Oxidative Stress and Bronchopulmonary Dysplasia

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ABSTRACT

Bronchopulmonary dysplasia (BPD) is the major cause of pulmonary disease in infants. The pathophysiology and management of BPD changed with the improvement of neonatal intensive care unit (NICU) management and with the increase of survival rates. Despite the improvements made, BPD is still a public health concern, resulting in frequent hospitalizations with high rates of mortality, impaired weight and height growth, and neurodevelopmental disorders. Lung injury in the neonatal period has multiple etiologic factors – genetic, hemodynamic, metabolic, nutritional, mechanical, and infectious mechanisms – act in a cumulative and synergic way. Free radical (FR) generation is largely recognized as the major cause of lung damage. Oxidative stress (OS) is the final common endpoint for a complex convergence of events, some genetically determined and some triggered by *in utero* stressors. Inflammatory placental disorders and chorioamnionitis also play an important role due to the coexistence of inflammatory and oxidative lesions. In addition, the contribution of airway inflammation has been extensively studied. The link between inflammation and OS injury involves the direct activation of inflammatory cells, especially granulocytes, which potentiates the inflammatory reaction. Individualized interventions to support ventilation, minimize oxygen exposure, minimize apnea, and encourage growth should decrease both the frequency and severity of BPD. Future perspectives suggest supplementation with enzymatic and/or non-enzymatic antioxidants. The use of antioxidants in preterm newborns particularly exposed to OS and at risk for BPD represents a logical strategy to ameliorate FRs injury, but further studies are needed to support this hypothesis.

Key words:
Bronchopulmonary dysplasia, oxidative stress, preterm newborns

INTRODUCTION

Bronchopulmonary dysplasia (BPD), also known as chronic lung disease of prematurity, is the major cause of pulmonary disease in infants. According to current views, BPD should be considered in any newborn, less than or greater than 32 weeks gestational age, who requires oxygen treatment for at least 28 days.[1] The pathophysiology and management of BPD changed over the past four decades with the improvement of neonatal intensive care unit (NICU) management and with the increase of survival rates. The first description of BPD was made by Northway in 1967 who published a study regarding the clinical, radiologic, and pathologic changes observed in 32 neonates born after approximately 32 weeks' gestation with severe respiratory distress syndrome, who were treated with prolonged artificial ventilation and high concentrations of oxygen.[2] Northway and associates coined the term, "bronchopulmonary dysplasia." The likelihood for developing BPD increases with the degree of prematurity and reaches 25–35% in very low-birth-weight and extremely low-birth-weight infants.[3] Despite the improvements made for the treatment of newborns with respiratory failure, BPD is still a public health concern, as it is one of the major causes of chronic respiratory diseases among infants, resulting in frequent hospitalizations with high rates of mortality, impaired weight and height growth, and neurodevelopmental disorders.

Lung injury in the neonatal period always has multiple etiologic factors – genetic, hemodynamic, metabolic, nutritional, mechanical, and infectious mechanisms – act in a cumulative and synergic way. Generation of free radicals (FRs) is largely recognized as the major cause of lung damage.[4,5] It is becoming more evident that oxidative stress (OS) is the final common endpoint for a complex convergence of events, some genetically determined and some triggered by *in utero* stressors.[6] OS occurs when the production of FRs exceeds the capacity of antioxidant defenses and this is a common process during the neonatal period.[7] Inflammatory placental disorders and chorioamnionitis also play an important role in the development of BPD due to the coexistence of inflammatory and oxidative lesions.[8,9]

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Thus, a high inspired oxygen concentration alone is not enough to determine an increased OS. Immaturity of antioxidant systems, inadequate nutrition, inflammation, and the type of mechanical ventilation lead to the increase of OS which might trigger changes leading to permanent lung damage.[10] This review explores the mechanisms involved in the pathogenesis of BPD and their link with oxidative damage.

