Proceedings from a special symposium on

Use of Inhaled Nitric Oxide in the Hypoxic Newborn

Presented at the 51st International Respiratory Congress of the American Association for Respiratory Care
December 2005 • San Antonio, Texas

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INO Therapeutics
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**Introduction**

Nitric oxide (NO) is a ubiquitous, highly reactive, gaseous, diatomic radical that is important physiologically at very low concentrations (Table 1). Atmospheric concentrations of NO usually range between 10 and 100 ppb, concentrations of 400 to 1000 ppm are routinely inhaled by people who smoke cigarettes, and NO is present in low concentration in the hospital compressed-gas supply. NO is an important messenger molecule, and many cell types have shown the capacity to produce NO. The action of common nitrovasodilators (eg, sodium nitroprusside and nitroglycerin) is a result of their release of NO. Since the mid-1980s, clinical and academic interest in NO has moved from environmental and public health to cellular biology and physiology. Since its synthesis in mammalian cells was first published in 1985, thousands of papers have been published related to the physiologic effects of this molecule. Nitric oxide was designated “Molecule of the Year” by the journal Science in 1992. There is much clinical interest in inhaled NO in the treatment of diseases characterized by pulmonary hypertension and hypoxemia.

**Biology of Nitric Oxide**

Arginine is the substrate for NO synthesis in biological systems and is produced in the presence of NO synthase (NOS) (Fig. 1). NO is lipophilic and readily diffuses across cell membranes to adjacent cells, thus serving as a local messenger molecule. NO typically diffuses from its cell of origin to a neighboring cell, where it binds with guanylate cyclase. Activation of guanylate cyclase results in the production of cyclic guanosine 3′,5′-monophosphate (cGMP) from guanosine triphosphate (GTP), which produces a biologic effect within the cell (eg, smooth muscle relaxation, vasodilation). The time between

**Table 1. Concentration of Nitric Oxide and Nitrogen Dioxide Is Usually Expressed in Concentrations of Parts per Million (ppm) or Parts per Billion (ppb).**

<table>
<thead>
<tr>
<th>%</th>
<th>ppm</th>
<th>ppb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/100</td>
<td>1/1,000,000</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>1000 ppb</td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 1. Biologic pathway for endogenous production of nitric oxide (NO).** NOS=nitric oxide synthase. GTP=guanosine triphosphate. cGMP=cyclic guanosine 3′,5′-monophosphate. PDE=phosphodiesterase. Dashed lines indicate inhibition.

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NO production and guanylate-cyclase activation is very short because of a half-life <5 s for NO in physiologic systems. Inhibitors of guanylate cyclase (eg, methylene blue) and inhibitors of NO synthase decrease cGMP levels, whereas inhibitors of phosphodiesterase (eg, sildenafil) increase cGMP levels.

Selective Pulmonary Vasodilation

The term selective pulmonary vasodilation is used to indicate two physiologic phenomena (Fig. 2). First, a selective pulmonary vasodilator reduces pulmonary vascular resistance without affecting systemic vascular resistance. Second, a selective pulmonary vasodilator affects vascular resistance only near ventilated alveoli. Inhaled vasodilators are delivered to those lung units that are ventilated. NO is not a selective pulmonary vasodilator per se, but becomes one when inhaled. Inhaled NO selectively improves blood flow to ventilated alveoli, which reduces intrapulmonary shunt and improves oxygenation. The selective pulmonary vasodilation demonstrated by inhaled NO is due in large part to the high affinity of hemoglobin for NO, which is approximately 10⁶ times as great as the affinity of hemoglobin for O₂.

In contrast to inhaled NO, intravenous vasodilators (eg, sodium nitroprusside, nitroglycerin, prostacyclin) are not selective. Although intravenous vasodilators lower pulmonary artery pressure, they also lower systemic blood pressure (Fig. 3). Moreover, these agents increase blood flow to both ventilated and non-ventilated lung units, increasing intrapulmonary shunt and lowering Pao₂.

In the early 1990s, several case reports and case series reported the use of inhaled NO for persistent pulmonary hypertension of the newborn (PPHN). This was followed by several multicenter, randomized, double-blinded studies of inhaled NO for PPHN. On December 23, 1999, the FDA approved INO Therapeutics to market INOmax (the trade name for inhaled NO) for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with pulmonary hypertension. The specific labeled indication is, “INOmax®, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.” On September 23, 2005, the Therapeutic Products Directorate (Health Canada) issued a Notice of Compliance for INOmax, NO for inhalation, in essence approving INO Therapeutics to market NO in Canada.

It is against this background that the symposium published here was organized. This was made possible by an unrestricted grant to the American Association for Respiratory Care by INO Therapeutics.
intent was to provide a panel of speakers who have considerable clinical experience with the use of inhaled NO. The speakers were instructed to specifically address the use of inhaled NO as it relates to the approved use of the drug. In this monograph we are pleased to publish the papers from this symposium. It is our hope that this will provide valuable practical information for respiratory therapists providing inhaled NO therapy.

Additional Reading


Inhaled Nitric Oxide in the Hypoxic Newborn: A Review of the Evidence

Timothy R. Myers BS RRT-NPS

Introduction

Respiratory failure in the neonatal population is a major cause of morbidity and mortality. Newborns with persistent pulmonary hypertension (PPHN) have severe hypoxemia that frequently requires a variety of therapeutic modalities. Relaxation of pulmonary vascular smooth muscle and a subsequent decrease in pulmonary hypertension can be achieved with intravenously administered vasodilators (nitroglycerin, nitroprusside, or prostacyclin), but frequently these vasodilators cause systemic vasodilation, or, worse, by increasing blood flow to perfused but under-ventilated lung regions they increase shunt and worsen PaO\textsubscript{2}.

When critically ill newborns do not respond to traditional medical management (eg, supplemental oxygen, conventional mechanical ventilation, high-frequency oscillatory ventilation (HFOV), hyperventilation, sedation, inotropic support, and vasodilating agents), treatment with more invasive measures such as extracorporeal membrane oxygenation (ECMO) have been used. In 1982 Bartlett et al\textsuperscript{1} reported that infants with hypoxemic respiratory failure had increased survival with ECMO.

Nitric oxide (NO) was originally considered a toxic contaminant that was produced naturally and by industrial combustion. In 1987, the physiologic properties of NO were identified as a potent vasodilator (by relaxing vascular smooth muscle) that could explain the mechanism of action of endothelium-derived relaxing factor (EDRF).\textsuperscript{2} Many cells in the human body naturally produce NO as a lipophilic, endogenous, free-radical compound.

Zapol et al\textsuperscript{3} hypothesized that inhaled NO (INO) would diffuse from the alveolus to the pulmonary vasculature of well ventilated alveoli, relax vascular smooth-muscle, and decrease pulmonary artery pressure. Its ability to produce pulmonary vasodilation and its relatively short biological half-life make INO an ideal selective pulmonary vasodilator. The effects of INO are limited to the pulmonary vasculature because of NO’s active binding with hemoglobin, which results in deactivation.\textsuperscript{4, 5}

In late 1999, the results of several randomized clinical trials led the Food and Drug Administration to approve INO for hypoxic respiratory failure associated with pulmonary hypertension of the newborn. Hypoxic respiratory failure can occur as a primary etiology or a secondary disorder (eg, sepsis, meconium aspiration, PPHN, pneumonia, hyaline membrane disease, congenital diaphragmatic hernia [CDH] or pulmonary hypoplasia).

The purpose of this paper is to review the evidence supporting the use of INO in the newborn with hypoxic respiratory failure.

Observational Trials

Roberts et al, 1992

One of the first reports of INO to treat PPHN was reported in Roberts et al (Table 1).\textsuperscript{6} In this small open-label observational study, they examined the effects of INO (20, 40 or 80 ppm) on oxygenation and systemic blood pressure, with 7 trials in 6 severely hypoxemic full-term newborns. After 10 min of INO, post-ductal arterial oxygenation, pre-ductal and post-ductal oxygen saturations (measured via pulse oximetry [SpO\textsubscript{2}]), and systemic arterial blood pressure were measured. In all patients with low pre-ductal saturation, inhalation...
of 80 ppm NO rapidly increased the pre-ductal \(S_{pO_2}\). In 6 of the 7 trials, INO raised the post-ductal \(S_{pO_2}\). In 5 of the 7 trials (71%), 80 ppm INO for 10 min significantly increased the post-ductal \(P_{aO_2}\) (p < 0.05). However, 20 ppm and 40 ppm INO did not significantly improve post-ductal oxygenation. There was no systemic hypotension in any of the trials.

**Kinsella et al, 1992**

Kinsella et al published their results from a small open-label observational trial of low-dose INO for up to 24 hours in 9 newborns with severe PPHN who were candidates for ECMO (Table 1). Enrollment criteria were severe refractory hypoxemia with oxygenation index (OI) > 40 or acute deterioration with \(P_{aO_2}\) < 40 mm Hg and standard medical treatment. The study protocol specified that the first patients would be briefly (< 4 h) administered INO, with treatment to 24 h in subsequent patients if no adverse effects were detected.

INO was administered for 15 min at 10 ppm and 20 ppm, and arterial blood gases and methemoglobin were measured at each dose. If no side effects were noted, the patient received the extended treatment protocol, and arterial blood gases, methemoglobin and systemic blood pressure were measured at predetermined intervals for 24 hours. The first 3 patients were treated with INO for < 4 h and were subsequently placed on ECMO. The next 6 infants were successfully treated for 24 h and did not require ECMO. In these patients, the \(O_1\) decreased from 60 to 20 within the first 30 min of INO, with no decrease in systemic blood pressure. The improvement in oxygenation was sustained over the course of 24 hours. None of the infants had a sustained increase in methemoglobin > 1.5% or a substantial decrease in systematic blood pressure with INO. All patients were weaned from ventilator support and supplemental oxygen within the first 30 days of life. There was no evidence of chronic lung disease. This small, but important, trial demonstrated improvement in oxygenation without tachyphylaxis in patients receiving INO for 24 hours.

**Goldman et al, 1996**

In this prospective, open-label, observational, single-center trial, Goldman et al evaluated the role of INO in the treatment of PPHN (Table 1). In this study, 25 consecutive near-term (> 35 weeks gestation) newborns with OI > 25 were placed on 20 ppm INO for 20 min. Patients were classified as responders if they had ≥ 20% increase in post-ductal \(P_{aO_2}\) and a decrease in the OI to < 40 with INO. Responders were continued on low-dose INO. Those placed on INO with an OI < 40 needed a ≥ 20% increase in post-ductal \(P_{aO_2}\) to be classified as responders. Patients who did not respond to a dose of 20 ppm were given a trial of 70 ppm for 10 min. In the responders who maintained an \(S_{pO_2}\) of 88–95% for the subsequent 6 hours with an \(F_{I_{O_2}}\) < 0.8, INO was decreased 1–2 ppm every 15–30 min while ventilator settings and \(F_{I_{O_2}}\) remained constant. Before INO was discontinued, \(F_{I_{O_2}}\) was increased by 0.1. If the \(S_{pO_2}\) fell below 88%, INO was reinitiated at 5 ppm.

In this trial, 92% of the newborns were responders to 20 ppm INO, with a significant improvement in post-ductal \(P_{aO_2}\) (from 33 ± 3.4 mm Hg to 93 ± 8.2 mm Hg; p < 0.0001). This improvement was associated with a significant decrease in OI (86 ± 16.6 to 21 ± 1.7; p < 0.001). Four patterns of response were identified. In 2 neonates (8%; Pattern 1), there was no response to the initial trial of INO; 1 survived. In 9 neonates (36%; Pattern 2), there was a response over the initial 36 hours of INO, but they failed to sustain this response; 6 survived and 5 of the six received ECMO. In 11 neonates (44%; Pattern 3), there was a sustained response to INO, and they were successfully weaned within 5 days; all survived to discharge. In 3 neonates (12%; Pattern 4), there was a response to INO, but they developed dependence at higher doses and could not be discontinued after 3 to 6 weeks; all of these patients died, and lung histology revealed severe pulmonary hypoplasia and dysplasia.

Although 92% of the newborns in this study demonstrated an initial response to INO, the authors concluded that an early response to INO may not be sustained. The authors hypothesized that neonates with pulmonary

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Design</th>
<th>Number of Subjects</th>
<th>INO Dose (ppm)</th>
<th>(PaO_2)</th>
<th>OI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roberts</td>
<td>1992</td>
<td>Single-center</td>
<td>6</td>
<td>20, 40, 80</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Goldman</td>
<td>1996</td>
<td>Single-center</td>
<td>25</td>
<td>20 – 70</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>Biban</td>
<td>1998</td>
<td>Single-center</td>
<td>21</td>
<td>10 – 40</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>Mercier</td>
<td>1998</td>
<td>Multi-center</td>
<td>121</td>
<td>10 – 80</td>
<td>NR</td>
<td>Improved</td>
</tr>
<tr>
<td>Gupta</td>
<td>2002</td>
<td>Single-center</td>
<td>229</td>
<td>25</td>
<td>Improved</td>
<td>Improved</td>
</tr>
</tbody>
</table>

INO = inhaled nitric oxide; OI = oxygenation index; NR = not reported
hypoplasia and dysplasia may have a decreased response and differing time course of response to INO.

