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Special Articles

Pulmonary Inflammation and the Role of Pre- and Postnatal Factors in the Pathogenesis of BPD

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Abstract Bronchopulmonary dysplasia (BPD) is an evolving process of lung injury and aberrant wound healing. An imbalance between proinflammatory and anti-inflammatory mediators, favouring proinflammatory mechanisms, and an impaired generation of growth factors which are crucial for a normal pulmonary development have been identified as central factors in the pathogenesis of BPD. Pre- and postnatal events such as chorioamnionitis and various interventions of neonatal intensive care induce an injurious inflammatory response in the immature airways and the pulmonary interstitium of preterm infants which may subsequently affect normal alveolarisation and vascular development of the immature lungs.

Key words Bronchopulmonary dysplasia; Cytokines; Growth factors; Oxidative damage; Preterm infants

"New" Bronchopulmonary Dysplasia (BPD)

Increased use of antenatal glucocorticosteroids, early surfactant treatment and more gentle ventilation techniques have definitely minimised the severity of lung injury in more mature infants with respiratory distress syndrome (RDS) and significantly reduced the incidence of severe BPD which was characterised by chronic fibroproliperative changes with areas of emphysema and atelectasis.[1] However, there is a new category of very immature infants with a "new" BPD who initially have minimal or absent signs of RDS whose need for supplemental oxygen and mechanical ventilation increases within the first two weeks of life.[2] Affected infants may be oxygen dependent for weeks and even months. A considerable number of these infants may have been exposed to intrauterine chorioamnionitis. Various postnatal factors such as pulmonary or systemic infections, high airway concentrations of inspired oxygen and mechanical ventilation may amplify and perpetuate the inflammatory reaction and subsequently affect normal alveolarization and pulmonary vascular development in preterm infants with "new" BDP.

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Inflammatory Cells, Pro- and Anti-inflammatory Cytokines

By now the pivotal and crucial role of neutrophils and macrophages in the pulmonary inflammatory response has clearly been demonstrated.[3,4] Preterm infants with various stages of developing BPD had much higher and persisting numbers of inflammatory cells in their bronchoalveolar lavage fluid compared with infants who recovered from RDS.[5-9] This phenomenon was shown to correlate with the extend of pulmonary oedema formation and an increased risk of developing BPD.[10-12] Prior to neutrophil migration cellular attachment to endothelial cells is mediated through a complex interaction of adhesion molecules. Increased concentrations of various cellular and endothelial adhesion molecules such as intercellular adhesion molecule (ICAM-1) and selectins have been detected in airway secretions and the circulation of preterm infants with BPD.[13-15] In

addition, a strong upregulation of ICAM-1 on endothelial cord cells and increased serum concentration of soluble ICAM-1 in preterm infants exposed to chorioamnionitis has been reported in preterm infants.[16]

The presence of well defined chemotactic and chemokinetic factors such as the proinflammatory cytokines tumour necrosis factor-α (TNF-α), interleukin 1 (IL-1), interleukin 8 (IL-8), and monocyte chemotactic protein-1 (MCP-1) in the bronchoalveolar fluid of preterm infants with BPD could explain the migration of cells into the lung tissue and airways, inducing an inflammatory reaction which causes lung damage. By blocking this influx with specific chemokine antagonists, the inflammatory reaction and consequent lung damage could be prevented. The increased levels and enhanced mRNA expression of proinflammatory cytokines present in the airways and pulmonary tissue of preterm infants may reflect a inability to regulate inflammation through an adequate expression of the anti-inflammatory cytokines IL-10, IL-4, IL-12 and IL-13 or IL-1 receptor antagonist.[17-20] Cellular IL-10 mRNA was undetectable in most airway samples of preterm infants with RDS, but it was expressed in all cell samples of term infants with meconium aspiration syndrome.[17] An imbalance between proinflammatory and anti-inflammatory cytokines can be considered as an important feature of lung injury.[21]

