muscularization and vascular obliteration in children with pulmonary hypertension.

**Persistenl Pulmonary Hypertension of the Newborn**

Based upon studies of near-term fetal sheep, it was clear that inhaled NO was a selective pulmonary vasodilator of the ovine perinatal pulmonary circulation. We therefore treated seven patients with PPHN with brief periods of NO inhalation to learn if NO would augment their PaO2. We chose not to invasively measure pulmonary hemodynamics in these critically ill newborns since the persistence of ductal shunting makes newborn pulmonary hemodynamics difficult to interpret, and we did not wish to delay a possibly lifesaving treatment. In each of the seven newborns, there was a prompt and significant increase of preduectual SpO2, and in five infants, an increased postductal PaO2 while breathing 80 ppm NO. The increased PaO2 persisted while breathing NO, and in one infant, the PaO2 remained elevated after NO breathing ceased. The six others were treated with ECMO. Kinsella et al reported treating nine babies with inhalation of 10 to 20 ppm NO for periods of up to 24 h. All nine babies improved their O2 exchange during NO inhalation, and six infants were treated with 6 ppm inhaled NO for 24 h with sustained clinical improvement. The PaO2 remained improved after the withdrawal of NO inhalation. The NO inhalation is presently being studied in a blinded randomized fashion in PPHN by two multicenter trials.

**NO Inhalation in Primary Pulmonary Hypertension and COPD**

Pepke-Zaba et al reported a study of 10-min inhalation periods of 40 ppm NO in air in eight patients with primary pulmonary hypertension. Apparently these patients breathed from previously prepared bags of mixed gas, and NO2 levels were not reported. They noted PVR was reduced but did not report PAP or CO. Fratacci et al have recently reported the results of inhaled NO in patients with COPD and pulmonary hypertension. They reported that breathing 40 ppm NO reduced the PVR and PAP and slightly increased the PaO2.

**The Future of NO**

Inhaled NO is now firmly established as a selective pulmonary vasodilator in a number of animal models and clinical pulmonary diseases of humans. Much remains to be learned. In our opinion, several important areas remain to be studied:

1. To define the toxicity of inhaled NO. For how long and at what levels is it safe for humans to breathe NO? Is it safe for the newborn to breathe NO? Is NO breathing safe for the acutely injured lung? Is genotoxicity a problem?
2. If NO breathing is safe, then in which respiratory diseases can NO cost effectively produce important benefits? PPHN? CHD? ARDS?
3. If proven safe, will prolonged NO breathing prevent additional lung injury or even save lives in the treatment of chronic pulmonary vascular diseases such as CHD? COPD? Chronic pulmonary hypertension?

4. Will NO be a useful human bronchodilator?

**References**


**Nitric Oxide Inhalation**

**Effects on the Ovine Neonatal Pulmonary and Systemic Circulations**

Vincent DeMarco, Ph.D.; Jeffrey Skimming, M.D.; Tamir M. Ellis, Ph.D.; and Sidney Cassin, Ph.D.

These experiments were designed to test the hypothesis that inhaled nitric oxide (NO), an endothelium-derived relaxing factor, causes a decrease in pulmonary arterial pressure and pulmonary vascular resistance (PVR) in the normal and constricted ovine neonatal pulmonary circulation (N = 7; age = 13.9 ± SD 3.3; mass = 5.7 ± SD 0.8 kg).

Using aseptic surgery, catheters were placed in the

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pulmonary, carotid, and femoral arteries, left atrium, and jugular vein. Additionally, the ductus arteriosus was ligated and a Doppler flow probe positioned around the pulmonary artery. Lambs were allowed a minimum of 5 days recovery before experimentation. Mean pulmonary arterial pressure, systemic arterial pressure (SAP), left atrial pressure (LAP), heart rate (HR), and pulmonary arterial flow (PAF) were monitored constantly using a Gould eight-channel physiograph. The effects of NO inhalation in the normotensive lamb were examined initially. Inhaling gas containing 80 ppm NO (FI02 = 0.60) caused a slight but significant decrease in PVR (repeated measures ANOVA; p <0.05). No changes occurred in the other hemodynamic variables or blood gases (pH, PCO2, PO2, total hemoglobin content, O2 saturation, or O2 content). Lambs were then infused with the constrictor, U46619 (1.9±.7 μg/min/kg), and SAP rose from 21.1 (±4.8) to 39.9 (±4.8) mm Hg and SAP from 82.6 (±10.8) to 98.1 (±6.8) mm Hg.