Biban et al, 1998

Biban et al9 evaluated the effect of INO on survival and the need for ECMO in 21 newborns (gestational age > 34 weeks) with acute hypoxemic respiratory failure (see Table 1). All had an OI > 25 and received an initial INO dose of 10 ppm. If oxygenation did not increase with the initial dose, the dose was increased by 10-ppm increments to 40 ppm. The median maximum dose was 30 ppm. All infants had substantial improvement in PaO2; after the first hour (from 33.2 to 52.5 mm Hg, p = 0.007) and at 24 hours (from 33.2 to 56.4 mm Hg, p = 0.02). The alveolar-arterial oxygen difference (P(A-a)O2) and OI decreased significantly in the initial hour, and this was sustained at 24 hours.

Patients were assigned post-hoc to groups based on outcome: survivors who did not need ECMO (n = 8) and survivors who did need ECMO or nonsurvivors (n = 12). Half of the patients in the ECMO/nonsurvivor group had a diagnosis of CDH. Those who were successfully managed without ECMO showed rapid and sustained improvement of oxygenation with INO. PaO2 increased from 34 mm Hg (95% CI=14.4 mm Hg – 53.7 mm Hg) to 75.7 mm Hg (95% CI=49.1 mm Hg – 102.3 mm Hg) after the initial hour and was 67.7 mm Hg (95% CI=53.1 – 82.4 mm Hg) at 24 hours. None of the oxygenation parameters improved in the 12 patients who ultimately required ECMO or died. These results suggest that INO may improve oxygenation in newborns with acute respiratory failure and may reduce the need for ECMO.

Mercier et al, 1998

In a multicenter observational trial, Mercier et al10 evaluated the effect of INO on oxygenation in newborns with refractory hypoxemia and whether the etiology of the respiratory failure affected the response to INO (Table 1). The study enrolled 121 full-term newborns with PPHN and OI > 40. INO was initiated at 10 ppm and increased every 15 minutes by 10 ppm (upper limit 80 ppm) or until a positive response was achieved. INO was lowered to 5 ppm for a minimum of 24 hours before discontinuation. Newborns receiving conventional ventilation could be switched to HFOV with clinical deterioration while continuing to receive INO at the same or incremental doses. INO was initiated at 26 ± 17 hours after birth and was continued for 59 ± 54 hours. A response occurred in dosages from 5 to 20 ppm, although INO was unsuccessfully increased to 80 ppm in the nonresponders. There were no reports of methemoglobin levels >5%.

Within the initial 30 min of INO, the OI significantly decreased in the 18 newborns with acute respiratory distress syndrome (RDS) (p < 0.0001), the 12 with idiopathic PPHN (p < 0.0001), the 30 with sepsis (p < 0.0001) provided there was no refractory shock (n = 5), and in the 21 with meconium aspiration syndrome (MAS) (p < 0.001). A change from conventional ventilation to HFOV improved the oxygenation in 5 neonates with MAS, but was not helpful in 2. Despite a significant reduction (p < 0.01) of OI with INO for the 40 infants with CDH, the OI remained > 40 in 18 others (45%). Overall, 16% of the newborns required ECMO (57% survival). Newborn survival with INO was associated with the magnitude of OI reduction at 30 min in disease etiologies other than CDH. The investigators concluded that INO improved oxygenation in newborns with severe hypoxemic respiratory failure, but the response was disease-specific.

Gupta et al, 2002

In a single-center observational study conducted over a 5-year span, Gupta et al11 evaluated the combined effect of INO and gentle ventilation (no hyperventilation and no induced alkalosis) in 229 consecutive newborns with PPHN (Table 1). Patients received 25 ppm INO if pulmonary hypertension and hypoxemia persisted despite optimal ventilation. Most of the infants (86%) were referred from outside hospitals for INO therapy and/or ECMO.

Criteria for initiating INO were PPHN with PaO2 < 40 mm Hg and pre-ductal SPO2 <80%. Once on INO, infants were categorized into 1 of 4 groups (nonresponders, transient responders, sustained responders, and INO dependent). INO response was defined as an increase in pre-ductal SPO2, to > 80% (an increment of at least 10%) within an hour of commencing therapy. If oxygenation improved with INO, FiO2 and ventilator settings were decreased, but the INO dose remained constant. When FiO2 was < 0.6, INO weaning was attempted in 5 ppm decrements every 2 to 4 hours as tolerated to 5 ppm. Once the infant was stable on 5 ppm, discontinuation of INO occurred while keeping the FiO2 constant. Infants with persistent PaO2 < 40 mm Hg and pre-ductal SPO2 < 80% were defined as nonresponders and received ECMO if there were no contraindications.

Mean duration of ventilation was 9.9 ± 14 days (median 6.5 days). HFOV was used in 31% (n = 71) of the newborns. A significant reduction in mean airway pressure was obtained in 196 infants transferred from referring centers with implementation of conservative ventilator settings following transfer (17.7 ± 4.3 cm H2O versus 13.2 ± 2.5 cm H2O; p < 0.001). Within the first 24 hours of INO, further significant decreases were obtained (12.6 ± 2.8 cm H2O; p < 0.001). The baseline OI before initiating INO therapy was 46.8 ±
24.5 and significantly decreased to 22.7 ± 21.4 within 24 hours of therapy (p < 0.001). The average duration of INO therapy was 90 ± 166 hours (median 44.5 hours).

Significant differences in response to INO were observed in infants with higher baseline pH and lower baseline OI (p < 0.02). The overall survival was 72% for the 229 newborns. Only 45 infants (20%) were placed on ECMO after failing INO therapy. Those with MAS and PPHN had the greatest improvement in $P_{aO_2}$ (from 32.9 ± 13.4 mm Hg to 80.6 ± 16.3 mm Hg; p<0.01) and OI (from 49.3 ± 24.1 to 20.1 ± 16.1; p < 0.0001) within 24 hours of INO therapy. Infants with MAS and PPHN also had the lowest mortality (8%) and significant less need for ECMO than historical controls (23.9% vs. 12.8%; p < 0.01). Infants with CDH and sepsis were more likely to require ECMO than were infants with MAS or PPHN. The authors concluded that INO was an effective and well-tolerated therapy for infants with severe pulmonary hypertension and hypoxemia, without using hyperventilation.

**Single-Center Controlled Trials**

**Day et al, 1996**

Day et al investigated potential factors associated with an increase in oxygenation in newborns with lung disease or lung hypoplasia who received INO. Newborns were enrolled if OI was > 25 (Table 2). Those with OI of 25–40 were randomized in a double-blind fashion to receive either conventional therapy or INO at 20 ppm. All those with OI > 40 were given a trial of INO. Oxygen variables were obtained prior to randomization and every 30–60 min of treatment. The $F_{IO_2}$ was 1.0 for all the patients, and the ventilator settings were not altered if possible prior to the first set of oxygen-variable measurements. The trial enrolled 50 infants, 22 of whom had OI of 25–40 and were randomized to INO (n = 11) or control (n = 11). Five infants in the control group developed an OI > 40 and were subsequently treated with INO. Another 28 patients presented with an initial OI > 40 and were immediately placed on INO. Thus, 44 patients received INO (10 with lung hypoplasia and 34 with lung disease). In those who received INO, there were significant improvements (p < 0.005) in pH, $P_{aO_2}$, OI, $P_{aCO_2}$, and ductal shunt in the entire group and the subgroup (n = 34) with lung disease.

**Hoffman et al, 1997**

Hoffman et al evaluated whether INO reduced the need for ECMO in newborns with PPHN, compared to matched prospective and retrospective cohorts (Table 2). Newborns admitted when INO was unavailable (prior to INO availability or when unavail-able because of use in another patient) were assigned to the control group (Group 1) and those admitted when INO was available were assigned to the treatment group (Group 2). Newborns in the treatment group had INO initiated at 25 ppm and titrated to a maximum of 50 ppm, using a protocol that required improved gas exchange for continuation of therapy. If a response occurred, the dose was decreased every 30 min by 5 ppm to the lowest dose that maintained the response, or until a dose of 1 ppm was reached. Newborns who did not respond to 25 ppm had the dose increased by 10 ppm every 30 minutes until a positive response was achieved. Those who did not respond to INO within 2 hours were discontinued from therapy. A positive response was defined as a > 25% increase in $P_{aO_2}$ or a > 25% decrease in OI, $P_{(A-a)O_2}$, or shunt.

Fifty patients (29 in Group 1 and 21 in Group 2) were included in the analysis. Newborns who met ECMO criteria were similar in each group (72% in Group 1 versus 76% in Group 2). INO significantly reduced the ECMO requirement (n = 16 in Group 1 versus n = 4 in Group 2; relative risk (RR) = 3.05; 95% CI 1.36–7.26, p < 0.003). The effective INO dose was 32 ± 10 ppm (range 20–50 ppm) with the mean duration of therapy was 7 ± 7 days (range 2 hours to 26 days). Newborns receiving INO had significant improvements in oxygenation and a higher rate of complication-free survival (bronchopulmonary dysplasia; p = 0.018; survival without intracranial hemorrhage, p = 0.048) and lower hospital cost per survivor (p = 0.021), compared with a matched control group. There were no differences in the duration of hospital stay, intensive-care-unit stay, or mechanical ventilation. The authors concluded that INO in neonates with

### Table 2. Major Clinical Outcomes from Single-Center Controlled Trials

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Subjects (number)</th>
<th>Initial NO Dose (ppm)</th>
<th>Mortality</th>
<th>ECMO Requirement</th>
<th>$PaO_2$</th>
<th>OI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>1996</td>
<td>11 Control 11 INO</td>
<td>20</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>Hoffman</td>
<td>1997</td>
<td>29 Control 21 INO</td>
<td>25</td>
<td>No difference</td>
<td>Decreased with INO</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>Wessel</td>
<td>1997</td>
<td>23 Control 26 INO</td>
<td>80</td>
<td>No difference</td>
<td>No difference</td>
<td>Improved</td>
<td>Improved</td>
</tr>
</tbody>
</table>

INO = inhaled nitric oxide; ECMO = entracorporeal membrane oxygenation; OI = oxygenation index
PPHN reliably and safely improved oxygenation and patient outcomes while decreasing hospital costs and the need for ECMO.

Wessel et al, 1997

Wessel et al conducted a single-center, randomized controlled trial to determine the effect of INO on clinical outcomes in 49 newborns with PPHN (Table 2). Of the 49 patients enrolled, 23 received placebo, 26 received INO, and 3 were protocol violations (analyzed according to the intention to treat). The primary outcome variables were oxygenation, mortality, and need for ECMO. Inclusion criteria were: gestational age ≥ 34 weeks with a PaO2 < 100 mm Hg while receiving mechanical ventilation and FIO2 of 1.0, after optimization of ventilatory and pharmacologic strategies. Patients were excluded if they had major congenital anomalies or low pulmonary vascular resistance on echocardiography. Previous treatment with surfactant therapy or HFOV was permitted.

This was an open-label trial, but crossover of patients from control to INO treatment was not permitted. Patients were randomly assigned to placebo or INO at a starting dose of 80 ppm. Patient-care decisions were made according to standard practice guidelines by the clinical care team. Attempts were made to wean mean airway pressure and FIO2, when PaO2 was > 60 mm Hg. INO was decreased from 80 ppm to 40 ppm after 1 hour of treatment. If tolerated, this dose was continued up to 12 hours, and dose reductions of 5 ppm were attempted each morning thereafter. INO was discontinued when the dose reached 5 ppm for at least 12 hours with PaO2 > 60 mm Hg on FIO2 of 0.5. INO was also discontinued if ECMO was initiated or when the attending physician chose to convert from conventional mechanical ventilation to HFOV. ECMO was initiated for OI >40 for at least 1 hour, hemodynamic instability despite inotropic support, or if the patient failed to wean from FIO2 of 1.0 after multiple attempts during 2–3 days.

There were no differences between the groups for mortality, need for ECMO, days of mechanical ventilation, duration of supplemental oxygen, or need for home oxygen. However, the improvement in oxygenation was significantly better 15 min after initiation of therapy among the patients who received INO, for PaO2/FIO2 (control = 22% versus INO = 145%, p=0.03), OI (control 5% versus INO 231%, p = 0.009), PaO2 (control 22% versus INO 43%, p = 0.04), and SpO2 (control 0% versus INO 4%, p = 0.006). Though the difference was not statistically significant, oxygenation was better in the NO group than in the control patients prior to ECMO, and there was a tendency for fewer adverse neurologic events (seizure and intracranial hemorrhage) in the NO group (4/26 versus 8/23). The authors concluded that, although mortality and ECMO use were similar for the treatment groups, the improvement in oxygenation with INO may have important clinical benefits.

Multicenter Randomized Controlled Trials

NINOS, 1997

The Neonatal Inhaled Nitric Oxide Study Group (NINOS) conducted a multicenter study to determine if INO reduced the need for ECMO or mortality in infants with hypoxic respiratory failure (Table 3). In this double-blind, randomized controlled trial, infants < 2 weeks old and ≥ 34 weeks gestation with an OI ≥ 25 received either 20 ppm NO or 100% oxygen (control group). The study enrolled 235 patients (121 infants in the control group and 114 in the INO group).