Hyperoxia, Mechanical Ventilation, Chorioamnionitis and Neonatal Infections

Both oxygen and mechanical ventilation can affect the alveolar-capillary integrity. In newborn animals hyperoxia has been sown to be a strong and independent inductor of various proinflammatory cytokines in airway cells and pulmonary tissue.[22,23] In addition, initiation of mechanical ventilation in preterm animals has caused a proinflammatory response, suggesting that any baro-/volutrauma of the immature lung may be injurious.[24-30] Recently, the effect of mechanical ventilation on generation of various inflammatory and anti-inflammatory cytokines in an isolated rat lung model in the presence or absence of endotoxin-induced sepsis was studied.[28] The highest levels of inflammatory cytokines were seen in those ventilatory strategies with high pressure and no positive end expiratory pressure. If animals were pretreated with lipopolysaccharide (LPS), BALF-concentrations of proinflammatory cytokines in an isolated, non-perfused lung model were impressingly increased even with a "less injurious" ventilation strategy.[31]

"Priming" of the fetal lung by intrauterine endotoxin or exposure to chorioamnionitis is most likely a considerable pathogenetic factor in the initiation of the pulmonary inflammatory sequence.[32] As a consequence basically every form of mechanical ventilation which acts as a "second strike" may aggravate or even amplify the inflammatory reaction in the immature lung (Figure 1). Epidemiological data suggest a strong association between chorioamnionitis and the development of BPD. Furthermore, chorioamnionitis, mechanical ventilation and postnatal sepsis have clearly been identified as modulators of BPD.[33] An association between early onset bacterial infections as well as systemic nosocomial infections and the development of BPD in very low birth weight infants has also been well established.[34,35] In addition, Ureaplasma urealyticum (Uu) colonisation of the airways was shown to be associated with pulmonary inflammation and a subsequent development of BPD.[34,36] In baboons antenatally colonised with Uu two patterns of disease were observed: Persistent colonisation induced a picture consistent with acute pneumonitis and worsening lung function. In contrast, colonised animals which subsequently cleared Uu from the lungs demonstrated early improved lung function but had still mixed bronchiolitis and interstitial pneumonitis. Inherent responses of the neonatal immune systeme which have not been understood yet most likely determine the pulmonary outcome of intrauterine Uu colonisation.[37]

Assessment of the apoptotic index (AI) in the lungs of human stillborn fetuses showed that those exposed to maternal chorioamnionitis had a significantly increased AI, compared to those without exposure to chorioamnionitis, and that the AI was even higher if pneumonitis was also present.[38] This implies that babies who do not respond properly to surfactant therapy and require extensive mechanical ventilation may already have irreversible cellular damage as reflected by an increased number of apoptotic cell.

Proteolytic Damage and Transfoming Growth Factor-β] (TGF-β])

Elastase, a powerful neutral proteinase stored in neutrophils is thought to play an essential role in the destruction of the alveolar-capillary unit. An imbalance between elastase and α_1-proteinase inhibitor (α_1-PI) within the airways may be a hallmark of lung injury in preterm infants.[2,36] The activity of α_1-PI is presumably inactivated by reactive oxygen species (ROS). The activity of reactive