INFLAMMATION AND OXIDATIVE STRESS

The contribution of airway inflammation to the development of BPD of prematurity has been extensively studied.[11-14] There is a dynamic and complex balance between pro- and anti-inflammatory cytokines in the human immune system. Several specific interactions between inflammation and OS injury have been suggested. All the mechanisms of this interaction are not still clear. It should be noted that while pro-inflammatory cytokines (tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-8) are liberated in response to infection, several other conditions including aspecific inflammation due to mechanical ventilation are also known to cause cytokine production. The link between inflammation and OS injury involves the direct activation of inflammatory cells, especially granulocytes, which potentiates the inflammatory reaction. Activated inflammatory cells release a large amount of oxygen radicals and proteases, resulting in endothelial peroxidation, increased vascular permeability, interstitial, alveolar, and airway edema. The production of superoxide anion, the most abundant radical species, is also the first stage of the bacterial killing reaction, which is followed by production of other FRs, such as hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD), hydroxyl radicals (OH^-) catalyzed by transition metals, and hypochlorous acid ($HOCl^-$) by myeloperoxidase. These substances not only contribute to killing bacteria but also favor tissue damage. Moreover, these agents increase capillary permeability that facilitates the passage of cytokines and contributes to the increase of inflammation and edema. As a consequence, trasudated plasma proteins and inflammatory cells impair extracellular surfactant.[15] Additionally, many of the pro-inflammatory cytokines can increase the expression of inducible nitric oxide synthase (NOS), which forms nitric oxide (NO). NO and superoxide radicals combine to produce peroxynitrite that spontaneously decomposes to form other potentially damaging metabolites such as hydroxyl radicals, nitrogen dioxide (NO_2), and nitrogen dioxide radical (NO_2^+). The reaction of nitrite with HOCl produced by the action of myeloperoxidase in neutrophils forms the reactive nitryl chloride (NO_2Cl). The hyperoxic exposure of rut pups also upregulates NOS, and therefore increases the concentration of NO and subsequently of reactive nitrogen species as well.[16] Peroxynitrite, an unstable product, rapidly nitrates tyrosine residues to form nitrotyrosine. Nitrotyrosine has been used as a marker of the presence of peroxynitrite in chronic lung disease. Plasma 3-nitrotyrosine content is increased during the first month of life in preterm infants who subsequently develop BPD.[17] Experimental studies have demonstrated that oxygen-rich environment inside the lung may predispose to NO toxicity, increasing the production of its metabolites, which further inactivates surfactant.[18] On the other hand, there is an emerging evidence of a lung vascular dysfunction in BPD, with the loss of the pulmonary vasodilator response to inhaled NO, which is attributed to diminished endothelial NOS in the pulmonary circulation.[19] Cytokine production could therefore enter in a "final common pathway" leading to lung damage through OS whether triggered by infection or by pulmonary damage due to the "stretching" of alveoli, airways, basement membrane, and pulmonary capillary endothelium. In addition, previous studies on premature infants demonstrated an increase of TNF-α in tracheal secretions, among other pro-inflammatory cytokines, and this was associated with the duration of mechanical ventilation and the development of BPD.[20,21] Studies on anti-inflammatory cytokines are not enough to explain their role in BPD. Some studies demonstrated that preterm infants with respiratory distress produce large amounts of IL-10 in the lower airways and the presence of this anti-inflammatory cytokine prevents the development of BPD.[22,23] In contrast, Jones and colleagues were unable to detect IL-10 in most of the airway samples from preterm infants.[24] The complexity of the effect of inflammation on lung maturation is well demonstrated by the experiments of Kramer, which were carried out by the injection of endotoxin in the amnion of preterm lambs.[25] The inflammatory response in the fetal lungs and cord blood increased with endotoxin dose. In particular, IL-1a is a potent mediator of the fetal inflammatory response syndrome. Intra-amniotic IL-1a injections induced a robust increase in monocytes, neutrophils, lymphocytes, and IL-8 protein in bronchoalveolar lavage (BAL) fluid.[26] It was hypothesized that after endotoxin injection, neutrophils producing oxidants cause a primary injury. Consequently, BPD, associated with chorioamnionitis, results from the simultaneous effects of disrupted lung development, lung injury, and repair, superimposed on the developing lung. Caveolins are implicated as major modulators of lung injury and remodeling by multiple signaling pathways. It has been demonstrated that antenatal lung inflammation can decrease the concentrations of caveolins, thus contributing to BPD.[27] Moreover, fetal innate immune responses to lipopolysaccharide (LPS)-induced chorioamnionitis would alter postnatal systemic immune and airway responsiveness determining decreased airway reactivity and changes in lymphocytes.[28] When maternal intramuscular betamethasone precedes intra-amniotic

injection of LPS, betamethasone treatment suppresses lung inflammation. Interestingly, betamethasone treatment after LPS does not counteract inflammation, but enhances lung maturation.[29] This complex system may have different expressions depending on the microorganism responsible for infection, duration of the stimulus, fetal and placenta growth, prenatal glucocorticoid secretion, and genetic determinants.[30] Taking into account the key role played by the oxidative injury in the development of the respiratory distress syndrome in adults, the possible unbalanced FRs production by lung phagocytes may be very important in the development of lung disease. The system is complicated by the different response of surfactant production to the cytokines as a function of gestational age.[31]