Though patient care was not dictated by the study protocol, guidelines were used to ensure patients were randomized after the most aggressive treatment strategies were applied. These guidelines included maintenance of a mean arterial blood pressure > 45 mm Hg, an alkaloic pH (7.45–7.60), treatment with surfactant, and a ventilation mode (conventional or high-frequency) that was not changed after randomization, except as part of ventilator weaning.

After randomized, patients could not be crossed over between study groups. Response to the study gas (INO or oxygen) was determined after 30 min. A response was defined according to the change in PaO2 (Table 4). Treatment with the study gas (20 ppm INO or 100% oxygen) was continued for infants who had a complete response. If the response was less than complete, treatment was stopped for 15 min (if tolerated), arterial blood gases were re-measured, and the INO was increased to a maximum concentration of 80 ppm. If a complete response occurred at 80 ppm, the patient continued at that administration dose. Infants who demonstrated a partial response continued treatment at the lowest gas concentration that produced at least a partial response.

Study-gas treatment was discontinued in infants who had no response at either 20 ppm or 80 ppm INO. An SpO2 decrease of >10% prior to the end of the initial phase of administration at either the high or the low concentration led to gas discontinuation. If the participant did not initially respond to the study gas, treatment could be reattempted again, at 6-h intervals (3-attempt limit). Algorithms were provided for study-gas weaning, dose-escalation for clinical deterioration, and re-initiating study gas after successful weaning. Administration of study gas was permitted for a cumulative maximum of 336 hours (14 days). Decisions related to the need for ECMO were made by the blinded clinical team on the basis of specific criteria.
There were no significant differences between the groups for pre-enrollment demographics or treatment at the time of randomization. For the primary outcomes (death or need for ECMO), the incidence was significantly lower for the INO group (46%) than the control group (64%) at 120 days (RR, 0.72; 95% confidence interval 0.57–0.91; \( p < 0.006 \)). There was no significant difference in mortality between the groups. The need for ECMO was significantly less in the INO group (39% versus 55%, \( p < 0.014 \)). The median time to ECMO initiation after randomization was significantly longer in the INO group (6.7 hours versus 4.4 hours, \( p < 0.04 \)).

Analysis for secondary outcomes in surviving infants demonstrated no difference in duration of hospital stay, days of respiratory support, or the incidence of air leak or bronchopulmonary dysplasia between the groups. Patients receiving INO had a significantly greater increase in \( \text{PaO}_2 \) than the controls (58.2 ± 85.2 mm Hg vs. 9.7 ± 51.7 mm Hg), a significant decrease in OI (a decrease of 14.1 ± 21.1 versus an increase of 0.8 ± 21.1), and a greater decrease in the alveolar-arterial \( \text{P}_O_2 \) difference (60.0 ± 85.1 mm Hg vs. 6.7 ± 57.5 mm Hg; \( p < 0.001 \)). More infants receiving INO had at least a partial response to the initial study-gas administration (66% vs. 26%, \( p < 0.001 \)). Most infants evaluated with the 80-ppm dose had no response to the higher dose. The authors concluded that INO decreased the need for ECMO, but had no apparent effect on mortality.

**NINOS, 1997**

A second NINOS, double-blind, multicenter randomized controlled trial was designed to determine whether INO in term and near-term infants with CDH would reduce the occurrence of death and/or the initiation of ECMO (Table 3).\(^\text{16}\) Infants were eligible for the trial if they were \( \geq 34 \) weeks gestation, \( < 14 \) days of age with CDH, without known structural heart disease, required mechanical ventilation for hypoxemic respiratory failure, and had 2 OI values \( \geq 25 \) taken at least 15 min apart. Infants received blinded treatment with 20 ppm INO or 100% oxygen as control. Infants who did not have a full response to 20 ppm INO (increase in \( \text{PaO}_2 \) > 20 mm Hg) after 30 min were evaluated at 80 ppm.

The 28 control and 25 treated infants enrolled by the 13 participating centers were not significantly different at randomization for any of the measured variables,

### Table 3. Major Clinical Outcomes From Multicenter Randomized Controlled Trials

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Subjects</th>
<th>INO Dose (ppm)</th>
<th>Mortality</th>
<th>ECMO</th>
<th>( \text{PaO}_2 )</th>
<th>OI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINOS</td>
<td>1997</td>
<td>121</td>
<td>Control 114 INO</td>
<td>20 and 80</td>
<td>No difference</td>
<td>Decreased with INO</td>
<td>Improved</td>
</tr>
<tr>
<td>NINOS</td>
<td>1997</td>
<td>28 Control 25 INO (all with CDH)</td>
<td>20 and 80</td>
<td>No difference</td>
<td>Increased with INO</td>
<td>No difference</td>
<td>No difference</td>
</tr>
<tr>
<td>Roberts</td>
<td>1997</td>
<td>28 Control 30 INO</td>
<td>80</td>
<td>No difference</td>
<td>Decreased with INO</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>Kinsella</td>
<td>1997</td>
<td>107 INO 98 HFOV</td>
<td>20 and 40</td>
<td>No difference</td>
<td>Not reported</td>
<td>Improvement with combined INO and HFO</td>
<td>Not reported</td>
</tr>
<tr>
<td>Davidson</td>
<td>1998</td>
<td>41 Control 114 INO</td>
<td>5, 20, 80</td>
<td>No difference</td>
<td>No difference</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>Clark</td>
<td>2000</td>
<td>122 Control 126 INO</td>
<td>20</td>
<td>No difference with INO</td>
<td>Decreased</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Sadiq</td>
<td>2003</td>
<td>42 Control 43 INO</td>
<td>10</td>
<td>No difference</td>
<td>No difference</td>
<td>Improved</td>
<td>Not reported</td>
</tr>
<tr>
<td>Konduri</td>
<td>2004</td>
<td>149 Control 150 INO</td>
<td>5 and 20</td>
<td>No difference</td>
<td>No difference</td>
<td>Improved</td>
<td>Improved</td>
</tr>
</tbody>
</table>

**INO** = inhaled nitric oxide; **ECMO** = extracorporeal membrane oxygenation; **OI** = oxygenation index; **NINOS** = neonatal inhaled nitric oxide study; **CDH** = congenital diaphragmatic hernia; **HFOV** = high-frequency oscillatory ventilation

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### Table 4. Response Criteria in NINOS Trial

<table>
<thead>
<tr>
<th>Response</th>
<th>( \text{PaO}_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>increase &gt; 20 mm Hg</td>
</tr>
<tr>
<td>Partial</td>
<td>increase of 10–20 mm Hg</td>
</tr>
<tr>
<td>None</td>
<td>increase &lt; 10 mm Hg</td>
</tr>
</tbody>
</table>
including pre-randomization therapy and initial OI (45.8 ± 16.3 for control, 44.5 ± 14.5 for INO). Death at < 120 days of age or the need for ECMO occurred in 82% of control infants and 96% of INO infants. Death occurred in 43% of controls and 48% of the INO group. ECMO was used for 54% of control infants and 80% of INO-treated infants. There was no significant improvement in $P_{A\text{O}_2}$ ($\Delta P_{A\text{O}_2} = 7.8 \pm 19.8 \text{ mm Hg vs } 1.1 \pm 7.6 \text{ mm Hg}$) nor significant reduction in OI ($-2.7 \pm 23.4 \text{ vs } 4.0 \pm 14.8$) associated with INO. There were no differences between the control and INO groups for the occurrence of intracranial hemorrhage, specific grades of intracranial hemorrhage, periventricular leukomalacia, brain infarction, and pulmonary or gastrointestinal hemorrhages.

The authors concluded that, although the immediate short-term improvements in oxygenation seen in some treated infants may be useful in stabilizing infants for transport and initiation of ECMO, for term and near-term infants with CDH and hypoxemic respiratory failure unresponsive to conventional therapy, INO therapy did not reduce the need for ECMO or death.

Roberts et al, 1997

Roberts et al (Table 3), for the Inhaled Nitric Oxide Study Group, conducted a double-blind, randomized, multicenter study to determine whether INO improved severe hypoxemia in infants with PPHN. Newborn infants (gestational age ≥ 37 weeks and a birth weight of > 2,500 g) where eligible for enrollment if they had severe systemic hypoxemia (post-ductal $P_{A\text{O}_2} \geq 55$ mm Hg on two consecutive determinations 30 min apart) despite mechanical ventilation with $F_{\text{I'O}_2}$ of 1.0 and pulmonary hypertension diagnosed with echocardiography. Exclusion criteria were any of the following: previous treatment with ECMO or HFOV, CDH or suspected lung hypoplasia, structural cardiac lesions (other than a patent ductus arteriosus), uncorrected hypotension (mean aortic pressure < 40 mm Hg), polycythemia (hematocrit > 70%), an unevacuated pneumothorax, or a phenotype consistent with a lethal chromosomal abnormality.

Infants were randomized (n = 58) assigned to either control gas (nitrogen) or INO (80 ppm) for 20 min. Successful treatment was defined as a $P_{A\text{O}_2}$ increase to > 55 mm Hg or a decrease in OI to < 40, without a concomitant decrease in mean systemic blood pressure to < 40 mm Hg. If the initial treatment was successful, the study-gas concentration was decreased after the initial 20-min study period and twice a day thereafter in the following fashion: If the $P_{A\text{O}_2}$ was > 55 mm Hg, gas concentration was decreased by 10 ppm while all adjunctive therapies remained unchanged. If the $P_{A\text{O}_2}$ declined by 15% or to ≤ 55 mm Hg within 10 min of weaning, the gas concentration was returned to the previous level. Study-gas concentration was decreased until it was either off or the study gas had been reduced by a maximum of 40 ppm. If the treatment was unsuccessful, the $F_{\text{I'O}_2}$ was increased to 1.0 and other therapies, including ECMO, were used as indicated.

There were no differences between the control group and the INO group at study randomization. INO increased systemic oxygenation in 16 of 30 infants (53%) (p = 0.002), whereas in the control group oxygenation increased in only 2 of 28 infants (7%). INO also produced a short-term increase in post-ductal $P_{A\text{O}_2}$ (41 ± 9 mm Hg to 89 ± 70 mm Hg; p < 0.0001) and a significant decrease in OI (43 ± 17 to 25 ± 14; p < 0.001), whereas there were no significant differences in either $P_{A\text{O}_2}$ or OI in the control group. In the INO group, the decrease in the OI was proportional to the degree of hypoxemia at baseline, as infants with the highest baseline OI had the greatest decrease in oxygenation index while they were breathing INO ($r^2 = 0.80$). Prolonged administration of INO resulted in a sustained improvement in systemic oxygenation in 75% of the infants who demonstrated an initial successful response. In the other 25%, systemic oxygenation decreased within 12 hours of initiating INO, and those infants were subsequently treated with ECMO. Overall, ECMO was initiated in 71% of the control group and 40% of the INO group (p < 0.02). There was no difference in mortality between the two groups. INO did not cause systemic hypotension or increase methemoglobin levels. The authors concluded that INO significantly improved systemic oxygenation in infants with PPHN and reduced the need for ECMO.

Kinsella et al, 1997

In a randomized multicenter study, Kinsella et al evaluated the roles of INO or HFOV, either alone or in combination, in the treatment of severe PPHN (Table 3). The enrollees were newborns of gestational age ≥ 34 weeks with severe hypoxemia (post-ductal $P_{A\text{O}_2} < 80$ mm Hg despite mechanical ventilation with $F_{\text{I'O}_2}$ of 1.0 and echocardiographic evidence of PPHN. Exclusion criteria were the presence of lethal congenital anomalies or the acute need for ECMO for hemodynamic collapse. Administration of surfactant therapy after randomization was prohibited. The patients were block randomized in four categories of disease etiologies: parenchymal lung disease or respiratory distress syndromes; meconium aspiration syndrome (MAS); PPHN, or pulmonary hypoplasia or other; and CDH.

The study randomized 205 neonates to receive 20 ppm INO for 4 hours and then decreased to 6 ppm for the remainder of the treatment period with conven-
tional ventilation or HFOV without INO. A positive treatment response was a sustained $P_{aO_2} \geq 60$ mm Hg. A trial of 40 ppm was allowed for newborns who did not have a positive response on 20 ppm. At 24 hours, INO therapy was discontinued if adequate oxygenation (as measured by OI) could be sustained. Patients who failed to adequately oxygenate could have INO therapy restarted for another 24 hours. Treatment was continued until INO withdrawal was not associated with a decline in oxygenation. Newborns in either group (conventional plus INO or HFOV) who did not have a positive treatment response (sustained $P_{aO_2} \geq 60$ mm Hg) were crossed over to combination treatment with INO and HFOV.

Patients were randomly assigned to HFOV ($n = 98$) or conventional ventilation and INO ($n = 107$). The disease categories were respiratory distress syndrome ($n = 70$), MAS ($n = 58$), CDH ($n = 34$), and other miscellaneous ($n = 43$). Patients were excluded from analysis after enrollment for cyanotic congenital heart disease ($n = 2$). There were no identifiable differences between the groups at study randomization. A positive treatment response occurred in 53 patients assigned to the initial therapy (23 with HFOV, 30 with INO). For these patients, survival was 100% and there were no differences in days of mechanical ventilation, air leak, or oxygenation requirement at 28 days. The two therapies were similarly effective in improving oxygenation ($p = 0.33$) and had no differences in ventilation variables ($pH$ and $P_{aCO_2}$).

