serve to keep the smaller airways open after birth (Sparrow and Lamb, 2003). The lack of cartilaginous support probably means that the airway smooth muscle layer around these smaller preterm airways is subjected to a higher amount of stretch which, when combined with ventilation-induced lung injury, may lead to future airway hyperresponsiveness. This would also explain why smaller airways are more vulnerable to the effects of positive pressure as was seen in the mouse model of CPAP described above.

There is ample evidence that ventilation causes lung injury through volutrauma. Similar to the effects of oxidative stress described earlier, disruption of the ECM is also seen in ventilator- induced lung injury (Cruz et al., 2018). Overdistension and mechanical stretch can cause fragmentation of the interstitial and basal membrane ECM components (proteoglycans and glycosaminoglycans) which, in turn, can lead to activation of inflammatory processes. Inflammatory cells (neutrophils and macrophages) accumulate as a result of the insult and, in turn, produces cytokines and changes in the ECM components such as HA, collagen and elastin (Cui et al., 2019). HA, in particular, seems to be an important driver of the inflammatory cascade in this type of lung injury. The pro-inflammatory low molecular weight hyaluronan (LMW HA) and its downstream signaling components have been found in increased concentration in the bronchoalveolar lavage fluid and lungs in several models of lung injury (Savani, 2018). LMW HA and hyaluronan synthase 3 (HAS3), the enzyme which synthesizes LMW HA, were both found to be increased in neonatal respiratory morbidities (e.g., BPD, respiratory distress syndrome) as well as juvenile respiratory diseases (e.g., asthma) (Savani, 2018; Garantziotis et al., 2009). Interestingly, CPAP and peak end expiratory pressure (PEEP) has been shown to be protective against this detrimental effect of ventilation in an adult rat model (Moriondo et al., 2012). This, however, may not be the case in the preterm airway that has not yet fully developed. It is possible that CPAP causes changes in the ECM, further making these airways vulnerable to future respiratory morbidity such as asthma.

While CPAP and other non-invasive modes of ventilation have been helpful in minimizing the adverse effects of invasive ventilation, we must be cognizant of their potential longer-term consequences in our preterm babies.

d Role of Prenatal Inflammation

Factors that affect postnatal developing airways may start while the fetus is still *in utero*. A large proportion of children who develop long-term respiratory morbidity tend to have abnormal lung function early in life (Morgan et al., 2005). Consequently, it may be worth looking at important prenatal factors which may affect lung or airway function after birth. For example, prematurity, intrauterine growth restriction (IUGR) or small for gestational age (SGA) have been associated with development of recurrent wheezing disorder [Fig. 2] (Kumar et al., 2008). In the same study, the highest rate of wheezing disorder was seen in the very preterm infants who were exposed to chorioamnionitis. This study underlines the potential role of prenatal inflammation in affecting later pulmonary morbidity. Additionally, *in utero* exposure to toxins such

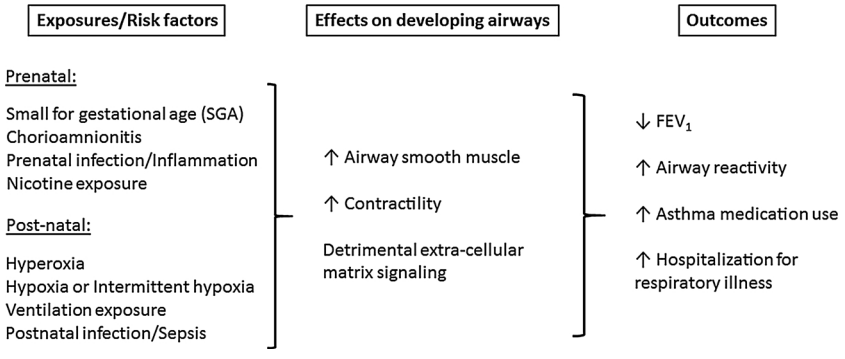

Fig. 2. An overview of the major risk factors or detrimental exposures associated with preterm birth, their pathophysiological effect on the developing airway and the subsequent occurrence of adverse clinical outcomes. IUGR = Intrauterine growth restriction, SGA = Small for gestational age, FEV_1 = Forced expiratory ventilation in one second.

