Inhaled Nitric Oxide: Update 2007

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We hypothesized that inhaled NO would diffuse into the pulmonary vasculature of ventilated lung regions and cause relaxation of pulmonary vascular smooth muscle. Since the NO is inhaled, the gas should be distributed predominantly to well ventilated alveoli and not to collapsed or fluid-filled regions of the lung. In the presence of increased vasomotor tone, the selective vasodilatation of well-ventilated lung regions by inhaled NO should cause a "steal" or diversion of pulmonary artery blood flow towards well-ventilated alveoli, and improve the matching of ventilation to perfusion, reducing right-to-left shunting and thereby enhancing arterial oxygenation (PaO₂). Such an effect would be in marked contrast to the increased mismatch of ventilation and perfusion caused by intravenously administered vasodilators such as nitroprusside, nitroglycerin, and prostacyclin. Although these intravenous agents decrease pulmonary artery pressure, they increase intrapulmonary shunting of deoxygenated blood, by non-selectively dilating hyperventilated lung segments, and reduce the systemic PaO₂. Also, inhaled NO should not produce systemic vasodilatation because, unlike available intravenous vasodilators, it is avidly bound to hemoglobin and rapidly converted to Nitrate and Nitrite and other NO aducts. See recent review article by Ichinose et al. (1).

Rossaint and coworkers compared the effects of inhaling 18 and 36 ppm (parts per million by volume) NO to intravenously infused prostacyclin in nine patients with ARDS (2). Inhaled NO selectively reduced mean pulmonary artery pressure from 37 ± 3 to 30 ± 2 mmHg (mean ± SE) and improved oxygenation by decreasing venous admixture (Q̇v/Q̇t). The improved efficiency in oxygen exchange during NO inhalation was reflected in an increase of the PaO₂/FIO₂ ratio from 152 ± 15 mmHg to 199 ± 23 mmHg. While the intravenous infusion of prostacyclin also reduced pulmonary artery pressure, mean arterial pressure and PaO₂ decreased as Q̇v/Q̇t increased. Subsequent reports have documented that inhalation of lower concentrations of NO (less than 20 ppm) also decreases pulmonary artery pressure and improves PaO₂ levels (3). Even very small inhaled concentrations of NO (as low as 250 parts per billion) may be effective in some patients (3). Right ventricular ejection fraction increases in some patients breathing inhaled NO, suggesting that decreasing pulmonary artery pressure may unload the right heart and be hemodynamically beneficial (3,4).

A marked variation has been reported for the hemodynamic and respiratory effects of clinical NO inhalation in ARDS, both among patients and within the same patient at different times in their illness. It is possible that pre-existing pulmonary disease as well as the concomitant administration of other vasoactive drugs and the effects of septic mediators and the accumulation of NO products may contribute to the observed variability. In general, the level of elevation of pulmonary vascular resistance predicts the degree of pulmonary vasodilation that is possible to achieve by NO inhalation. Those with the greatest degree of pulmonary hypertension appear to respond best to NO inhalation. Several recent trials have shown no effects on outcome (survival weaning from ventilation, etc.) of NO breathing in ALI (5). A large randomized trial of 385 severe ALI patients (not due to sepsis and without evidence of nonpulmonary organ system dysfunction) who breathed 5 ppm NO or nitrogen, resulted in short duration oxygenation improvement, but had no substantial impact on the duration
of ventilatory support or mortality (6).

**NO Inhalation in Neonatal Respiratory Failure**

In the fetus, intense pulmonary vasoconstriction causes oxygenated blood returning from the placenta to shunt right-to-left across the patent foramen ovale and ductus arteriosus to bypass the collapsed lungs. At birth, the lungs are distended with air and there is a sustained decrease in pulmonary vascular resistance and an increased pulmonary blood flow. In some babies, pulmonary blood flow does not increase after birth. Persistent pulmonary hypertension of the newborn (PPHN) is characterized by an increased pulmonary vascular resistance, right-to-left shunting of deoxygenated blood across the ductus arteriosus and foramen ovale, and severe systemic hypoxemia. Although breathing high levels of oxygen and induced alkalosis decreases pulmonary hypertension in some patients with PPHN, these therapies are often unsuccessful. The use of intravenous vasodilator therapy is limited by severe systemic hypotension, which may further reduce the PaO₂ by increasing right-to-left shunting in patients with PPHN. Extracorporeal membrane oxygenation (ECMO) is often used to support babies who remain hypoxemic despite maximal ventilator and medical therapies. Endogenous production of NO by the pulmonary vasculature is likely to be decreased in PPHN. Therefore, a therapeutic strategy that selectively increases NO activity in the lung may be beneficial to many infants with pulmonary hypertension.

Several clinical studies of NO inhalation have been performed in term gestation neonates (7,8), and infants and children with pulmonary hypertension (9,10). Each demonstrates that inhalation of NO selectively decreases pulmonary hypertension and increases PaO₂. In three prospective randomized trials in term gestation newborns with hypoxic respiratory failure breathing NO acutely increases systemic oxygen levels and decreases the need for ECMO (11,12,13). The FDA approved the clinical use of inhaled NO for the treatment of full term hypoxic newborn respiratory failure in December 1999. Additionally, in children with many forms of congenital heart disease inhaled NO decreases pulmonary hypertension (9). This has led to widespread use of inhaled NO to treat infants and children after open heart surgery. A review of 400 pediatric patients treated with inhaled NO showed marked responses in those with total anomalous pulmonary venous connection, congenital mitral stenosis, and in children and infants with post-operative left-to-right shunts and other lesions (10). Inhaled NO was used to discriminate those patients with anatomical obstruction to pulmonary blood flow from those with pulmonary vasoconstriction.

In pediatric as well as adult patients the pulmonary vasodilator response to NO inhalation is variable. In the neonatal lung, the degree of improvement of arterial oxygenation with NO treatment depends on the initial degree of pulmonary vasoconstriction and hypoxemia (8) and requires recruitment of an adequate lung volume.

Four recent randomized studies have focused on using 5–20 ppm Inhaled NO to treat the premature infant. Three trials examined treating hypoxic premature infants receiving mechanical ventilation (13,14,15) and one examined treating the premature infant developing chronic lung disease (16). A variety of positive and negative endpoints were reached in some of these studies including a reduction of death and chronic lung disease evolution, as well as a reduction of Intraventricular Hemorrhage (IVH) and periventricular leukomalacia. Another large trial is ongoing in Europe to attempt to reach a final conclusion.

**REFERENCES**


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