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Surfactant and Inhaled Nitric Oxide in Acute Lung Injury

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Abstract Surfactant replacement and inhaled nitric oxide are two important respiratory therapies for neonatal respiratory distress and persistent pulmonary hypertension. However, limitation of each therapy alone in various respiratory disorders raised questions as to whether we should use them in a combined manner, or in combination with other effective treatment modalities, so that the problems in both alveolar space and intrapulmonary vasculature may well be dealt with simultaneously. In recent years, a number of experimental and clinical studies have demonstrated that combined surfactant and inhaled nitric oxide consistently showed better effects than that of the independent therapy, suggesting that the adequate use of these two therapies may have a potential to improve clinical management of severe respiratory problems in infants and children.

Key words Nitric oxide; Pulmonary surfactant; Respiratory distress syndrome; Respiratory therapy

Pulmonary surfactant is routinely used in immature newborns for the prevention and treatment of respiratory distress syndrome (RDS). Inhaled nitric oxide (INO) is a new respiratory therapy, recently approved by the Food and Drug Administration, for selective pulmonary vasodilation in persistent pulmonary hypertension of the newborns (PPHN) and in hypoxic respiratory failure in neonates and infants. It is noteworthy that these two most eminent therapies, developed in 80's and 90's, respectively, revolutionized neonatal respiratory care, and are still the foci of basic and clinical investigation for infants, children and adults with acute lung injury (ALI) and acute (or adult type) RDS (ARDS), the pathogenesis of which differs from primary surfactant deficiency in RDS and primary or secondary PPHN, but is related to, among other mechanisms, surfactant dysfunction and abnormal metabolism, and impairment of pulmonary vasodilatation due to hypoxic vasoconstriction.

Pulmonary surfactant is a phospholipid-protein complex produced by the type II alveolar epithelial cells. Theoratically, in a normal adult lung, about 0.3 μg of tightly packed dipalmitoylphosphatidylcholine (DPPC) monolayer is needed to cover 1 cm^2 of alveolar inner surface during expiration,[1] hence is an alveolar pool size of 0.6 mg/m^2 (0.3 μg × 10000 × 2) of total phospholipids (assume 50% of surfactant phospholipids are disaturated). This amount is close to most of the experimental data regarding alveolar surfactant phospholipids obtained by bronchoalveolar lavage. More than 90% of the surfactant is recycled between the type II alveolar epithelial cells and alveolar lining layer as a normal metabolic process. In contrast, in the fetal and neonatal lungs near or at partum, the amount of total surfactant phospholipids in both alveolar and tissue compartment may be several times higher than that of the adult lungs in that sufficient surfactant, restored during later gestation, is required for postnatal adaptation of extrauterine life. It was estimated that the lowest surfactant concentration in the lung fluid should be above 2 to 3 mg/ml, corresponding to a pool size of 40 to 50 mg/kg birth weight, so that as air enters into alveolar spaces, it enables immediate openning of potentially fluid-filled surfactant-rich alveoli, formation of air-liquid interface, and facilitate lung fluid absorption. Subsequently in the later postnatal time, total amount of surfactant diminishes to adult level and intracellular surfactant reserve becomes less, under which circumstance it is prone to surfactant dysfunction and interruption of surfactant recycling and reutilisation.[2] Furthermore, experimental studies demonstrated that tumor necrosis factor-α (TNF-α) inhibits surfactant production and surfactant protein expression in the type II cells,[3] and serum proteins, especially fibrinogen, inhibit surfactant activity.[4] These situations are often encountered in lung

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inflammation, or simply during mechanical ventilation. Thus, it provides rationales for the use of exogenous surfactant in the mature lungs at high risk of surfactant dysfunction, and account for the benefitial effects of surfactant in various respiratory disorders in neonates, such as meconium aspiration syndrome (MAS), pneumonia, pulmonary hemorrhage, etc. Apart these, exogenous surfactant also has a potential to facilitate intrapulmonary vasodilatation[5] and modulation of adherence and release of proinflammatory cytokines of neutrophils.[6]