Of the neonates who did not respond after initial assignment to HFOV ($n = 75$), 16 (21%) were successfully treated with INO and conventional therapy after crossover. Of the neonates who did not respond to their initial assignment to INO and conventional ventilation, 11 (14%) were successfully treated with HFOV after crossover. Of 125 patients in whom both treatment strategies failed, 32% responded to combination therapy of HFOV plus INO with a significant improvement ($p < 0.05$) in oxygenation. Combination therapy was significantly more effective in infants with RDS and MAS ($p < 0.05$), while INO (with or without HFOV) was significantly more effective ($p < 0.05$) than HFOV alone in patients without parenchymal lung disease (non-CDH pulmonary hypoplasia and idiopathic PPHN). No acute or chronic adverse events were associated with INO or HFOV treatment. The authors concluded that, in newborns with severe PPHN, combination treatment of HFOV plus INO is more successful than either HFOV or INO alone.

Davidson et al, 1998

The multicenter, randomized, placebo-controlled trial by Davidson et al19 was conducted in 25 tertiary care centers (Table 3). It was designed to assess the dose-related effects of INO as an adjunct to early conventional therapy for term infants with PPHN on outcome, oxygenation, and safety. The primary outcome was the effect of INO on the Major Sequelae Index (MSI), which is a composite end point, including mortality, ECMO, neurologic sequelae, and development of bronchopulmonary dysplasia or reactive airway disease.

Eligible newborns were ≥ 37 weeks gestation and were receiving mechanical ventilation with $F_{1O_2}$ of 1.0 within 72 hours of birth. Newborns who received surfactant or HFOV were excluded from the study. In addition, the patients had $P_{aO_2}$ between 40 and 100 mm Hg on mean airway pressure ≥10 cm H2O and $F_{1O_2}$ of 1.0. PPHN was identified either via Doppler echocardiogram or via pre-ductal vs post-ductal $S_{pO_2}$ difference ≥10%.

Newborns were randomized to either control (0 ppm) or INO (5, 20, or 80 ppm) administered until success or failure criteria were met. For treatment successes and failures, sequential 20% decrements in treatment gas were made at a minimum of 30 min and maximum of 4 hours. Treatment success was defined as improved oxygenation ($P_{aO_2} \geq 60$ mmHg, while receiving $F_{1O_2} < 0.6$, and mean airway pressure <10 cm H2O). Treatment failure was defined as a $P_{aO_2}$ decrease to <40 mm Hg for 30 min (in the absence of a reversible mechanical problem) with a mean systemic arterial pressure <35 mm Hg, the newborn meeting ECMO criteria, 14 days duration of study treatment, or if study continuation was not in the patient’s best interest. Newborns who had excessively high inspired NO2 levels (>3 ppm for 30 min) or a methemoglobin level >7% were also discontinued.

Because of a slow enrollee-recruiting process (1,282 patients screened), the trial was stopped at 155 participants (planned enrollment was 320). The most common conditions preventing enrollment are listed in Table 5. Of the 155 randomized patients, the distribution of treatment gas (0, 5, 20, and 80 ppm) in each group was 41, 41, 36, and 37 respectively. Baseline variables were compared between the control group

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygenation &lt; 40 or &gt; 100 mm Hg</td>
<td>26</td>
</tr>
<tr>
<td>Lack of evidence of PPHN</td>
<td>19</td>
</tr>
<tr>
<td>Surfactant therapy</td>
<td>12</td>
</tr>
<tr>
<td>High-frequency ventilation</td>
<td>9</td>
</tr>
<tr>
<td>Gestation age &lt;37 weeks</td>
<td>8</td>
</tr>
<tr>
<td>Lung hypoplasia syndromes</td>
<td>8</td>
</tr>
<tr>
<td>Birth age &gt;72 hours</td>
<td>5</td>
</tr>
<tr>
<td>PPHN = persistent pulmonary hypertension of the newborn</td>
<td></td>
</tr>
</tbody>
</table>
and the pooled INO groups and were similar for demographic, ventilatory, and hemodynamic variables at study entry. There was a significant increase in $P_{O_2}$ at 30 min (no ventilator changes) for all INO groups compared to baseline ($p < 0.05$). A significant increase in $P_{O_2}$ was achieved by the pooled INO groups (from 64 ± 39 mm Hg to 109 ± 78 mm Hg), compared to the control group. The baseline adjusted time-weighted $OI_{2}$ was significantly reduced in the INO groups (-5 ± 8) for the first 24 hours of treatment. There were no significant differences in the $MSI$ rate (control 59% and INO 50%; $p = 0.36$) or ECMO rate (control 34% and INO 22%; $p = 0.12$). Though the incidence of death for the INO group (29%) was significantly lower for the INO group (29%) than the control group (39%), this difference was not statistically significant ($p = 0.25$). Elevated methemoglobin (>7%) and NO$_2$ (>3 ppm) were observed only in the 80-ppm NO group; otherwise no adverse events were attributed to INO, including BPD. Davidson and colleagues concluded that INO use for full-term PPHN newborns produced both acute and sustained oxygenation-improvement for 24 hours, without short-term adverse effects (with 5 ppm and 20 ppm INO), and possibly decreased the need for ECMO.

Davidson et al, 1999

Davidson et al$^{20}$ conducted a randomized, placebo-controlled, double-blind, dose-response, multicenter clinical trial to examine the effect of withdrawal of INO therapy in newborns with PPHN. The primary end points were change in oxygenation, mortality, or need for ECMO during or immediately after withdrawal of INO. The study included the 155 infants enrolled in the Davidson et al, 1998 multicenter study described above.$^{19}$

After successful or failed treatment with INO, the study protocol called for treatment-gas withdrawal (0, 5, 20, or 80 ppm) in 20% step decrements approximately every 4 hours. Upon achieving success or failure criteria, weaning was begun and no manipulations in ventilator settings or $F_{I_2}$ were permitted. In the infants classified as treatment successes, the mean duration of therapy was 88 hours, and decreases in $P_{O_2}$ were observed only at the final withdrawal step. An escalating dose-related $P_{O_2}$ reduction was observed when INO was discontinued from 1 ppm (11 ± 23 mm Hg; $p$ = not significant), 4 ppm (28 ± 24 mm Hg; $p < 0.05$), and 16 ppm (50 ± 48 mm Hg; $p < 0.05$). One death was possibly related to INO withdrawal. The authors concluded that INO withdrawal is not problematic when the OI is <10 and the dose is gradually reduced to 1 ppm before cessation.

Clark et al, 2000

Clark et al$^{11}$ conducted a clinical trial to determine whether low-dose INO would reduce the need for ECMO in neonates with pulmonary hypertension (Table 3). This double-blind, randomized multicenter study enrolled 248 newborns who were ≥34 weeks gestation, <4 days old, required assisted ventilation, and had hypoxemic respiratory failure defined as an OI ≥ 25. To ensure an equal distribution of pulmonary-disease diagnoses in the two treatment groups, patients were assigned to 1 of 5 diagnostic groups and then randomly assigned to a treatment group. Patients were randomized to either placebo ($n = 122$) or INO ($n = 126$) at 20 ppm for ≤24 hours, followed by 5 ppm for <96 hours. The primary outcome variable was the need for ECMO.

After the first 4 hours of study-gas administration (nitrogen or NO), arterial blood gases and methemoglobin were measured. If $P_{O_2}$ ≥ 60 mm Hg and the pH ≤ 7.55, the study gas was decreased to 5 ppm. If these criteria were not met, the study-gas was continued at 20 ppm and the patient was reevaluated every 4 hours until the criteria were met or 24 hours had elapsed. Study gas was returned to 20 ppm for $P_{O_2}$ ≤ 60 mm Hg on $F_{I_2}$ of 1.0 during the first 24 hours. After 24 hours, the dose was decreased to 5 ppm in all patients. Treatment was continued at 5 ppm until the $F_{I_2}$ was < 0.7, 96 hours had elapsed, or the neonate reached seven days of age (whichever came first). If the dose could not be decreased at 24 hours or discontinued at 96 hours, the treatment was considered a failure.

The need for ECMO was significantly less ($p = 0.001$) in the INO group ($n = 48$; 38%) than in the control group ($n = 78$; 64%). This difference occurred for all diagnostic groups except CDH. There was no difference in the 30-day mortality between the two groups (8% in the control group vs 7% in the INO group, $p = 0.82$). After the initial hour of treatment, the $P_{(A-a)O_2}$ increased more in the INO group than in the control group (0.10 ± 0.14 mm Hg vs. 0.05 ± 0.13 mm Hg, $p = 0.02$). Chronic lung disease (need for supplemental oxygen at 30 days) occurred less often in patients who received INO (7% vs. 20%, $p = 0.02$). The authors concluded that INO significantly decreased the need for ECMO in neonates with hypoxemic respiratory failure and pulmonary hypertension.

Sadiq et al, 2003

Sadiq et al$^{22}$ conducted a multicenter randomized controlled study to determine if INO would improve $P_{O_2}$, prevent progression of PPHN, or improve outcomes. They screened 87 newborns with moderate PPHN included 43 in the INO group, 45 in the control...
group, and 2 excluded (Table 3). Newborns > 34 weeks gestation, from 12 centers, with moderate pulmonary hypertension and $P_{A-a}O_2$ of 500–599 mm Hg on 2 consecutive blood-gas measurements within 1 hour were randomly assigned to standard medical therapy (control group) or INO (treatment group).

Newborns assigned to the INO group initially received an NO dose of 10 ppm with increases every 30 min by 10–20 ppm until there was no further improvement in $P_{A-\theta}O_2$, or until a maximum dose of 80 ppm was reached. Once a response was obtained, the NO dose was maintained while other support was weaned according to protocol. Nonresponders (≤ 20% initial improvement in $P_{A-a}O_2$ or OI) had INO therapy discontinued over several minutes.

No differences existed between groups at baseline. Five patients with congenital anomalies were enrolled in the trial: 4 with CDH (2 per group) and 1 with gastrochisis and sepsis in the INO group. Data from the 5 patients with congenital anomalies was excluded from the analysis to allow study results to be comparable to previous studies. Statistical significance for the primary and secondary outcomes was not affected by exclusion of the congenital anomaly data.

Failure of therapy occurred in 23 of 40 control patients (58%) compared to 6 of 40 patients (15%) in the INO group (p < 0.0005). All treatment failures in the control group occurred in the first 36 hours, while most patients who received NO had a maximum response in $P_{A-\theta}O_2$ within the first 3 hours of receiving study gas. $P_{A-\theta}O_2$ for INO-treated infants increased from $101 \pm 29$ mm Hg to $208 \pm 118$ mm Hg ($p < 0.0005$), whereas in control patients $P_{A-\theta}O_2$ increased from $112 \pm 48$ mm Hg to $133 \pm 100$ mm Hg ($p = 0.132$) in the initial 3 hours. The maximum $P_{A-\theta}O_2$ increase occurred with 10 ppm in 30% of patients. Overall, the maximum response occurred at an NO median dose of 30 ppm (range 10–70 ppm).

A significant decrease in ventilatory support was associated with INO for the first 36 hours and persisted for as long as 120 hours of treatment. There were no other differences in secondary outcomes (death, ECMO, duration of mechanical ventilation, supplemental oxygen, or hospitalization). The investigators concluded that INO improves $P_{A-\theta}O_2$, reduces the amount of ventilatory support needed, and prevents progression to severe PPHN in newborns with moderate PPHN.

Konduri et al, 2004

Konduri et al., with the Neonatal Inhaled Nitric Oxide Study Group (NINOS), conducted a multicenter randomized study to determine whether use of INO early in respiratory failure reduced the need for ECMO or decreased the number of deaths in term and near-term neonates (Table 3). They also investigated whether an INO dose of 5 ppm improved oxygenation better than a 20-ppm dose. Newborns (≥ 34 weeks of gestation) were eligible for enrollment if they were diagnosed with respiratory failure (PPHN, respiratory distress syndrome, perinatal aspiration syndrome, pneumonia/sepsis, or suspected pulmonary hypoplasia), required assisted ventilation, and had an OI of 15–25 on $F_{I-\theta}O_2 ≥ 0.80$ for 2 consecutive arterial blood gas measurements made at least 15 min apart but no longer than 12 hours apart. Use of surfactant or HFOV was permitted if it was initiated before randomization. Exclusion criteria were ≥ 14 days of postnatal age, structural heart disease, life-threatening congenital malformations or diaphragmatic hernia, or prior use of INO.

The mode of ventilation was not changed during study-gas administration except as part of a weaning strategy from HFOV to conventional ventilation. Study gas was initiated at a concentration of 5 ppm for infants with OI of 15–25, and at 20 ppm for OI ≥ 25. A response was defined as a > 20 mm Hg increase in $P_{A-\theta}O_2$. If the change in $P_{A-\theta}O_2$ was ≤ 20 mm Hg with 5 ppm, the dose was increased to 20 ppm. The dose was kept at 20 ppm when the infant had a ≥ 10 mm Hg $P_{A-\theta}O_2$ increase after 30 min at that dose (partial response). If the infant had < 10 mm Hg $P_{A-\theta}O_2$ increase at 20 ppm (no response), the dose was returned to 5 ppm. Weaning of study gas was done at 12-hour intervals, to 0.5 ppm, before final discontinuation of study gas. The decision to initiate ECMO was made by the blinded clinical team.

