

Latest insights into the pathogenesis of bronchopulmonary dysplasia

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Preterm infants at risk of BPD, even without RDS

The classic form of BPD occurs most commonly in very premature, low birthweight infants, and is often a consequence of high inspiratory oxygen concentrations and volutrauma during the treatment of RDS.^[1] However, a new form of BPD has been identified among 'low-risk' preterm neonates having little or no initial lung disease, whose need for oxygen and MV increases over time.^[2] Most of these infants have been exposed to chorioamnionitis. In the new BPD, lung function deteriorates at approximately 7 days after birth, and eventually becomes virtually indistinguishable from that of infants with classic BPD. However, the new BPD is characterised by reduced fibrosis, impaired alveolisation and impaired capillary development.^[3]

This presentation examines factors which contribute to and influence BPD, with emphasis on the role of the inflammatory response.

Importance of inflammatory response in BPD

Infants with BPD have an approximately 20-fold increase in inflammatory cell numbers, and experience a stronger inflammatory response than infants with RDS or non-pulmonary diseases.^[4] Analysis of interleukin (IL)-8 in lung effluent indicates that infants with BPD have markedly higher levels of this cytokine between days 5–15 than control infants who had recovered from neonatal RDS.^[5] This increased inflammatory response may also apply to the new form of BPD. The presence of chemoattractants and chemokines, such as tumor necrosis factor- α (TNF- α), IL-1, IL-8, and monocyte chemoattractant protein-1 (MCP-1) in the bronchioalveolar 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. This suggests that by blocking this influx with specific chemokine antagonists, the inflammatory reaction and consequent lung damage could be prevented.

Oxygen and MV increase BPD risk

Both oxygen and MV can affect alveolar and vascular development in the lungs of preterm infants.^[6]

Animal studies have shown that oxygen is a potent, independent inducer of inflammatory responses in the lungs, with increased levels of chemokines observed following its administration. In rats, treatment with 100% oxygen was shown to induce the upregulation of the pro-inflammatory cytokines TNF- α , IL-6 and MCP-1 between 3–10 days following birth.^[7]

Choice of MV strategy important

MV is particularly harmful to preterm infants. Animal studies have shown that overdistension of the lungs (volutrauma) from MV causes disruption of structural elements and the release of pro-inflammatory mediators, with subsequent leukocyte influx.^[7-10] This results in increased permeability and interstitial and alveolar oedema, and occurs within minutes of the initiation of MV.

As previously discussed, certain ventilation strategies cause more damage than others. For example, in an isolated rat lung model, high volume ventilation with zero PEEP caused significantly greater production and release of inflammatory cytokines than a moderate volume with high PEEP, which allows stabilisation of the alveoli.^[10]

Selection of the least harmful MV strategy is therefore important if lung damage is to be minimised.

Infection, chorioamnionitis exacerbate ventilation-associated damage

Although ventilation itself causes lung injury, its effects may be even more severe in lungs that are already damaged by intrauterine cytokine exposure during chorioamnionitis – in such cases, MV is a ‘second strike’ which causes damage even when a strategy that would not ordinarily be injurious is employed.

This has been illustrated in a CPAP rat model.^[11] In this study, cytokine release was greater following endotoxin priming prior to removal of the lung than in saline controls, and the damage was greatest in the endotoxin-primed lungs which underwent CPAP. Histological analysis showed infiltration of neutrophils into the interstitium. Prenatal infection causes a large increase in pro-inflammatory cytokine levels.^[12] In a study in which *Ureaplasma urealyticum* was injected into the amniotic fluid during gestation, premature baboons with *Ureaplasma* colonies after day 14 had severe lung damage during MV.^[13] Lung damage was also observed in animals which had clearance of *Ureaplasma* colony-forming units by day 14 following immune response, although it was unclear whether this damage was due to MV or the inflammatory response following infection. However, endotoxin-induced chorioamnionitis has been shown to trigger an inflammatory response in preterm lambs.^[14]

Imbalance of cytokines in preterm infants increases susceptibility to BPD

Preterm infants are more likely than term infants to experience lung damage following injurious events. This appears to be due to an imbalance of pro- and anti-inflammatory markers in the less developed lungs of preterm infants.^[15] Mature macrophages of term newborns with acute pulmonary disease produce TNF- α , IL-1 β and IL-8 and other pro-inflammatory cytokines. However, anti-inflammatory cytokines such as IL-10 are also generated, and these have been shown to downregulate the inflammatory response, thus preventing neutrophil migration into the airways and interstitium. In contrast, anti-inflammatory cytokines are not produced by the immature macrophages in the lungs of premature infants. The resulting neutrophil migration leads to disruption of the endothelium and alveolar damage.