To test the effects of NO inhalation on lambs with acute pulmonary hypertension, lambs breathed gases containing NO at concentrations of 5, 10, 20, 40, and 80 ppm (FI02 = 0.60). Lambs breathed control gas prior to and following each experimental gas. Significant changes in PAP and PVR occurred (repeated measures ANOVA; p <0.05 for each variable). Each gas containing NO, except 5 ppm, caused a significant decrease in PVR relative to the preceding control period; however, NO at any concentration did not return PVR to normotensive values. No changes occurred in any of the other hemodynamic variables or in blood gases. In a third study, mild pulmonary hypertension (PAP = 26.9±6.2 mm Hg) resulting from breathing a hypoxic gas mixture (FI02 = 0.08) was reversed (PAP = 20.3±5.6 mm Hg) during inhalation of the hypoxic gas with 80 ppm NO. The following day, lambs were again made hypertensive by infusion of U46619 (2.0±0.4 μg/min/kg). They then breathed 80 ppm NO for a period of 3 h. Blood was sampled every half hour for blood gas analysis. The PAP and PVR returned to normotensive values throughout the 3-h period. No changes occurred in any of the other hemodynamic variables or in blood gases during the period of infusion of U46619. Following 30 min of NO inhalation, mean methemoglobin (Co-oximeter, Instrumentation Laboratories, Lexington, Mass) increased significantly to 3.6 percent (±1.1) from a control mean of 1.5 percent (±0.9). Methemoglobin peaked at 4.7 percent (±1.7) in the third hour.

In conclusion, NO inhalation reverses acute pulmonary hypertension in the newborn lamb without causing systemic hypotension. These data are similar to those reported in older lambs. However, unlike the older lambs, methemoglobin levels increase significantly in neonates.

Efficacy of Inhalational Nitric Oxide Therapy in the Clinical Management of Persistent Pulmonary Hypertension of the Newborn*

John F. Kinsella, M.D.; and Steven H. Abman, M.D.

Persistent pulmonary hypertension of the newborn (PPHN) is a clinical syndrome associated with various neonatal cardiopulmonary diseases. It occasionally presents as a relatively isolated pathophysiologic disturbance marked by severe pulmonary hypertension and altered pulmonary vasoreactivity without concomitant lung disease (idiopathic PPHN, "PFC"). However, PPHN is more commonly associated with variable degrees of pulmonary parenchymal disease (eg, meconium aspiration, pneumonia, surfactant deficiency, etc.) Therefore, the therapeutic approach to PPHN requires attention to both the pulmonary vascular component of this syndrome as well as the accompanying alveolar disease.

We have previously reported acute improvement in oxygenation in severe PPHN using inhalational nitric oxide (NO) therapy at doses as low as 10 ppm,2 and sustained improvement with prolonged treatment up to 72 h at 6 ppm NO.3 Moreover, we have observed that conventional mechanical ventilation alone is often ineffective when PPHN occurs in association with severe pulmonary disease. In PPHN complicated by parenchymal lung disease (particularly homogenous lung disease with underinflation), high frequency oscillatory ventilation (HFOV) is an important adjunctive treatment, allowing adequate lung inflation and potentially improving the efficacy of inhalational NO therapy.3

In this report, we summarize the results of a pilot study in 15 consecutive patients with refractory PPHN, emphasizing the roles of selective pulmonary vasodilatation with inhaled NO and optimal pulmonary management with HFOV.

Methods

Fifteen consecutive patients with severe PPHN who were candidates for extracorporeal membrane oxygenation (ECMO) were enrolled in this study. Patients were eligible if they had severe respiratory failure, echocardiographic evidence of PPHN, and met criteria for extracorporeal membrane oxygenation (ECMO) therapy. The study was approved by the Institutional Review Board of the Children's Hospital, and by the United States Food and Drug Administration under an investigator-initiated Investigational New Drug exemption. Patients were enrolled after informed consent was obtained from the parents.

Patients with significant parenchymal lung disease or pulmonary hypoplasia were offered a trial of HFOV before enrollment in the NO protocol. At enrollment, baseline echocardiographic

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