Enrollment was stopped after 75% of the target sample size (n = 302; INO = 150, control = 149, 3 exclusions for major cardiac malformations) was reached because of lack of enrollment. There were no clinically important differences between groups at baseline. There was a ≥ 20 mm Hg $P_{A-\theta}O_2$ increase in 73% of the INO group compared to 37% of the control group (p < 0.001). Infants enrolled in the control group were crossed over to INO and deteriorated to OI > 40 more often than did the infants who received INO (INO 57% vs control 44%, p < 0.03). There were no differences in the incidence of death (INO 6.7% vs control 9.4%), ECMO (INO 10.7% vs control 12.1%), and their combined incidence (INO 16.7% vs control 19.5%). There were also no differences in a post hoc subgroup analysis in the primary outcomes for infants with OI 15–20 (INO 10.2%, control 16 of 88, p = 0.13) or with OI 20–25 (INO 25.8%, control 21.3%, p = 0.56). There were no differences in discharge outcomes (hospital stay, duration of ventilation, days on oxygen and incidence of chronic lung disease) between the groups. The investigators concluded that
INO improved oxygenation but it did not reduce the incidence of ECMO or mortality when initiated at an OI of 15–25 compared with initiation at OI >25.

Cochrane Review

A Cochrane review was conducted to determine whether INO for hypoxemic term and near-term newborn infants improves oxygenation or reduces mortality, the requirement for ECMO, or long-term neurodevelopmental outcomes. The selection criterion for the review was based on randomized and quasi-randomized studies of INO in term and near-term infants with hypoxic respiratory failure. For categorical outcomes, relative risk and risk difference were calculated. For continuous variables, weighted mean differences were calculated with 95% confidence intervals. A fixed-effect model was assumed for meta-analysis.

Twelve eligible randomized controlled studies were identified for term and near-term infants with hypoxia. Entry criteria were consistent, except for the one trial that studied only infants with CDH, and one trial that enrolled both pre-term and term infants but that reported the majority of the results separately for the two groups. The final analysis indicated that INO appears to significantly reduce the incidence of the combined end point of death or need for ECMO in hypoxemic term and near-term infants. However, this appears to be entirely a reduction in need for ECMO, as mortality was not significantly reduced. Oxygenation improved in approximately 50% of infants receiving INO. The OI decreased by a weighted mean of 15.1 within 30–60 min of initiating INO therapy, while the PAO2 increased by a mean of 53 mm Hg. Whether the infants had clear echocardiographic evidence of PPHN did not appear to affect outcome. The outcome in infants with CDH was not improved with INO therapy, and there was a suggestion that outcome was slightly worsened. The incidence of disability, incidence of deafness, and infant development scores were all similar between the tested survivors who received or did not receive INO.

The rationale behind the potential success of INO in the management of newborns with hypoxic respiratory failure is that INO appears to increase oxygenation (specifically Pao2) by dilating pulmonary arteries, which in turn reduces pulmonary vascular resistance. Optimizing ventilation in the lung potentially redistributes pulmonary blood flow away from under-ventilated and non-ventilated lung areas that have low ventilation/perfusion ratios toward regions with normal or better ventilation/perfusion, creating a better oxygenation environment.

Conclusions

A number of studies and a Cochrane review have demonstrated that INO significantly improves oxygenation and decreases the need for ECMO in term and near-term (> 34 weeks gestation) infants with PPHN. The exception may be patients with CDH, for whom INO has not been shown to reduce the need for ECMO. Utilization of INO for hypoxic respiratory failure has not demonstrated significant improvement in mortality. Based on one clinical trial, treatment with HFOV plus INO in some patients may be more successful than HFOV or INO alone.

References


Inhaled Nitric Oxide in the Hypoxic Newborn: Patient Selection, Dosage, Monitoring Response, and Weaning

Peter Betit RRT-NPS FAARC

Introduction

The availability of inhaled nitric oxide (INO) for the treatment of newborns with hypoxic respiratory failure has improved outcomes and reduced the need for the more invasive and risky alternative, extracorporeal membrane oxygenation (ECMO). INO is now a standard treatment in most tertiary newborn intensive care units. The successful application of INO can be optimized if a thoughtful and systematic treatment approach is employed. The key components of an INO treatment program should take into account patient selection, pre-treatment considerations, dosage, clinical response and non-response, monitoring of adverse effects, and withdrawal of therapy.

The Hypoxic Newborn

Persistent pulmonary hypertension of the newborn (PPHN) is the principal cause for hypoxic respiratory failure in newborns. This disorder can occur soon after birth, in which the transition from fetal circulation to normal circulation is disrupted by inability of the pulmonary vasculature to dilate despite the presence of oxygen. Extrapulmonary shunting of blood occurs across a patent ductus arteriosus and/or a patent foramen ovale, leading to shunting of venous blood to the systemic circulation and eventual failure of vital organs. PPHN can be idiopathic, but is more commonly associated with meconium aspiration syndrome, pneumonia, sepsis, respiratory distress syndrome, and congenital diaphragmatic hemia. In each case, hypoxemia worsens pulmonary vasoconstriction. The selective and potent pulmonary vasodilator properties of INO abate the extrapulmonary shunting and aid in restoring normal circulation.

Patient Selection

The population best suited for INO therapy includes term and near-term newborns (ie, > 34 weeks gestation) less than 14 days old, who require mechanical ventilation for hypoxic respiratory failure. Clinical evidence of PPHN is typically determined by the presence of a gradient between pre-ductal and post-ductal $\text{SpO}_2$. Echocardiography is often used to confirm the presence of pulmonary hypertension and to determine if cardiac structures and their function are normal. While it is reasonable to consider INO therapy based on clinical impression, treatment failure may be associated with poor cardiac function, in which case echocardiography may be a valuable tool. Administering INO therapy in the presence of a ductal-dependent cardiac lesion such as total obstructed pulmonary veins may result in a decrease in cardiac output from under-filling of the heart. Cardiac output may also be compromised from an over-filled heart, which may occur in the presence of a failing left ventricle of the profoundly septic newborn.

The oxygenation index (OI) is used as an indicator of illness severity and a starting point for INO therapy. The OI is calculated from the mean airway pressure ($P_{aw}$), fraction of inspired oxygen ($F_{I\text{O}_2}$), and $P_{a\text{O}_2}$:

$$OI = \left( P_{aw} \times F_{I\text{O}_2} \times 100 \right) / P_{a\text{O}_2}$$

An OI > 40 has been used as part of the criteria for initiating ECMO support. Mortality rate increases when the OI is > 40. An OI of ≥ 25 was commonly used as an indication for INO in many of the clinical trials, the aim being to begin treatment before the
patient’s condition worsened. Some investigators used an OI of 15-25 as an indication to begin INO therapy, and they found that starting therapy earlier, or at a theoretically more stable point, did not yield any significant differences in treatment response or outcome. Although accepted indications for INO use an OI ≥ 25, it is important to appreciate that OI is only one piece of the decision-making process when considering INO therapy.

Pre-Treatment Strategies

The hypoxic newborn’s symptoms often appear precipitously and require the clinician to provide prompt treatment and make decisions in a rapid and sequential manner. The administration of INO should be considered adjunctive to other widely acceptable clinical strategies including an appropriate FIO₂, moderate alkalosis (eg, > 7.45, induced pharmacologically and/or by hyperventilation), sedation, and possibly muscle relaxation. The patient’s blood pressure should be supported with fluids and vasoactive agents as necessary to minimize hypotension, which may worsen right-to-left extrapulmonary shunting.

Mechanical ventilation strategies aimed at optimizing alveolar recruitment improve the response to INO. High-frequency oscillatory ventilation (HFOV) may produce well-inflated lungs in a less injurious manner than conventional mechanical ventilation, and it has been found to improve the response to INO, particularly in the presence of parenchymal lung diseases such as meconium aspiration and respiratory distress syndrome. Surfactant replacement therapy may also play a role in the preservation of lung volume, but should be cautiously considered if the patient is not stable enough to tolerate the instillation procedure because an acute episode of hypoxemia during the surfactant administration may worsen pulmonary hypertension. Table 1 outlines general patient selection and stabilization prior to initiating INO therapy.

Dosage and Response

The recommended starting dose for INO is 20 parts per million (ppm). The typical response is an immediate improvement in oxygenation and a decrease in the pre-ductal to post-ductal SPO₂ difference. A Pao₂ increase of ≥ 20 mm Hg is considered a positive response. There has been some debate as to whether 20 ppm is necessary as a starting dose, and whether doses as low as 5 ppm may be as effective. Some investigators have observed that higher doses provide immediate stabilization and that lower doses may lessen the response if subsequent higher doses are needed. A dose of 20 ppm has not been associated with greater toxicity or adverse effects, and 20 ppm remains the widely accepted initial dose.

The maximum dose used clinically is 80 ppm. Beyond 80 ppm the safety profile decreases and adverse effects increase, particularly if used for prolonged periods. Rarely is an initial dose of 40 ppm needed to establish improved oxygenation. If there is not a brisk improvement in oxygenation at 20 ppm, it is reasonable to try 40 ppm, provided that all other treatments and ventilator strategies have been reviewed and optimized. A moderate response to INO may be due to the lungs being under-recruited or a change in hemodynamics.

There is a very small, and rare, subset of patients who present with hypoxic respiratory failure but have varying degrees of lung hypoplasia or dysplasia. It is these patients who pose the greatest challenge, because they seem to have a varying response to INO and the response is often not sustained.

INO therapy has been used in patients with congenital diaphragmatic hernia (CDH), but with mixed results probably because of the varying degrees of lung hypoplasia and pulmonary hypertension. It has become an increasingly common practice to use INO in patients with CDH for stabilization and during transport. INO may support or even improve right-ventricular function in the most severe CDH cases until ECMO can be established, and may be useful in transitioning patients as ECMO support is discontinued.

Some newborns with severe hypoxic respiratory failure may have only a modest improvement with INO therapy, or no improvement at all, and require ECMO support. Part of the prudent use of INO therapy is to establish treatment-failure criterion that take into account the distance to an ECMO center and the ability to provide INO during transport. It has been recommended that INO be continued during the transport of non-responders and that non-ECMO centers should

Table 1. Patient Selection and Stabilization

<table>
<thead>
<tr>
<th>Indications</th>
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<tbody>
<tr>
<td>Hypoxic respiratory failure</td>
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<tr>
<td>&gt; 34 weeks gestation, &lt; 14 days old</td>
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<tr>
<td>Oxygenation index ≥ 25</td>
</tr>
<tr>
<td>Pre-ductal/post-ductal SPO₂ gradient</td>
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<tr>
<td>Pulmonary hypertension via echocardiography</td>
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<table>
<thead>
<tr>
<th>Stabilization</th>
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</thead>
<tbody>
<tr>
<td>FIO₂ = 1.0</td>
</tr>
<tr>
<td>Moderate alkalosis (pH &gt; 7.45)</td>
</tr>
<tr>
<td>Vasoactive agents/fluids</td>
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<tr>
<td>Sedation and/or muscle relaxation</td>
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<table>
<thead>
<tr>
<th>Lung Recruitment</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-frequency oscillatory ventilation</td>
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<tr>
<td>Surfactant-replacement therapy</td>
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</table>
have a low threshold for initiating transport. There have been some attempts at predicting which patients have a higher probability of needing ECMO by looking at the dose/duration relationship. Patients who require 20 ppm on day 4 have a higher probability of needing ECMO. Some centers base the decision to transport on lack of improvement in OI after a certain number of hours or on $P_{aO_2}$ after a number of consecutive blood-gas measurements.

**Monitoring Adverse Effects**

One concern related to the use of INO therapy is the development of nitrogen dioxide (NO$_2$), which occurs when NO combines with O$_2$. The higher the concentration of NO and O$_2$, and the longer the amount of time they spend in contact with each other, the greater the NO$_2$ concentration. The worst-case scenario for the development of NO$_2$ is an $F_{I_O_2}$ of 0.90 and NO of 80 ppm with a non-continuous-flow ventilator, in which there is potentially more contact time of the 2 gases. NO$_2$ concentrations should never exceed 3 ppm. When an INO dose of 20 ppm is used with a continuous-flow ventilator, which is often the case with neonates, NO$_2$ concentrations are typically less than 1 ppm, and become negligible as $F_{I_O_2}$ is decreased. There are also pre-treatment purging and testing procedures that help minimize NO$_2$ production. Moreover, the concentrations of O$_2$, NO$_2$, and NO are continuously monitored in the gas-delivery system during INO therapy, and alarms are set to alert the caregiver if the delivered NO$_2$ concentration increases.

