The diverse role of inhaled nitric oxide in experimental BPD: reduced fibrin deposition and improved lung growth

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Dramatic improvements in neonatal care over the past decade have improved the overall survival of premature infants; however, more than one-third of infants born at less than 1,250 g will ultimately be diagnosed with bronchopulmonary dysplasia (BPD), a complex, multifactorial disease (21). Preterm birth interrupts normal pulmonary alveolar and vascular development and leads to long-term abnormalities in pulmonary growth and function. Necessary therapies for the management of neonatal respiratory distress syndrome, including mechanical ventilation and oxygen therapy, further contribute to lung injury by releasing toxic free radicals and inflammatory cytokines and disrupt production of critical growth factors in the lung. Although the interactions of numerous growth factors are important for normal pulmonary development, it has been well established that nitric oxide (NO) is among the most critical.

Nitric oxide synthase is abundant in epithelial and endothelial cells during fetal development and is responsible for NO oxide production in the lung. Endogenous NO production plays a critical role in both pulmonary vascular and alveolar development, as disruption of NO signaling results in alveolar simplification, impaired pulmonary vascular growth and function, and pulmonary hypertension (3, 9). After birth, NO continues to play an important part in normal lung function by exerting such diverse effects as pulmonary vasodilation (1), bronchodilation (7), improved surfactant function (4), reduced lung inflammation (6, 11), and inhibition of smooth muscle cell proliferation (8). The use of exogenous, inhaled NO (iNO) has been shown to improve lung growth and function in animal models of hyperoxic lung injury and BPD through a variety of mechanisms (13, 18), and there is keen interest that iNO may be useful to prevent or ameliorate BPD in premature infants.

Several recent, large-scale clinical trials have examined the early use of iNO for the prevention of BPD in premature infants, with promising results (5, 12, 16, 20). Although each of the trials utilized a different strategy for the timing and dosing of iNO, a reduction in BPD and/or death was demonstrated either overall or in subgroups of patients in each of the trials. Schreiber et al. (16) treated mechanically ventilated infants born at less than 34 wk gestation with iNO (5–10 ppm) during the first week of life and found a reduction in death or survival with BPD in the NO-treated infants. Kinsella et al. (12) demonstrated a 50% reduction in BPD in infants born at 1,000–1,250 g after treatment with iNO (5 ppm) started within 48 h of birth and continued for a mean of 14 days, although iNO did not reduce BPD for the entire study group. In addition, Ballard et al. (5) treated infants born weighing less than 1,250 g requiring mechanical ventilation at 7–14 days of life with 5–20 ppm iNO and found improved survival without BPD and shorter duration of oxygen therapy overall. Results of these clinical trials are encouraging and suggest that refinement of dosing, timing, and duration of therapy may lead to a further improvement in certain patient populations at risk for BPD. The authors of each of these studies point out that the exact mechanisms by which iNO improves pulmonary outcomes is unclear but likely is a combination of direct stimulation of alveolar and pulmonary vascular growth, improved airway mechanics, pulmonary vasodilation reducing ventilation/perfusion mismatch, and anti-inflammatory properties of iNO.

In this issue of *AJP-Lung*, ter Horst et al. (19) present interesting new research suggesting further roles for iNO (19), which may contribute to improved outcomes after neonatal lung injury. In this study, the authors treated neonatal rats with iNO during hyperoxia after birth and examined its effects on survival, lung growth, and inflammation. Although this study largely confirms past observations, the authors extend previous findings by demonstrating reduced fibrin deposition in the lung, downregulation of inflammatory cytokines (IL-6 and CINC-1), and upregulation of genes involved in alveolarization (FGFR-4 and amphiregulin). As in similar studies, the authors demonstrate modest improvements in lung growth after iNO treatment, including decreased septal thickness and increased alveolar surface area, although iNO-treated lungs exposed to hyperoxia remained markedly simplified when compared with control lungs. In addition, iNO caused an upregulation of FGFR-4 gene expression, which may contribute to improved lung growth, and presents an interesting target for further therapeutic studies. Interestingly, although iNO prolonged survival by 1.5 days in this study, none of the study animals survived the neonatal period after hyperoxia exposure, as iNO did not improve actual survival in this model despite improvements in lung growth and inflammation.

Hyperoxia-induced lung injury has been extensively studied in both adult and neonatal animal models and provides an important experimental model for BPD. iNO, when given during periods of hyperoxia in adult rats, improves survival, diminishes inflammation, and protects both the pulmonary endothelium and epithelium from oxidative injury (10, 14, 15). Although iNO upregulates other growth factors, most notably vascular endothelial growth factor (2), and stimulates alveolar and pulmonary vascular growth in neonatal rats exposed to hyperoxia (13, 18), iNO has not previously been shown to improve neonatal survival after lung injury. Given the results of the recent clinical trials in premature infants, it appears that iNO may improve survival without BPD in premature infants, but likely has far-reaching effects beyond direct stimulation of lung growth.

Ter Horst et al. (19) provide evidence of a novel role for iNO in acute neonatal lung injury, as an inhibitor of fibrin deposi-

Address for reprint requests and other correspondence: T. R. Grover, Univ. of Colorado HSC, PO Box 6508, F441, Aurora, CO 80045 (e-mail: grover. theresa@UCHCden.org).
tion within the lung (19). Respiratory distress syndrome is characterized by a fibrin-rich exudate within the alveoli, likely as a result of capillary leak with extravasation to the extravascular space in the alveolar lumen or membrane. Because fibrin is a proinflammatory and potentially injurious substance capable of surfactant inactivation, this complication has potentially serious consequences in the developing lung. The premature lung must tightly balance the regulation of coagulation vs. fibrinolysis to appropriately respond to capillary leak, or fibrin deposition will result. In fact, premature infants who go on to develop BPD show evidence of impaired fibrinolytic activity early in their neonatal course and have abnormal expression of various fibrinolytic enzymes including plasminogen activator, plasminogen activator inhibitor-1 (PAI-1), and urokinase-type plasminogen activator (uPA) (17). Ter Horst clearly shows that iNO diminishes capillary leak in the setting of neonatal hyperoxic lung injury, decreases fibrin deposition fourfold in the alveolar wall, and induces transcriptional regulation of the fibrinolytic cascade resulting in decreased PAI-1 and uPA receptor expression. Although early fibrin deposition likely plays a less prominent role in histopathology of “new BPD” as a result of capillary leak with extravasation to the extravascular space in the alveolar lumen or membrane. Because fibrin deposition will result. In fact, premature infants who go on to develop BPD show evidence of impaired fibrinolytic activity early in their neonatal course and have abnormal expression of various fibrinolytic enzymes including plasminogen activator, plasminogen activator inhibitor-1 (PAI-1), and urokinase-type plasminogen activator (uPA) (17). Ter Horst clearly shows that iNO diminishes capillary leak in the setting of neonatal hyperoxic lung injury, decreases fibrin deposition fourfold in the alveolar wall, and induces transcriptional regulation of the fibrinolytic cascade resulting in decreased PAI-1 and uPA receptor expression. Although early fibrin deposition likely plays a less prominent role in histopathology of “new BPD” than in the past, it may represent an overlooked but important component of acute lung injury in premature infants. It is unclear whether iNO improves survival in infants with BPD through regulation of fibrinolysis and its anti-inflammatory properties, although this study suggests an even more diverse role for iNO in the management and prevention of neonatal lung disease.

REFERENCES