OXIDATIVE STRESS AND LUNG INJURY

Over the last decade, a large amount of data indicated that OS is involved in the development of BPD.[32,33] Premature infants who will develop BPD have qualitative and quantitative differences in oxidation of lipids and proteins, when compared to infants who do not develop BPD.[23] Such differences in oxidation patterns are most obvious in the first few days of life. The emerging evidence supports the concept that the lung injury process leading to BPD occurs within hours to days from delivery and that oxidation is a major contributor to this pathological process. An OS occurs at birth in all newborns as a consequence of the hyperoxic challenge due to the transition from the hypoxic intrauterine environment to extrauterine life. FRs sources such as inflammation, hypoxia–hyperoxia, ischemia, glutamate, and high free iron release increase OS during the perinatal period. In addition, preterm babies have reduced antioxidant defenses that are not able to counteract the harmful effects of reactive oxygen species, leading to the so called "FR-related disease" of newborns including BPD.[34]

BPD is characterized by a tissue remodeling, and is divided into different phases ending in the chronic phase with an increased number of fibroblasts and fibrotic areas. Matrix metalloproteins (MMPs) are important in regulating fibrotic processes. They degrade extracellular matrix proteins and fibrillar collagen. The balance between MMPs and their inhibitors is of primary importance in the development and regulation of fibrosis. Their expression is regulated by cytokines, growth factors, and extracellular matrix components. OS increases both MMPs and their inhibitors,[35] so it may lead to lung damage by increasing collagenase activity, causing disruption of the extracellular matrix.

The two likely causes of oxidative damage in the babies who will develop BPD are FRs generated as a result of hyperoxia and respiratory burst activity of invading inflammatory cells.

Hyperoxia can induce the fibrotic process in newborns with BPD.[35] Hyperoxia results in augmentation of the surfactant proteins SP-A, SP-B, and SP-C85, while oxidized SP-A loses its surfactant and immune defense functions. Hyperoxia also reduces surfactant phospholipid production.[15] It seems that glycerol-3-phosphate acyltransferase, which catalyzes the first reaction in phosphoglyceride synthesis and is a rate-limiting enzyme, is extremely sensitive to oxidative damage.[35] The "new" form of BPD was observed to have a less fibrotic component than its earlier counterpart and with a significant delayed alveolar development and perhaps permanent alveolar underdevelopment.[36] Recent studies found higher values of leukotriene-4 (LTE-4) on the 7th day than in the "classic" BPD, suggesting that ongoing inflammatory process could be an important mechanism in "atypical" BPD.[37] In contrast, in the "classic" BPD, the 8-Hydroxydesoxyguanosin (8-OHdG) values on the 3rd day were significant, suggesting that oxidative DNA damage could be the crucial mechanism in the pathogenesis of current BPD.[37]

OS is also able to inactivate surfactant; this was demonstrated in rats treated with the combination of hyperoxia and hypoxanthine infusion. As a result of inflammation and edema, transudated plasma proteins and inflammatory cells impair extracellular surfactant.[38]

Animal models have shown that SOD decreases with mechanical ventilation in preterm but not in term gestation animals.[39] Thioredoxins and piridoxins are located in the inner mitochondrial membrane, where they scavenge FRs. They also appear to act as a potent activator of SOD, providing protection against FRs and cytokine-induced injury. In rats, the levels of these molecules were low during the embryonic stages, but started to increase after birth, especially in the epithelium of the bronchi and bronchioles and some alveolar cells.[40] It has also been noted in preterm animals, in contrast with term animals, that induction of their antioxidant capacity does not occur following OS.[41]

Phagocytic cells in the lung mediate their antimicrobial functions through the release of lysozymes, peroxidases, and proteases, in addition to oxygen radicals and NO. Activated phagocytes and type II pneumocytes produce oxygen FRs during the respiratory burst as a crucial part of the defense against microorganisms:

$$NADPH + 2O_2 \rightarrow H^+ + 2O_2^-$$

Activated neutrophils and pulmonary type II cells are important inducers of the Fenton reaction leading to pulmonary injury and consequently to BPD. In addition, activated neutrophils increase the adhesiveness to the endothelium during ischemia/reperfusion. The

release of inflammatory mediators can stimulate the endothelium to produce adhesion molecules, resulting in transendothelial migration facilitating the passage of cytokines.[42] The increase in phagocyte number and interleukin concentrations in BAL fluid obtained from premature infants with BPD indicates that oxygen toxicity and inflammation are involved in the development of lung injury.[43]

An increased concentration of products of lipid peroxidation, pentane and ethane, in exhaled gas was demonstrated a few days after birth in premature infants and higher levels were found in those who subsequently developed BPD.[44] A positive correlation was found between the duration of oxygen and ventilatory therapy and lipid peroxidation by Inder *et al.*[45]

Plasma 3-nitrotyrosine concentrations were found significantly higher in infants with BPD, increasing approximately fourfold during the first month of life.[17] The plasma 3-nitrotyrosine levels correlated with the fraction of inspired oxygen required by infants.