During the initial years of studying INO, investigators had the knowledge that NO and NO$_2$ were byproducts of pollution and that safety organizations (eg, OSHA) have established exposure limits. During that time there was concern about caregiver exposure, and attempts were made to scavenge exhaled gases and monitor the patient-care environment for NO and NO$_2$. As more experience was gained and delivery systems improved, it became clear that caregiver exposure was minimal. Moreover, scavenging devices had the potential to interfere with the proper functioning of some ventilators. There were even observations made that the air in some cities had NO and NO$_2$ levels that were more concerning than those observed at the bedside of patients receiving INO therapy. Modern ICUs provide ample exchanges of fresh air to minimize caregiver exposure to INO, and scavenging is not necessary.

The development of methemoglobinemia is another potential toxicity of INO therapy. As NO crosses from the alveolus to the pulmonary blood stream, it reacts rapidly with hemoglobin, and produces methemoglobin (metHb), which cannot carry oxygen and thus results in oxygen desaturation. Fortunately, the metHb is normally reduced quickly to normal oxygen-binding hemoglobin, so clinical effects are rare. However, with a high INO dose, there is a greater potential for a high metHb level. During INO therapy metHb level needs to be monitored to determine if the patient has the ability to metabolize metHb. Shortly after the start of INO, a metHb level should be obtained. A metHb concentration of 5% is a commonly used threshold for decreasing the INO dose. The frequency with which metHb levels are obtained differs among centers, but typically metHb is measured daily and with increases in INO dose. Potentially toxic metHb levels are rare during INO therapy.

**Weaning and Discontinuation**

The duration of INO therapy for newborns with hypoxic respiratory failure does not typically last beyond 5 days. Once there is sustained improvement in oxygenation and hemodynamics, a systematic approach to weaning the INO dose is employed. The $F_{I_O_2}$ should be reduced to potentially less toxic levels (eg ≤ 0.60) prior to weaning the INO dose. Throughout the weaning process a minimally acceptable $P_{aO_2}$ (eg, 60-80 mm Hg) and $S_{PO_2}$ (eg, > 90%) should be established. Mechanical ventilation is weaned concomitantly as tolerated to maintain clinically acceptable $P_{aCO_2}$ and pH. An incremental reduction in the INO dose by roughly 50% is a common weaning approach. The dose is weaned from 20 ppm to 10, 5, and then 1 ppm. Throughout the weaning process, if the $S_{PO_2}$ decreases by > 5% and is < 90% and O$_2$ requirements increase, the INO is returned to the previous dose, and weaning is suspended for a few hours. Throughout the duration of the INO therapy, the other previously described clinical strategies are evaluated to ensure that lung volume is maintained, hemodynamics are supported, and the patient is comfortable. The final INO dose is typically 1 ppm at which point the $F_{I_O_2}$ should be increased to 20% above the current $F_{I_O_2}$, and the INO discontinued. Table 2 outlines an INO weaning schema.

The greatest decline in $P_{aO_2}$ often occurs during the discontinuation of INO therapy, but can be lessened if the $F_{I_O_2}$ is increased first, because O$_2$ has pulmonary vasodilator properties. Still, there are patients who experience a precipitous drop in oxygenation even though a gradual weaning approach is used and the $F_{I_O_2}$ is increased. A sudden drop in $S_{PO_2}$ and changes in hemodynamics during the discontinuation of INO are characteristic of what is referred to as a “rebound” effect, in which there is an abrupt
episode of pulmonary hypertension and subsequent systemic hypotension. Rebound pulmonary hypertension is not that common in newborns with hypoxic respiratory failure, unless there is some other underlying disorder that is associated with irreversible pulmonary hypertension such as alveolar capillary dysplasia. It has also been suggested that patients who require a prolonged INO therapy duration may require multiple attempts at discontinuing therapy.

INO therapy should be resumed at the last INO dose (eg, 1 ppm) if the $F_{IO\text{2}}$ cannot be weaned to its pre-discontinuation level after 1-2 hours. In this situation there may be a moderate degree of residual pulmonary hypertension. A subsequent trial off INO therapy should be attempted several hours later.

Summary

The clinical use of INO has become an important adjunct for newborns with hypoxic respiratory failure. A dose of 20 ppm is safe and effective, provided that acceptable pre-treatment strategies are also considered, particularly lung-recruitment strategies. Continuous monitoring of $O_2$, NO, and NO$_2$ concentrations are routine, and metHb should be periodically evaluated. A systematic weaning approach and increasing the $F_{IO\text{2}}$ prior to discontinuation ensure safe transition off INO therapy. Development of failure criterion, including early recognition of non-responders and prompt transport with INO to an ECMO center are essential.

Additional Reading


Finer NN, Barrington KJ. Nitric oxide for respiratory failure in infants born at or near term. The Cochrane Database of Systematic Reviews 2005; Issue 3.


Table 2. INO Weaning Schema

<table>
<thead>
<tr>
<th>Initial dose: 20 ppm → clinical response</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{A\text{O}\text{2}}$ &gt; 60 mm Hg, $S_{P\text{O}\text{2}}$ &gt; 90%, $F_{IO\text{2}}$ ≤ 0.60: ↓ 10 ppm</td>
</tr>
<tr>
<td>$S_{P\text{O}\text{2}}$: ↓ 5% or &lt; 90%: ↑ 20 ppm, hold weaning</td>
</tr>
<tr>
<td>$P_{A\text{O}\text{2}}$ &gt; 60 mm Hg, $S_{P\text{O}\text{2}}$ &gt; 90%, $F_{IO\text{2}}$: ≤ 0.60: 10 ppm</td>
</tr>
<tr>
<td>INO → 5 ppm → 1 ppm</td>
</tr>
<tr>
<td>$S_{P\text{O}\text{2}}$: ↓ 5% and &lt; 90%: resume previous INO dose</td>
</tr>
<tr>
<td>$P_{A\text{O}\text{2}}$ &gt; 60 mm Hg, $S_{P\text{O}\text{2}}$ &gt; 90%, $F_{IO\text{2}}$: ≤ 0.40: ↑ $F_{IO\text{2}}$</td>
</tr>
<tr>
<td>0.60 → 0 ppm</td>
</tr>
<tr>
<td>$F_{IO\text{2}}$: &gt; 0.60: 1 ppm, retry 4-8 hours later</td>
</tr>
</tbody>
</table>
Introduction

Safe and accurate delivery of inhaled nitric oxide (INO) is paramount to the successful application of this unique gas therapy. An ideal nitric oxide (NO) delivery system must also measure the inspired concentration of NO, nitrogen dioxide (NO₂), and oxygen (F₁₀₂). NO delivery should also be accomplished without excessive production of NO₂. Early use of INO was both facilitated and hampered by the necessity to construct homemade delivery systems. These devices met with various degrees of success and consequence.¹⁻⁴ The current delivery of INO in the United States is limited to a single FDA-approved device, the INOvent (Datex-Ohmeda, Madison, WI). This paper will be limited to discussion of this device.

System Description

The INOvent is an integrated system that includes the delivery and monitoring system mounted on a cart that also holds two NO cylinders, regulators for each cylinder, and high pressure gauges (Figs. 1 and 2). Originally developed for delivery of NO during mechanical ventilation, the INOvent can deliver NO into virtually any system where flow can be measured and the resulting gas mixture can be monitored. This includes neonatal to adult ventilation, pressure-limited and volume-limited breaths, high-frequency oscillation, continuous positive airway pressure, and oxygen delivery systems (eg, nasal cannula, face mask).

Figure 3 shows the INOvent’s principle of operation. Gas from the cylinder flows from an external high-pressure regulator to a low-pressure regulator within the INOvent. NO gas is controlled by two flow controllers: one for low flows and the other for high flows. An injector module is inserted into the path of gas flow to the patient. During mechanical ventilation the position is in the inspiratory circuit between the ventilator output and the humidifier. The injector module contains a hot-film flow sensor and a gas-
injection tube. The hot-film flow sensor should not be exposed to water vapor, because water vapor alters cooling of the sensor and affects the accuracy of flow measurement. Flow traveling through the injector module is measured and used for calculation of the amount of NO that must be injected into the gas flow to achieve the NO level set on the INOvent. This design allows a precise and constant NO concentration in the inspired gas, with any flow pattern.

NO flows through either a high-flow or a low-flow controller contained within the electronic components of the machine. The high-flow and low-flow controllers assure that the delivered NO concentration is accurate over a wide range of ventilator flows and desired NO concentrations. The NO flow required is calculated with the formula:

\[
\text{NO flow} = \frac{(\text{NO set in ppm}) \times (\text{inspiratory flow in L/min})}{(\text{NO Cylinder concentration in ppm}) - (\text{NO set in ppm})}
\]

Flow is precisely measured and NO is injected proportional to that flow to provide the desired NO dose. For non-constant flow, the NO flow added to the inspiratory gas varies with the inspiratory flow. By delivering NO proportionate to gas flow, residence time is reduced and NO\textsubscript{2} production is minimized. This small flow of NO adds to the gas flow delivered to the patient. This results in additional volume in the circuit, albeit a very small volume, which dilutes the gas concentration. The maximum flow of NO at 800 ppm from the injector module is 6.2 L/min.

The maximum NO dose that can be delivered from a cylinder that has an NO concentration of 800 ppm changes with the gas flow rate. At a constant flow of 120 L/min, the maximum deliverable NO is 40 ppm (Fig. 4). During mechanical ventilation of adults these high flows are intermittent and for short periods of time, minimizing the effect on delivered NO concentration. This does, however, have implications for high-flow systems for noninvasive support. Because the flows used with neonates are much lower, this should never be an issue for neonatal use of INO.

Monitoring and Alarms

The INOvent includes gas monitoring of O\textsubscript{2}, NO, and NO\textsubscript{2}. During mechanical ventilation, gas is sampled downstream from the point of injection, at least 15 cm proximal to the Y-piece in the inspiratory circuit during mechanical ventilation. Monitoring inspired gas must be accomplished at a position that prevents contamination by expired gases. NO, like carbon monoxide, is taken up by the body, and expired gases contain lower NO concentrations. A sample that contains both inspired and expired gases will underestimate the true delivered NO.

Gas concentrations are measured using electrochemical cells, which are calibrated at regular intervals. The NO

![Fig. 2. Control panel of the INOvent. The display shows the monitored gas concentrations, alarm settings, and set NO value.](image)

![Fig. 3. INO vent principle of operation. See text for description.](image)

![Fig. 4. The effects of continuous gas flow on the maximum delivered NO concentration. With a cylinder of 800 ppm NO, the maximum NO concentration falls as flow exceeds 55 L/min.](image)
cell is capable of monitoring a range of 0–100 ppm NO, with a resolution of 0.1 ppm between 1 and 10 ppm, and a resolution of 1 ppm between 10 and 100 ppm. The NO₂ monitoring cell has a range of 0–15 ppm, with a resolution of 0.1 ppm. Both sensors have an accuracy of ± 3% of full scale and a rise time (10–90%) of 30 seconds. This slow response time is appropriate for monitoring delivered gas concentrations, but cannot detect breath-to-breath changes.

The gas monitoring system uses a side-stream sampling system, with a sample flow of 230 mL/min. Occlusion of the sample line or filter by water or external pressure will result in an alarm. Similarly, if the pressure in the gas flow system exceeds 70 cm H₂O, the elevated pressure will result in an alarm.

Gas delivery alarms can be set by the user for high NO, low NO, high NO₂, high O₂, and low O₂. Additional alarms include those for loss of source-gas pressure, weak or failed gas-monitoring cells, calibration required, delivery-system failures, and monitoring failure. Monitoring failure is caused by occlusion of the sample line, pump failure, high pressure in the sample line, or leaks around the sensors because of improper seating. The dry-sample-gas alarm detects low relative humidity in the inspired gas. Gas sensors perform as intended in the presence of humidity. Prolonged exposure to low levels of humidity reduces sensor life. A common alarm, “service advisory,” which sounds ominous, is often a simple problem detected during operation. In most cases turning the power off and on will correct the service advisory alarm.

Certain conditions judged as potentially dangerous will result in shutdown of the INOvent. These conditions include an NO > 100 ppm or delivered NO greater than twice the maximum setting. This alarm may occur with improper calibration, sensor failure, or improper system setup.

The monitoring and delivery systems of the INOvent operate independently. There is no servo-control that adjusts set values to monitored values. This design permits NO delivery independent of monitoring, which is an important safety feature. Additionally, the monitoring system can be calibrated without interruption of NO delivery. More simply, when monitoring fails or is disconnected or interrupted, NO delivery continues as set.

**Manual Delivery System**

A manual NO delivery system, which is separate from the set NO, is integral to the system (Fig. 5). The manual delivery system is mechanical and does not require the INOvent to be connected to electrical power. As such, it will operate during an electrical failure or injector-module failure. With an oxygen flow to the manual delivery system set at 15 L/min, the INOvent titrates NO to provide a concentration of 20 ppm. As with any manual ventilation system for NO, it is important to squeeze the bag 3–5 times to clear residual NO₂ before attaching it to the patient.

**Battery Operation**

The INOvent contains an internal battery that charges while the unit is connected to electrical power. When fully charged, the battery will operate the INOvent for approximately 1 hour.