as nicotine has the potential to disrupt fetal lung and airway development (McEvoy and Spindel, 2017). Maternal smoking has been associated with significant increase in healthcare cost for children in their first few years of life, of which, a sizable amount is related to respiratory illnesses (Stoddard and Gray, 1997).

An animal study investigated the effects of prenatal administration of lipopolysaccharide (LPS) and found that it resulted in disrupted lung development and increased inflammation in the postnatal lung (Kramer et al., 2009). This prenatal inflammation is further worsened by postnatal factors such as oxidative stress, barotrauma and sepsis leading to further injury of the already disadvantaged lung and airway. Interestingly, infants who are exposed to chorioamnionitis or other virulent infections *in utero* rarely have positive blood cultures or tracheal aspirates, which means the fetal response to these noxious stimuli *in utero* is probably more important than the actual stimuli themselves (Gomez et al., 1998). Indeed, increased amount of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-1-beta (IL-1β) and interleukin-8 (IL-8) in the amniotic fluid have been associated with poor postnatal pulmonary outcomes (Yoon et al., 1997).

There may be some evidence suggesting that the cytokine effect on lung development is related to the gestational age of the fetus (Glumoff et al., 2000). It is, however, worth mentioning that the results from various studies linking pulmonary outcomes with prenatal inflammation are conflicting (Bry et al., 1997) and more studies are needed to better understand the elaborate inflammatory pathway underlying this association.

e Role of Postnatal inflammation

The developing lung is at risk and particularly vulnerable to postnatal inflammation for numerous reasons. Preterm infants are more likely to be subjected to ventilator-induced lung injury which may be from barotrauma and/or oxidative stress secondary to recurrent hyperoxia and hypoxic episodes. Additionally, they are at increased risk for prenatal or postnatal infection which are added to the previously mentioned insult. The additive effect of oxidative stress and inflammatory mechanisms may result in long-term pulmonary and airway injury in these preterm infants (Viscardi, 2012).

Postnatal anti-oxidant treatment (recombinant human superoxide dismutase) have been tried as a therapy in a clinical trial (Davis et al., 2003). While it did not change the rate of BPD, it was effective in reducing airway hyperresponsiveness along with the need for emergency department visits and inpatient admissions. Reducing postnatal inflammation is the basis behind use of postnatal steroid therapy with the goal of decreasing time on invasive ventilation. Increased use of non-invasive ventilation in the recent years has seen a significant decrease in use of postnatal steroids, especially considering the burden of negative neurodevelopmental outcomes that come with this treatment (Committee on Fetus & Newborn, 2002).

Inhaled nitric oxide (iNO) has been successfully used in a rat model of BPD and was shown to reduce long-term lung morbidity along with pulmonary inflammation (ter Horst et al., 2007). The positive data from animals, however, did not translate into clinical trials as multiple well designed studies with iNO in preterm infants have failed to show much promise (Cole et al., 2011). Surprisingly, one of the trials that employed prolonged iNO therapy starting in early postnatal period found that the use of bronchodilators at one year of age was significantly lower in the subset of patients who received iNO therapy (Ballard et al., 2006). Off-label use of iNO still occurs in severely ill preterm infants in many NICUs with mixed results (Manja et al., 2019).

6. Conclusion

In conclusion, there is a compelling need to decrease longer term respiratory morbidity in former preterm infants. Assessment of later morbidity has focused primarily on airway function as this is most easily measured and will likely remain our primary outcome measure. Therefore, the developmental aspects of airway function and injury must be a focus of future preventive and therapeutic approaches to neonatal respiratory management.

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