Chorioamnionitis increases apoptotic index

Chorioamnionitis is more common in preterm infants. *In utero* cytokine exposure due to chorioamnionitis leads to a systemic inflammatory response in the foetus, with increased neutrophil influx and upregulation of IL-8 in the lungs. An increased concentration of intercellular adhesion molecule (ICAM) receptors in airway secretions and systemic circulation is observed in preterm infants exposed to chorioamnionitis, compared to those with no exposure.^[16] Assessment of the apoptotic index (AI) in the lungs of stillborn foetuses showed that those exposed to maternal chorioamnionitis had a significantly increased AI, compared to those without exposure to chorioamnionitis, and that the AI was higher still if pneumonitis was also present.^[17] This implies that babies who do not respond to surfactant therapy may already have irreversible cellular changes leading to apoptosis. The risk of BPD is greatest in infants with exposure to chorioamnionitis plus either MV for >7 days and/or postnatal infection. Interaction between antenatal infection, postnatal ventilation and nosocomial infection further increases the risk of BPD.^[18]

Why is oxygen so damaging in preterm infants?

The activity of reactive 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 glutathione peroxidase (GP) have protective activities against ROS. However, there is little or no activity of these enzymes at lower gestational ages.^[19] 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

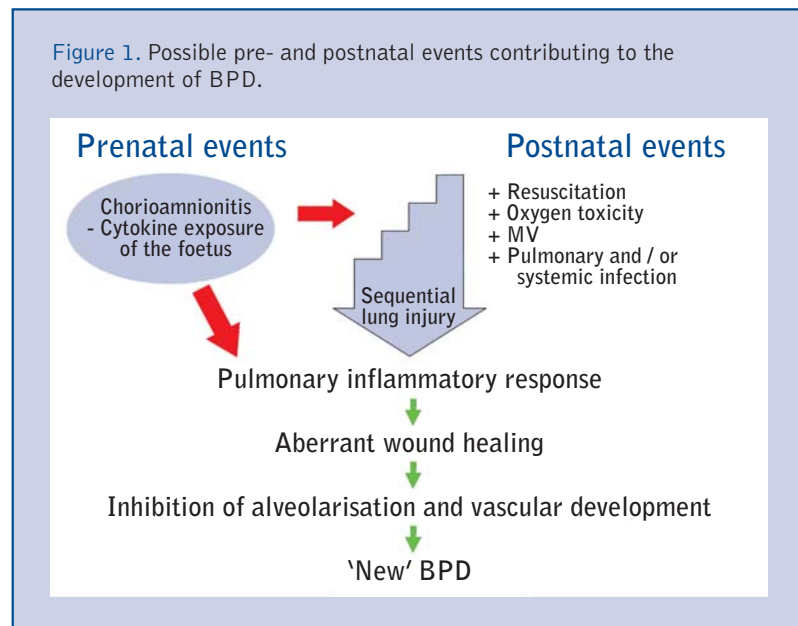
and tissue inhibitor of metalloproteinases (TIMP).^[20–22] This lack of protection against neutrophil elastases and other proteases results in damage of the alveolar-capillary unit with subsequent protein influx and surfactant inactivation. As a consequence, lung function deteriorates and profibrotic factors are generated.

CTGF pathway linked to fibrosis

BPD appears to occur after a cascade of events, which include the release of transforming growth factor- β (TGF- β) and connective tissue growth factor (CTGF), is induced by trauma.^[23,24] In classic BPD, levels of both of these cytokines are elevated.

However, reduced levels of CTGF,

which is responsible for the development of fibrosis, have been observed in neonates with the new BPD. This gives a preliminary conclusion as to why the histology of the new BPD may differ from the classic form. Observations in babies have been confirmed in animal studies. In premature lambs, high levels of TGF- β were observed following endotoxin challenge, but CTGF levels were reduced.



Summary of pre- and postnatal events leading to new BPD

There are multiple pre- and postnatal events contributing to the development of BPD in preterm infants (Figure 1). 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, aberrant wound healing and inhibition of alveolarisation and vascular development, causing the new BPD.

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