**Use of the INOvent With Mechanical Ventilation**

The INOvent was designed to provide INO therapy during mechanical ventilation. INOvent setup with a traditional mechanical ventilator is shown in Figure 6.
The injector module is placed between the ventilator outlet and the humidifier; the arrow is in the direction of the gas flow. The injector module should always be kept dry to assure adequate function. The sample line is placed in the inspiratory limb, 15–30 cm proximal to the Y-pipe. Gas is drawn through the sample line across the gas sensors. In this configuration the INOvent is capable of delivering between 1 and 80 ppm, with the maximum delivered concentration constrained by ventilator flow, as stated previously. The INOvent is capable of operating in all conventional ventilation modes.

Two independent evaluations of the INOvent have been published by Kirmse et al and Young et al. Kirmse studied the INOvent connected to two ventilator models: a Puritan Bennett 7200 and a Siemens Servo 900C, at inspired NO concentrations of 2, 5, and 20 ppm, and during pressure-limited or volume-limited breaths. The error between the target and delivered dose was 1.3% with the PB 7200 and 3.9% with the Siemens 900C. They also found reduced NO2 production, from a mean of 5.8 ppm, with a pre-mixing system with compressed air to 0.5 ppm with the INOvent. They concluded that, “the INOvent provides a constant NO concentration independent of ventilatory pattern, and NO2 formation is minimal.” Young et al evaluated the INOvent at 10 ppm and 40 ppm, using tidal volumes of 500, 700, and 900 mL, respiratory rates of 10, 15, and 20 breath/min, with constant, sinusoidal, and descending-ramp flow patterns at 30, 40, and 50 L/min. Delivered NO was 10.2–10.7 ppm, with a setting of 10 ppm and 40.5–42 ppm with a setting of 40 ppm.

**Effects of NO Delivery Into the Ventilator Circuit**

The principles of INOvent operation, the addition of NO/N2 by the injector module, and withdrawal of 230 mL/min by the sampling system create predictable effects on ventilator operation. These changes are small, but may result in changes in ventilator operation and variables that must be understood by the clinician.

- Oxygen dilution—The addition of NO/N2 gas from the injector module causes a predictable reduction in oxygen delivered to the patient. At the highest NO setting of 80 ppm, FIO2 is reduced by 10%. If the ventilator is set for an FIO2 of 0.50, the patient will receive an FIO2 of 0.45. The clinician must decide whether to increase the FIO2 to compensate for this change.

- Volume changes—The addition of NO/N2 gas adds to the tidal volume during volume-controlled ventilation, but has no effect during pressure-controlled ventilation. During volume-controlled ventilation at the highest NO concentration (80 ppm), the volume addition is 10%. At a tidal volume of 500 mL, this adds 50 mL. However, the sample flow of 230 mL/min (3.84 mL/s) reduces tidal volume, based on respiratory rate and inspiratory time. In most instances the changes in delivered tidal volume are small and more likely to be seen when volume monitoring is accomplished at the airway. Small adjustments can be made by the clinician if required to maintain the desired tidal volume.

- Triggering—The sample flow can cause auto-triggering in ventilators using a low flow-sensitivity setting (≤ 1 L/min). After introducing the INOvent components to the circuit, the clinician should assure that the triggering sensitivity is set properly.

- NO2 production—NO2 production results from the mixture of O2 and NO. The rate of reaction is increased with increasing NO and O2 concentrations, longer residence times, and higher pressures. Under usual conditions this reaction is slow. The operation of the INOvent is associated with very low NO2 production. The exception to this is in the high pressure (psig) portions of the INOvent where NO2 can become elevated between uses. This is the reason for the purge procedures prior to use on a patient. Purging the system eliminates NO2 which accumulated while the system was idle.

![Diagram of INOvent setup](image-url)
Use With High-Frequency Oscillation

The use of the INOvent with the high-frequency oscillator is in some ways simpler than conventional ventilation. The injector module is added to the continuous flow prior to the humidifier, as with a traditional ventilator. However, the active exhalation phase of the oscillator can cause flow to travel back through the injector. This problem usually manifests as delivery of NO at a dose twice the set value. For this reason, a one-way valve is placed below the injector module (Fig. 7). This one-way valve prevents the problem of retrograde flow.

A common problem with the high-frequency oscillation (HFO) circuit is proper placement of the sample line for gas monitoring. The sample line is placed at the site of the temperature probe in the circuit. Placement of the sample line at the endotracheal tube will result in low measured NO because of exhaled gas sampling. Fujino et al evaluated the use of the INOvent with HFO and found that NO delivery was stable and accurate at all settings.7

Use With High-Frequency Jet Ventilation

The INOvent is not currently approved for use with high-frequency jet ventilation (HFJV). Use of the INOvent with HFJV has been described by Platt et al8 and Mortimer et al,9 (Figs. 8 and 9). Both groups found that acceptable NO levels were achieved during HFJV.

There are 3 concerns about the use of the INOvent with HFJV. First, the high pressure in the injector module exceeds the pressure specified by the manufacturer, which could cause inaccurate flow measurement, or the high pressure might cause disconnection of tubing at the injector module or in the INOvent. If this occurred, NO delivery would be interrupted and pressure would be lost. The second concern is related to entrainment of gas from the conventional ventilator, which will reduce delivered NO. During neonatal ventilation this is a small problem that can be corrected by setting NO to desired effect. Finally, the high pressure may cause monitoring failure by altering pressure in the gas-sampling system. While many clinicians use the INOvent with HFJV, this practice places the liability burden on the clinician, since the manufacturer has not included HFJV in the product label.10

Use With an Anesthesia Ventilator

NO can be used in the operating room in patients with pulmonary hypertension and cardiac disease. Setup of the INOvent in an anesthesia system is shown in Figure 10. When used with a traditional partial rebreathing or circle system, several issues must be considered. In low-flow anesthesia (fresh gas flow < 2 L/min), the anesthesiologist conserves anesthetic gas by allowing the patient to rebreathe gases, eliminating carbon dioxide with an absorber. When connected into the inspiratory limb of the anesthesia circuit, the injector module measures flow and titrates NO to the
desired setting. However, when rebreathing is allowed, the gas entering the injector module will contain NO from the previous breaths. The result is a gradual rise in NO concentration with time. Additionally, this type of system can promote NO2 accumulation due to long residence time. These problems can be avoided by either of two techniques. The first is to maintain the anesthesia fresh-gas flow greater than the patient’s minute ventilation; in other words, preventing rebreathing. This was confirmed by Ceccarelli et al, who evaluated NO delivery techniques with an anesthesia ventilation system.11 The second approach is to use an ICU ventilator in the operating room and intravenous anesthesia.

**Use With a Nasal Cannula**

The INOvent can be used with a nasal cannula (Fig. 11). The maximum delivered NO with the cannula is 40 ppm. The minimum oxygen flow should be 1 L/min. The maximum cannula flow depends on the cannula size. If the oxygen flow and cannula diameter result in a pressure > 70 cm H2O, the monitoring-failure alarm may be triggered. Clinicians should evaluate the oxygen flow and diameter of the connecting tubing to avoid that problem. When using NO via nasal cannula, the NO concentration should not be increased by more than 5 ppm in a 5-min period. The increase in NO concentration increases NO flow and can result in a bolus of NO to the patient. If concentration needs to be increased more quickly, the system should be purged.10

Use of the Vapotherm high-flow oxygen-delivery device can result in excessive pressure. The Vapotherm is not approved for use with the INOvent. Clinicians have successfully used the INOvent with the Vapotherm, but this requires modifications to the sample line to vent excess pressure, which, like HFJV, places the burden of liability on the user.

**Use With a Face Mask**

Use of the INOvent with a face-mask system occurs most commonly in the cardiac catheterization laboratory, for testing pulmonary vascular responsiveness. The system is very similar in setup to the cannula-delivery system (Fig. 12). It is important to use 1-way valves, a reservoir system, and/or a high flow to prevent entrainment of room air into the mask.

*References*


Other Issues

The INOvent can be used with noninvasive ventilation, but care should be used in systems in which rebreathing may occur, as NO$_2$ could rise above the acceptable level. The INOvent is incompatible with helium-oxygen mixture (heliox), because the properties of helium (thermal conductivity) compromise the accuracy of the injector module. Additionally, NO and NO$_2$ sensors are not calibrated to work in the presence of helium. Use of heliox typically results in NO delivery > 100 ppm and electronic shutdown. Heliox should not be used with the INOvent.

The INOvent is compatible with the high-frequency operation of the Infant Star ventilator. However, clinicians should be aware of two concerns. First, do not use the 1-way valve with this high-frequency system. The pressure-relief valve of the Infant Star is mounted such that placement of the 1-way valve would disable the pressure-relief function. Second, the NO concentration should be set to < 20 ppm, because at higher doses there is the potential for over-delivery.

If an UpDraft nebulizer is used during mechanical ventilation, the position of the nebulizer is important to NO delivery. The aerosol should not be directed through the injector module, because doing so would result in inaccurate measurement of flow and fouling of the sensor. If the nebulizer is positioned after the injector module, the delivered NO will decrease because the volume is diluted by nebulizer flow. The clinician must decide if during nebulizer therapy the NO should be increased to account for the additional flow. If this is done, it is imperative to return the set NO concentration to pre-nebulizer settings. The ideal position for the nebulizer with respect to INOvent performance is between the sample line and the Y-piece. This prevents aerosolized medication from entering the sample flow and prevents any effects on sensors. The nebulizer aerosol can leave a powder on sensors, which may affect sensor accuracy. Even if the nebulizer is placed downstream of the sample line, NO is still diluted.

Cylinders

NO in a balance of nitrogen represents the pharmaceutical drug INOmax, so the INOmax cylinder is actually a drug capsule. In the US, these aluminum cylinders contain 800 ppm of NO for inhalation (INOmax, INO therapeutics, Clinton, NJ). The cylinders contain 1,963 L of NO/N$_2$ at 2,000 psig and weigh 44 lbs when full. The connection to a cylinder of INOmax is a Compressed Gas Association 626 valve.

Environmental Contamination

There have been concerns regarding environmental contamination with NO and NO$_2$, and the potential for adverse effects on health-care providers. The OSHA exposure limits for NO (a time-weighted average of 25 ppm for 8 hours in the workplace) is higher than the typical NO dose (20 ppm). There are several reports on the presence of NO/NO$_2$ in the intensive care unit.

Krebs et al measured NO and NO$_2$ levels during NO delivery using the Dräger and Siemens ventilators. They positioned a funnel-shaped connector at positions 10, 20, and 50 cm from the ventilator exhalation valve, as well as 20 cm lateral to the patient’s head. Monitoring was accomplished using chemiluminescence, for a minimum of 16 hours. They found that mean NO concentrations were < 50 ppb and peak concentrations were < 100 ppb. They noted that when continuous flow of NO was added to the inspiratory limb, the ambient NO level was higher than the ventilator systems that use phased inspiratory injection. Murgeon et al monitored NO and NO$_2$ levels in a Parisian intensive care unit and compared those values with those measured near a Parisian traffic circle. They observed weather conditions (e.g. cloud cover) and recorded the days during which NO was and was not used in the ICU. They found that the ambient NO and NO$_2$ levels in the ICU were “entirely dependent on outdoor concentrations.” Qureshi et al measured NO concentrations in collar-mounted tubes worn around the necks of ICU nurses. They found that when patients were receiving 5–20 ppm of NO, the time-weighted average for exposure was 0.49 ppm for NO and 0.29 ppm for NO$_2$. Phillips et al studied the extent of exposure during simulated and actual INO treatment of newborn and pediatric patients. They concluded that detectable exposures were brief, infrequent, and well below OSHA’s permissible exposure limits. These investigations suggest that scavenging exhaled gases during NO therapy is unwarranted.
Most modern intensive-care-unit environments require frequent air exchanges for infection control and patient comfort. If room-air exchanges are maintained at > 6 exchanges/hr, ambient NO levels should remain very low. Figure 13 depicts room NO and NO₂ concentrations one hour following administration of 100 ppm of NO into a room at 8 l/min. This example represents a worse-case scenario, yet both NO and NO₂ remained at < 150 ppb (0.15 ppm).

**Summary**

The INOvent allows safe and accurate delivery of inhaled nitric oxide via various techniques. There remain technological challenges and the clinician’s understanding of operational principles of the INOvent helps prevent mishaps. Clinicians should be wary of using the INOvent in situations in which compatibility with other devices has not been systematically evaluated.

**References**

Cost-Effectiveness Analysis

A cost-effectiveness analysis (CEA) should estimate an intervention’s likely costs and its effects, expressed in units comparable to other cost analyses. The reasons to perform a cost analysis are to determine whether a new therapy is worth using with respect to existing therapies and whether resources should be allocated to pay for a new therapy. A cost-effectiveness ratio is the incremental change in costs divided by the incremental change in effects of an intervention.

\[
\text{Cost-effectiveness ratio} = \frac{\text{Cost (treatment)} - \text{Cost (placebo or control)}}{\text{Effects (treatment)} - \text{Effects (placebo or control)}}
\]

Because cost-effectiveness ratios incorporate differences in two dimensions (costs and effects), they are often displayed graphically (Fig. 1). Quality-adjusted life years (QALYs) are the recommended unit of effects, because they incorporate both the duration and the quality of survival. Other examples of effects are lives saved, life years saved, and events (such as intraventricular hemorrhages) prevented. Cost-effectiveness analyses should specify the time horizon over which costs and effects are estimated (for example, hospital discharge, one year post-discharge, or lifetime). In general, shorter time horizons lead to estimates with less uncertainty, but may also lead to estimates that are less useful. For example, a therapy with a very expensive cost-effectiveness ratio in hospitalized patients may become more cost-effective over time if it leads to decreased post-discharge costs while having continued benefits. If the time horizon extends beyond that over which data were collected (which is almost always the case for lifetime estimates), then assumptions need to be made about ongoing costs and effects. These assumptions must be explicitly stated and should be subjected to sensitivity analyses to understand the degree to which they influence the cost-effectiveness ratio.

