Inflammatory mediators and bronchopulmonary dysplasia

Exposure of the immature developing lung to barotrauma and hyperoxia leads to bronchopulmonary dysplasia (BPD) in many infants of extremely low birth weight. The mechanisms of the acute lung injury, that is followed by altered lung repair, are incompletely understood. Inflammation occurs both as a result of the toxic effects of oxygen on the lungs as well as the mechanical injury. There is growing evidence to suggest that an inflammatory pulmonary reaction following lung trauma may be an early event in the development of BPD, finally leading to lung fibrosis. Inflammation includes production of chemotactic factors in response to a stimulus (trauma, hypoxia/reperfusion, hyperoxia), migration of inflammatory cells, increased expression of adhesion molecules on endothelial and epithelial cells, adhesion of neutrophils, secretion of proteases and toxic oxygen radicals, and increased microvascular permeability. The data discussed here have been derived predominantly from studies investigating inflammatory mediators in tracheobronchial effluent fluid of ventilated newborns. Recently reviewed data on reactive oxygen metabolites in the pathogenesis of BPD will not be addressed.1

Inflammatory cells
Several studies have shown that respiratory distress syndrome (RDS) and mechanical ventilation with oxygen are associated with increased recruitment of inflammatory cells within the airways, 2,3 the predominant reactive cell type of which is the neutrophil. In infants who recover from RDS the neutrophil cell count in tracheobronchial aspirates decreases but it remains high in infants who finally develop BPD. This course is also observed when oxygen burden and mechanical trauma of the lung has been reduced by surfactant administration. Surfactant replacement itself increases cell count in bronchoalveolar lavage fluid (BAL) only within the first 3 days of life. 4

The situation regarding alveolar macrophages is less clear. During the development of BPD, decreased numbers of these cells have been found in tracheobronchial secretions compared with data from controls. 3, 4 In contrast, another study has shown that in infants with BPD most cells obtained by BAL after 48 hours were macrophages immunoreactive for tumour necrosis factor-α. 5 In patients with BPD who had a bronchoalveolar lavage performed at a mean age of 4 months, alveolar macrophages represented 90% of the recovered cell population. Compared with controls, these cells produced increased amounts of hydrogen peroxide, indicating an activated status. 6 Post mortem studies have also shown increased numbers of activated macrophages within the pulmonary tissue of infants with BPD. 7

Chemoattractants and adhesion molecules
Local production of chemotactic active agents is one of the earliest events in inflammation. In parallel to neutrophil influx, chemotactic activity of tracheobronchial aspirate fluid is increased in infants with developing BPD. 8 Leukotriene B4 (LTB4), the anaphylatoxin C5a, and interleukin-8 (IL-8), important chemoattractants for human neutrophils, have been detected in the BAL of these infants. LTB4 is produced by neutrophils and alveolar macrophages themselves within the lung, and serves as an autocrine upregulation system. In the absence of infection concentrations of LTB4 in pulmonary effluent were found to be generally low, but significantly higher in neonates at risk for BPD than in controls within the first 15 days of life. High concentrations have been found in the advanced stages of BPD. 9 C5a is also present in the pulmonary effluent of infants with early BPD, with concentrations comparable with those of plasma. C5a may derive from local activation induced by tissue trauma, cleavage from locally produced precursors, or from plasma as a result of increased pulmonary leakage. Interleukin-8, which probably represents the most important chemoattractant within the lung, mediates pulmonary neutrophil recruitment induced by hyperoxia and hypoxia/reperfusion. IL-8 is produced locally by alveolar macrophages, neutrophils, fibroblasts, type II alveolar cells, and endothelial cells. Concentrations in tracheobronchial aspirate fluid are 200 times higher than those of plasma, and are increased in infants at risk of BPD compared with controls. 8 It has been suggested that increased concentrations in bronchoalveolar lavage fluid may represent a marker for development of BPD. 10

Intercellular adhesion molecule-1 (ICAM-1) is a glycoprotein that allows cell to cell contact. It is expressed in response to IL-1 stimulation. ICAM-1 binds to the C11/C18 complex on neutrophil granulocytes and regulates neutrophil diapedesis. Increased expression on alveolar epithelial cells suggests a role for ICAM-1 in oxygen-induced, neutrophil-mediated parenchymal injury. Increased concentrations of the soluble form of ICAM-1
have been found in the tracheal aspirates of infants with early BPD.11