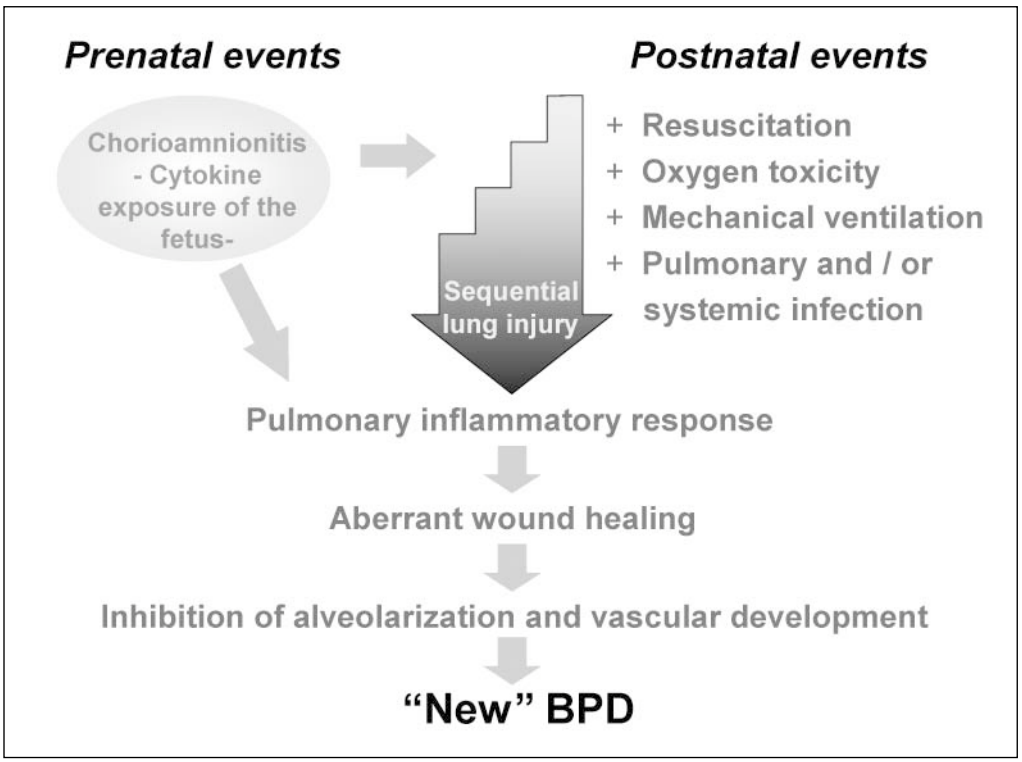

Figure 1 Possible pathogenetic sequence of pre- and postnatal events which induce lung injury and pulmonary inflammation in preterm infants with "new" BPD.[53]

oxygen species (ROS) is normally balanced by the antioxidant system. However, preterm infants are particularly susceptible to hyperoxia and damage caused by ROS since the antioxidant system has yet to mature. Following term birth, enzymes such as superoxide dismutase (SOD), catalase and Gluthationperoxidase (GP) have protective activities against ROS. However, there is little or no activity of these enzymes at lower gestational ages.[39] This means that preterm infants will be deficient in protective antioxidant enzymes at the time during which they are receiving oxygen.

Neutrophils and macrophages release toxic oxygen radicals during the process of phagocytosis. In addition, xanthine oxidase is one of the enzymes which produce reactive oxygen radicals which contribute to acute and chronic lung damage by inactivating systems protecting the alveolar basement such as the α_1-proteinase inhibitor and tissue inhibitor of metalloproteinases (TIMP).[16,40,41] This lack of protection against neutrophil elastases and other proteases results in damage of the alveolar-capillary unit with subsequent protein influx and surfactant inactivation. As a consequence lung function deteriorates and profibrotic factors are generated.[42]

Inflammation induced by tissue injury is normally followed by a phase of repair.[43,44] Lung injury leads to an induction of transforming growth factor-β] (TGF-β]) which limits some of the inflammatory reactions and plays a key role in mediating tissue remodelling and repair.[43,45] If the reparative processes are exaggerated and not adequately localised fibrosis will ensue. This is typically associated with increased levels of TGF-β] as well as connective tissue growth factor (CTGF) and overexpression of TGF-β] has been shown to result in severy pulmonary fibrosis.[46] In preterm infants with BPD increased levels of TGF-β] have been detected in the airway secretions.[47-49] However, reduced levels of CTGF which is responsible for the development of fibrosis have been observed in preterm animals with "new BPD".[50] This gives a preliminary conclusion as to why the histology of the "new BPD" may differ from the classic form. Moreover, low airway concentrations of keratinocyte growth factor and hepatocyte growth factor were found to be associated with more severe lung disease in preterm infants.[51,52]

Increasing evidence indicates that BPD results – at least in part – from an imbalance between the proinflammatory and anti-inflammatory mechanisms, with a persistent

imbalance that favours proinflammatory mechanisms. In addition, an impaired generation of growth factors crucial for a normal pulmonary development has recently been implicated as possible feature in the pathogenesis of BPD. During the last decade it has become evident that there are multiple pre- and postnatal events contributing to the development of BPD in preterm infants. Chorioamnionitis and cytokine exposure *in utero*, plus sequential lung injury caused by postnatal resuscitation, oxygen toxicity and volutrauma or barotrauma all lead to a pulmonary inflammatory response which is most likely associated with aberrant wound healing and inhibition of alveolarization as well as vascular development, causing the "new BPD".

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