Protein oxidation was also demonstrated by Gladstone and Levine with higher carbonyl content in lung lavage samples from preterm infants with an oxygen requirement of over 40% or who were ventilated for longer than 72 h compared with those requiring less oxygen or less time on mechanical ventilation.[46] In tracheal aspirates from premature infants requiring intensive care, including oxygen therapy, Varsila *et al.* showed that those who subsequently developed BPD had a significantly higher carbonyl concentration in the tracheal aspirate during the first 6 days of life than those who did not.[47] Similarly, Ballard *et al.* found an association of protein carbonyl concentration with severity of lung disease in the second and third weeks of life and with the occurrence of BPD at 36 weeks' of postmenstrual age.[5] This association of carbonyl content with disease severity was independent of gestational age and birth weight, factors that influence the occurrence and severity of infant lung disease.

The higher mean concentration of lipid peroxidation and protein carbonylation in babies who develop BPD indicates a higher level of oxidative damage during their time on the ventilator.[4,5,48] However, despite this evidence, the ability of oxidant and antioxidant concentration to predict the development of BPD is weak. In a multi-factorial condition such as BPD, it is perhaps naive to expect clear predictive outcomes from such data. It has been recognized that prenatal factors, such as inflammation, are important for its development and that the changes leading to BPD are triggered before birth.[35]

Finally, recent studies showed how this OS persists during adolescence in ex-premature babies affected by BPD.[49] The authors showed higher 8-isoprostane levels in the exhaled breath condensate, demonstrating the persistence of OS for many years after premature birth and suggesting that long-term respiratory abnormalities after preterm birth may be associated with an ongoing airway disease and not just a stabilized structural lung damage.[49] If this is the case, it holds important implications for future therapeutic approaches.

FUTURE PERSPECTIVES

BPD has a complex pathogenesis, but an increasing amount of data supports the role of FRs-mediated damage. The chronic exposure of infants who need oxygen after 32 weeks to a higher oxygen saturation range will increase the incidence of BPD.[50] Also, a brief exposure of very preterm infants to high oxygen concentrations can initiate lung injury resulting in BPD. That is why, resuscitation of very preterm infants should be initiated with 30–50% oxygen.[51] Individualized interventions to support ventilation, minimize oxygen exposure, minimize apnea, and encourage growth should decrease both the frequency and severity of BPD.[50] Anyway, future perspectives suggest to consider supplementation with enzymatic and/or non-enzymatic antioxidants useful in decreasing injury due to FRs, particularly in disorders such as BPD and other "FR-related diseases." Vitamins A, C, and E are the important factors in normal physiology as well as antioxidant defenses.[52] These vitamins are able to inhibit FRs-induced lipid peroxidation and scavenge FRs. In infants with BPD, plasma β-carotene and vitamin A concentrations are lower, likely reducing antioxidant protection. This action may explain higher plasma 3-nitrotyrosine and protein carbonyls, signs of protein damage in those preterm infants at highest risk for BPD.[53] In the preterm baby, the perinatal transition is accompanied by the immaturity of the antioxidant systems and the reduced ability to detoxify cells from FR attack giving rise to the "FRs-related disease" spectrum; consequently, exogenous antioxidants such as vitamins A, E, and recombinant human SOD (rhSOD) have been administered in an attempt to prevent BPD.[54] A Cochrane meta-analysis suggests that vitamin A supplementation is able to reduce BPD, but subsequent studies showed how neurodevelopmental and pulmonary outcomes at 18–22 months corrected gestational age (CGA) were not significantly different.[55,56] Trace elements, such as copper, zinc, iron, and selenium, are also essential for normal antioxidant enzyme function, and supplementation with these nutrients could optimize total antioxidant capacity.[57] However, studies examining trace elements as active cofactors in extremely low-birth-weight infants showed that lower trace element concentrations did not substantially influence antioxidant enzyme concentration or the BPD development.[50] The use of antioxidants in

preterm newborns particularly exposed to OS and at risk for BPD represents a logical strategy to prevent or ameliorate FRs injury, but further studies are needed to support this hypothesis.[55]

CONCLUSIONS

BPD remains the most common severe complication of preterm birth. Preterm newborns are highly prone to OS and to the toxic effect of FRs. At birth, the relatively hyperoxic environment caused by an increased oxygen bioavailability exposes the newborn to a flood of FRs. Additional sources, such as inflammation, hypoxia, ischemia, glutamate, and free iron release, magnify OS. Although OS has a growing role in the pathogenesis of BPD, careful research still needs to be done to better clarify this phenomenon and its impact on infants' health. The use of antioxidants in preterm newborns particularly exposed to OS and at risk for BPD represents a logical strategy to ameliorate FR injury, but further studies are needed to support this hypothesis.

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