Elastase: the secretory product of neutrophils
Neutrophils attracted to injured tissue by chemotactic active agents may contribute to lung damage by degranulation and secretion of proteases as well as reactive oxygen metabolites. Increased concentrations of elastase have been found in the lung secretions of infants with BPD. The activity of the most important antiprotease, α1-protease inhibitor, was low in these studies.9 12 It has therefore been suggested that an imbalance between protease and antiprotease is an important mechanism of lung damage in BPD. This is an attractive hypothesis, although elastase might be harmful to the lung even without obvious signs of an imbalance in tracheobronchial aspirate fluid. However, the data regarding the protease-antiprotease imbalance are puzzling. The relation of elastase to secretory leucocyte protease inhibitor, an antiprotease that is produced locally within the airways, was higher in infants who developed BPD compared with controls, suggesting an unfavourable balance.13 In this study the highest peak of elastase was found on the first day of life. In another study high concentrations of free elastase in tracheobronchial aspirate fluid were found shortly after birth and were associated with the development of pulmonary interstitial emphysema.14 However, in infants at risk for BPD, but without severe hypoxia or barotrauma, the secreted elastase was predominantly bound to α1-protease inhibitor.8 In another study the elastase load in lung effluent fluid, comprising free and complexed elastase, correlated well with myeloperoxidase activity as a marker of inflammatory activity.15 Most of the elastase present in tracheobronchial aspirate fluid, however, was also complexed with antiprotease, and only very few infants exhibited free elastase activity. In ventilated infants high concentrations of complexed16 and free elastase17 have been found in infants with lung secretions colonised with micro-organisms. Increased elastase in combination with low α1-protease inhibitor and high secretory leucocyte protease inhibitor have been described in infants with pneumonia.18 Recently, it has clearly been shown that elastolytic degradation of lung fibres occurs in ventilated neonates.19 Desmosin, which is an elastolytic degradation product of mature cross-linked elastic fibres, was identified in tracheobronchial secretions following detection of free elastase in some infants. Necropsy specimens have also indicated structurally abnormal lung parenchymal elastic fibres. Hyperoxic exposure and lung infection were associated with elastase release in this study. Thus there are at least two periods when an imbalance of protease-antiprotease within the airways is commonly detected: one shortly after birth, which may be related to severe lung injury, and another later on, associated with nosocomial colonisation.

INFLAMMATORY MEDIATORS AND PULMONARY MICROVASCULAR PERMEABILITY
Persistently abnormal lung permeability is one of the most important pathophysiological factors of early BPD. During infarction, several factors may affect microvascular permeability: modulation of vascular perfusion in the inflamed area, effect of inflammatory mediators (directly or mediated by neutrophils), and a direct effect of toxic oxygen radicals. Many lipid mediators with known effects on microvascular permeability, including leukotrienes, prostacyclin, and platelet activating factor (PAF) have been detected within the airways of infants with BPD.9 20 C5a and IL-8 (via activation of neutrophils and/or inducing PAF production) may also affect permeability. However, at present there is only an association between pulmonary inflammation and microvascular permeability; clear causality has still to be proved.

OTHER INFLAMMATORY MEDIATORS
During RDS, tumour necrosis factor-α has been detected in the respiratory fluids of ventilated infants, with increasing levels depending on duration of mechanical ventilation.21 In the sera of patients with BPD, increased concentrations of soluble IL-2 receptor have been found.22 This may represent a marker of T cell activation and may indicate an early sign of transition from inflammation to fibrosis.

INFLAMMATORY MEDIATORS AND DEXAMETHASONE
The main effect of dexamethasone on the underlying pathophysiology in infants with BPD is an improvement in gas exchange and lung mechanics, in association with a decreased pulmonary microvascular permeability.23 After dexamethasone treatment the number of neutrophils as well as levels of nearly all of the inflammatory indicators studied decreased in tracheobronchial aspirate fluid.23 24

INFLAMMATORY MEDIATORS AND AIRWAY INFECTION
There is no principal difference between the inflammatory reaction evoked by microbes or by unspecific stimuli like hypoxia or trauma. Therefore, increased concentrations of inflammatory mediators are also present in the respiratory fluids of patients with bacterial colonisation or infection of the airways.25 In our experience the concentrations of some mediators are much higher compared with the secretions of infants with BPD and non-infected airways. The frequency and magnitude of tracheobronchial colonisation with bacteria after birth depends on birth mode, time of tracheal intubation, measures to delay or reduce superficial bacterial contamination and duration of intubation. In most infants born by caesarean section, intubated immediately after birth, and nursed with special hygiene measures the airways show no signs of significant colonisation during the first 10 to 14 days. The situation will be quite different after spontaneous birth, intubation later on, and prolonged mechanical ventilation. After more than 20 days of mechanical ventilation, the respiratory secretions of most infants are colonised. Thus for studies of airway inflammation during the development of BPD, tracheal bacterial contamination has to be ruled out. After 28 days, when BPD is definitely present, increased concentrations of inflammatory mediators in airway secretions are predominantly due to a response to microbial colonisation, and will not reflect inflammation due to lung injury. On the other hand, pulmonary infection predisposes to elastolytic lung damage. Prospective studies on the role of infection (both bacteria and Ureaplasma urealyticum) in the pathogenesis of BPD, including measurements of inflammatory mediators, are yet to be undertaken.

Conclusion
An increasing number of studies indicate a role for inflammation in the pathogenesis of early BPD. The reports of the downregulating effects of dexamethasone on pulmonary inflammation support this. However, studying the
inflammatory process by investigating the mediators in respiratory effluent fluid may be confounded by the reaction caused by local microbial colonisation, especially in neonates ventilated long term. Animal studies focusing on early inflammatory events following mechanical ventilation would be an additional useful approach in the future.

PETER GRONECK

Department of Paediatrics,
Children’s Hospital of the City of Cologne

CHRISTIAN P SPEER

Department of Neonatology,
University Children's Hospital,
Rümelin Strasse 23, D-72070, Tübingen, Germany
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P. Groneck and C. P. Speer

Arch Dis Child Fetal Neonatal Ed 1995 73: F1-F3
doi: 10.1136/fn.73.1.F1

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