Application of surfactant and INO was merged when the clinical trial of INO was intensified in the mid-90's. In a clinical trial using INO for PPHN, more than 70% of the enrolled newbrons were treated with surfactant and failed to have sustained improvement in blood oxygenation prior to randomization for INO. It concluded that the use of INO significantly reduced the need for extracorporeal membrane oxygenation (ECMO).[7] In the clinical trials for adult patients with ARDS, INO failed to show benefits in mortality reduction although improvement of oxygenation was observed.[8-11] To test surfactant in term neonates with severe hypoxia and respiratory failure, Lutze et al.[12] conducted a 44-center trial on 328 patients and concluded that early use of surfactant may reduce the need for ECMO, but the effects were mainly confined to those with relatively lower oxygenation index (OI<23, OI=FiO_2 × Mean airway pressure [cm H_2O] × 100/PaO_2 [mmHg]) and to those with MAS. No significant changes were found with respect to the need for ECMO and the risk for major complications in those with higher OI (>23), or in PPHN and sepsis. These findings suggest that each of these therapies has certain limitation in the acute phase of respiratory failure of specific patient populations, and raised hypothesis that, in order to enhance each of these therapies, to combine both with adequate ventilation strategy would be an alternative solution.

In a case report, Struber et al.[13] found that a combined use of surfactant and INO restalled respiratory function in a patient with respiratory failure due to hypoxia and reperfusion injury as a result of sudden cardiac arrest. In surfactant-depleted animal lungs after lavage during mechanical ventilation, Gommers et al.[14] found that exogenous surfactant is better than positive end-expiratory pressure to recruit alveolar unit and to facilitate pulmonary vasodilation by INO, whereas in a meconium aspiration model, Rais-Bahrami et al.[15] found effects of INO may be enhanced by preceding surfactant treatment. From my laboratory, Zhu et al.[16] found that a combined surfactant and INO exerted synergistic effects in lung mechanics, blood oxygenation and alveolar expansion in oleic acid-induced ARDS, and revealed that such a combination altered ventilation-perfusion mismatching in the lungs as reflected by improved PaO_2/FiO_2, intrapulmonary shunting, wet-to-dry lung weight ratio (fluid absorption), and alleviated neutrophil accumulation in bronchoalveolar lavage fluid at the end of the experiment. Using the same model, Zhou et al.[17] found that such effects may be achieved by using pressure support ventilation that markedly reduced mean airway pressure, and that neutrophil accumulation in the lungs was further mitigated. By direct measurement of pulmonary arterial pressure during a 24-hour experimental period, we again confirmed that such effects were sustained in association with reduced pulmonary arterial pressure and maintenance of lung structural integration, and that INO does not affect surfactant protein A and D mRNA expression and surfactant phospholipid production (Zhou et al., unpublished data). We drew preliminary conclusion from above studies that the combination of surfactant therapy and INO stands for ventilation-perfusion match and ensures a sustained improvement of gas exchange and oxygenation, that INO only does not protect the lung structural integrity, and that no adverse effects were observed. Thus, this combined modality should have profound advantages in combating ALI and ARDS.

Inflammatory injury in the lungs is one of the most important mechanisms in ALI/ARDS. In the early phase of ARDS, the lung is the site of an intense inflammatory process with sequential activation of cytokines, chemokines, and secretion of proteases, along with collagen synthesis.[18] Mechanical stretching of the lung by positive airway pressure ventilation may induce neutrophil accumulation and proinflammatory cytokine releasing in the lungs.[19] This process includes rolling, adherence, deformation and migration of neutrophils from vascular to interstitial to alveolar compartment under the influence and interaction of various proinflammatory cytokines,[20-22] such as TNF-α, L- and P-selectin, intracellular adherence molecule (ICAM), integrin β_2 (CD11/CD18), interleukins (IL-1, 6, 8) and others. The pathway for initiation of the cytokine production and releasing is through nuclear factor kappa B (NFκB) in the affected cells, i.e. neutrophils, alveolar macrophages and alveolar epithelial cells.[23] In addition, inflammatory lung injury by local bacterial assult, or as a result of systemic inflammatory response of sepsis, may also provoke this procedure. The most important pathophysiology in the lungs in this procedure consists of pulmonary vascular constriction and elevated permeability, interstitial and alveolar edema, suppression of endogenous surfactant production, elevated protease activities and impaired antioxidant system. Benefits of INO is not merely confined to selective pulmonary vasodilation. Like surfactant, it has a potential to modulate vascular-to-alveolar permeability, cytokine release in neutrophils and enhance antioxidant activity in epithelial cells in ALI.[24]

Inhaled NO for septic lung injury is also the target of INO therapy. Krafft et al.[25] first reported that INO is effective in septic ARDS, but several clinical trials of INO

for ARDS failed to show any improvement in long term outcome,[8-11] in which a large proportion of the patients were septic or pneumonia. In my laboratory using endotoxin-induced ALI model, Zhao et al.[26] reported that a combined surfactant therapy and INO mitigated lung injury, facilitated gas exchange and blood oxygenation, improved surfactant activity and lung fluid clearance, and reduced neutrophil accumulation in the lungs of the animals, however, depressed expression of SP-A mRNA was not reversed. This finding is in accordance with that of the Lewis et al.[27] that impairment of surfatant in sepsis may be an early marker of lung injury, again justifying the use of surfactant therapy for septic ARDS. In another study in my laboratory using a dog model of endotoxin-induced ARDS, Miao et al. found that even if there is severe lung injury and hypoxic respiratory failure, the animals responded to INO at 10 to 20 ppm, and no further benefit was observed when INO was 40 to 80 ppm, and that INO suppressed proinflammatory cytokine, such as TNF-α, IL-8 and CD11b, expression in concert to a clinical recovery of lung mechanics and peripheral neutropenia (unpublished data).

The potential adverse effects of NO are still a concern,[24] especially in relation to the formation of peroxynitrite. Normal structure and function of surfactant protein A (SP-A) may be affected by protein tyrosine nitration as a result of pernoxinitrite formed by NO and oxidant in tissue. Another recent study found that INO at 20 ppm significanly reduces tyrosine nitration in rats with endotoxic lung injury.[28] This finding might explain a previous report that INO increases the survival of rats exposed to >90% oxygen and 100 ppm NO for 120 hours,[29] a condition unlikely to be adopted in the clinical situation though. Lorch et al.[30] observed that 3-nitrotyrosine formation in the airway epithelium after hyperoxia was mitigated by INO 20 ppm for 72 hours, and S-nitrosocysteine in airway epithelium was significanly enhanced, suggesting a major modulation of airway proteins. Inhibition of surfactant metabolism was reported in cultured type II cells.[31] However, in our laboratory, exposure of healthy piglets to 40 ppm NO for 48 hours (i.e. time weighted NO exposure at 1960 ppm.h) does not cause deterioration of surfactant related lung function, nor for alteration of surfactant phospholipid composition and expression of SP-A and SP-D mRNA (Zhang H et al., unpublished data). It is expected that, with the use of surfactant and INO, our knowledge in the mechanism, prevention and treatment of ALI and ARDS will be widened. More investigation is needed as to how surfactant and INO modulate intrapulmonary neutrophil function, whether INO affects endogenous surfactant activity and metabolism in injured lungs, what kind of ventilation mode is less injurous to the lung. A combined, or alternative, use of surfactant therapy and INO, assisted by adequate ventilation strategy may throw light on respiratory care for severe ALI and ARDS in children and adults.

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