Incorporating Cost Evaluations Into Randomized Controlled Trials

Powerful, unbiased estimates of an intervention’s cost-effectiveness can be made by collecting the necessary data as part of a randomized controlled trial (RCT). This data-collection is somewhat complicated by three issues: 1.) efficacy versus effectiveness, 2.)
Most RCTs measure efficacy (whether a therapy has an effect under ideal, controlled conditions) rather than effectiveness (whether a therapy has an effect in common practice). If a cost analysis is part of the trial, and the estimate of effect is generated from the trial, then the cost analysis will be a cost-efficacy ratio, rather than a cost-effectiveness ratio. The differences between such ratios are not trivial. There are two ways to deal with this problem. First, the RCT design can be adapted to measure effectiveness. However, this is expensive, with the need for either additional study arms or separate trials. Furthermore, study sponsors may be unwilling to expose their therapy to an effectiveness trial where the likelihood of demonstrating effect is reduced, especially before the therapy has been approved.

A second, more practical approach is to enter the costs and effects generated from the RCT into an economic decision model. This model can then be exposed to a sensitivity analysis driven by data about current practice patterns and by assumptions of likely use of the therapy. Such models can approximate the impact of a therapy’s use outside the controlled environment of the RCT. They explore how the costs and effects are

![Figure. Displaying cost-effectiveness (CE). Differences in effects are usually presented on the X (horizontal) axis, and differences in costs on the Y (vertical) axis. This creates four quadrants, with two for which health-care policy decisions are obvious; therapies that are cheaper and more effective (lower right) and therapies that are more expensive and less effective (upper left). If a cost-effectiveness ratio lies in one of the other two quadrants, tradeoffs must be made between effectiveness and cost. To capture uncertainties in both costs and effects, an ellipse is drawn around the point estimate for cost-effectiveness. An affluent society, such as that in the US, can usually afford interventions with a cost-effectiveness of less than $100,000 per quality adjusted life year (QALY). Ratios to the right and lower than the dotted line lie below that threshold.](image-url)
changed by loosening the RCT’s patient eligibility criteria (including treating patients not likely to benefit), treating patients with alternative therapies, and prescribing the therapy inappropriately. Clinicians are often skeptical of such decision models. The models rely on assumptions, on data garnered from multiple sources, and on simulated (rather than real) patients. While such skepticism may have been warranted in the past, simulation modeling plays an important role in many other sciences and currently represents the most practical solution to this problem. Guidelines of the U.S. Public Health Service Panel on Cost-Effectiveness in Health and Medicine (PCEHM) should lead to improved standardization and comparability of such models in health care; and an American Thoracic Society workshop used these guidelines as a framework to develop recommendations on performing cost analyses specifically in critical care.

Measuring Costs

A cost-effectiveness ratio is the incremental change in costs divided by the incremental change in effects between two study arms. Therefore, only those costs that behave differently between study arms affect the ratio. This is convenient, because attempting to measure all costs, including all indirect costs (such as patient and family suffering), would be a gargantuan task. In practice, the costs most likely to differ between therapies are the direct hospital costs (including the estimated “street” price of the therapy) and the costs of managing post-discharge problems that occur at different rates between groups (eg, if acute renal failure is a more frequent complication in one arm, then the costs of post-discharge hemodialysis must be estimated). The detail with which the cost of a particular element is measured depends on the sensitivity of the ultimate ratio to that cost. For example, the cost of mechanical ventilation should be measured very carefully if the only element that differs between intervention and control patients is the duration of mechanical ventilation, because the cost-effectiveness ratio will be exquisitely sensitive to the cost of mechanical ventilation, whereas it is unlikely to be sensitive to the price of acetaminophen.

There are several methods by which to estimate the costs of health care. Most methods rely on existing cost-accounting and billing systems (including detailed hospital bills, summary bills, and resource tracking), collecting information prospectively on resources consumed, or measuring length of stay (LOS). The number of resources consumed can be converted to costs by multiplying the number of each resource by an estimated cost (number of units of resource Y times the estimated cost per unit Y). LOS can be converted to cost by multiplying LOS by estimates of daily costs (such as the cost of a typical ICU day). Each of these methods represents a different balance between the expense of collecting the information and the accuracy of the information. Detailed measures may not be available in certain situations or may require both patient consent and hospital or provider cooperation.

Costs vary greatly in importance depending on who is paying, and cost-effectiveness is usually very different to patients, hospitals, payers, and society. Because costs (and effects) are not borne equally across society, the perspective with which a cost analysis is conducted is crucial. To account for all costs and effects of a therapy and maximize utility, the PCEHM recommends that policy decisions be made based on cost-effectiveness analyses conducted from the societal perspective.

Resource Use

Morbidity is commonly measured in terms of resource use (eg, duration of mechanical ventilation, ICU LOS). However, this approach is problematic in the determination of cost effectiveness. If used as a measurement of morbidity, resource use becomes an effect in a cost-effectiveness ratio. Yet resource use related to an intervention is part of the cost of the intervention. There is no clear rule determining at what point resource use would stop being counted as a cost required by a therapy and would start becoming the effect of that therapy. Furthermore, if the sequelae of an intervention are considered only in terms of their costs, and not in terms of their effects on quality of life, then the ratio of costs per effects becomes severely distorted by the omission of important non-cost effects of a therapy.

While resource use is important to determine, the solution is to avoid using it as a proxy for morbidity. Rather, all costs should be counted as costs and all effects as effects. For example, if one therapy produced more renal failure than another therapy (and that persisted after discharge), an evaluation of that therapy would incorporate both the increase in costs associated with ongoing hemodialysis (cost) and the decrease in quality of life (QOL) associated with living with renal failure (effect). To consider post-discharge renal failure only as the cost of hemodialysis (without considering renal failure’s effect on QOL) fails to attribute the full penalty of the additional renal failure to the therapy under study.

Quality of Life

QOL incorporates survival with its perceived value. As such, it is inherently patient-oriented and is widely adopted as the principal method by which to compare the relative benefits (effects) of different therapies in
different diseases. QOL has been suggested by the US PCEHM as the primary end point for cost-effectiveness analyses. Unfortunately, QOL measures are only sporadically used in studies of critical illness. There are several reasons for this. First, they are expensive to collect. Second, there is little agreement over the most appropriate way to measure QOL. Third, many still question the entire approach because of its lack of objectivity. Q quality is, by its very nature, a subjective opinion, often only weakly correlated with physiology and functional capability. Fourth, it is difficult to determine the extent to which a decrease in QOL is due to a critical illness as opposed to being the result of underlying disease, especially since pre-critical illness QOL is rarely known. Fifth, QOL can only be measured in survivors of critical illness, and therefore does not account for a therapy’s impact on non-survivors, such as those suffering at the end of life. Finally, measuring QOL in children is particularly difficult. Babies and young children are not capable of understanding questions or articulating answers to QOL measures. While parent reports are often used to estimate QOL of their children, no one knows the meaning of QOL to an infant, nor to someone who has lived a lifetime with a chronic disease or disability. However, only through more routine measurement of QOL will the relationship between QOL and other objective measures be defined and will better measures of QOL be developed.

Cost-Effectiveness of Inhaled Nitric Oxide in Hypoxemic Newborns

RCTs have shown that INO decreases the use of extracorporeal membrane oxygenation (ECMO), nonsignificantly improves survival, and increases overall length of stay in hypoxemic newborns. Several studies have examined the cost-effectiveness of INO in this population. Two from Jacobs et al were based on outcome and resource use data from trials done by the Canadian Inhaled Nitric Oxide Study Group. Two, including one from our group, used decision models and data from several sources to estimate the cost-effectiveness of INO. We will briefly discuss all four studies, which highlight important facets of the cost-effectiveness of INO. In addition, because of our familiarity with our own work, we will use our study as a more detailed example of the conduct of a cost-effectiveness analysis (CEA) when cost data were not collected as part of the RCT.

Jacobs et al conducted a CEA based on 123 subjects enrolled in the Canadian arm of two parallel RCTs of INO for hypoxemic respiratory failure (27 babies with and 96 babies without congenital diaphragmatic hernia (CDH)). Published in 2000, the study was conducted from the provider perspective, and the time horizon was to hospital discharge. Costs were estimated from the resources used by babies at a single center. For babies without CDH, the authors found that patients receiving INO had mean costs of $2,404 (this and subsequent dollar values are in US dollars) higher than patients receiving placebo (p = 0.25), with a cost-per-life-saved of $23,908 (95% confidence interval $140,542 cheaper to $201,956 more expensive per life saved). Babies with CDH who received INO had both higher mortality and higher costs. Of note, ECMO costs were $3,236 (for cannulation and decannulation) plus $1284/day, which is substantially lower than many US estimates.

Jacobs et al subsequently incorporated 18–24 month follow-up cost and outcome data on the 96 babies without CDH, 68 of whom completed follow-up (20 died). Average costs remained higher for babies who received INO (p = 0.15), with 90% of costs being incurred during the birth hospitalization. However, post-discharge costs were $200 lower for INO patients because of decreased post-discharge medication, clinical services, and rehospitalization. Babies who received INO had a significantly reduced rate of seizures (by 20%) and non-significantly improved outcomes overall.

Lorch et al created a decision model incorporating outcomes data from 6 published RCTs of INO in hypoxemic newborns and from a cohort of 123 babies with persistent pulmonary hypertension of the newborn (PPHN) treated at a single hospital over an 11-year period. Costs were estimated from the resources used by the single-center cohort. They conducted their analysis from the US societal perspective. In this study, INO increased the cost of care by $1,141 per infant, with a cost-effectiveness of $33,234 per life saved and $19,022 per QALY gained (when using a time horizon to one-year post-discharge). Extending the time horizon to lifetime improved the ratio to $976 per QALY.

Our group also used a decision model to assess the cost-effectiveness of INO. We used outcome data from the two largest INO RCTs, one of which included babies with CDH, and resource use data from one of them. We used several sources to convert resources used to costs, including an analysis of the detailed hospital bills of 260 babies referred to 1 of 4 ECMO centers for possible ECMO. Similar to Lorch et al, we adopted the US societal perspective. However, we restricted the time horizon to the first year of life, conservatively assuming that all costs and effects of INO have disappeared at one year. Although there is ample evidence that sequelae of severe neonatal illness extend well into later childhood and adoles-
ence,\textsuperscript{19} whether INO differentially impacts those sequelae awaits further research. We found that if INO were used only in ECMO centers, it was both more effective and cheaper than placebo (cost savings of $1,880 per case [95\% CI: $7,420 cheaper to $3,550 more expensive]). The cost savings was predominantly due to decreased need for ECMO in the INO group. The cost-effectiveness was $62,666 saved per QALY.

Our estimates were sensitive to patient selection. As the use of INO is broadened to include patients who would never need ECMO, then its cost-effectiveness diminished. Similarly, if ECMO were not available as a rescue therapy, the use of INO would be much less cost-effective. Quality of life of infants and young children is difficult to evaluate, and standardized approaches are lacking.\textsuperscript{19,20} However, our conclusions were not substantially different if we changed our assumptions about the quality of life of infants with pulmonary or neurologic morbidity. If the beneficial effects of INO also minimize subsequent health care costs and family burden, the cost-effectiveness would further improve.

The relatively small sample sizes of the two INO RCTs on which we based our analyses led to considerable uncertainty around the point estimates of cost-effectiveness. To better understand the uncertainty, we performed Monte-Carlo simulation (as did Lorch et al\textsuperscript{17}) and, consistent with Lorch et al,\textsuperscript{17} found that INO appears favorable, from a societal perspective, under a large proportion of scenarios.

The findings of these 4 studies using data from 3 cohorts of patients receiving INO were consistent within their reported uncertainties. The major element of discrepancy between the studies is in the estimates of ECMO costs, which were estimated differently for each study. Because the cost savings from INO are due primarily to INO’s ability to decrease the need for ECMO, it is not surprising that the most favorable cost-effectiveness ratio was found in our study, which had the highest estimated ECMO costs.

ECMO use and costs of care vary substantially between the US and other countries.\textsuperscript{21} Given the sensitivity of the cost-effectiveness ratio to hospital costs and costs of therapy, small differences in the financing and organization of factors such as ECMO delivery could have a profound effect on the cost-effectiveness of INO.\textsuperscript{22} This is exemplified by the estimate of Jacobs et al of ECMO costs in Canada being less than one third of the costs that we found using cost estimates from the US.\textsuperscript{14} Therefore, the relevance of US findings to other countries is unclear.

There are approximately 24,000 ventilated term neonates each year\textsuperscript{23} and, prior to the introduction of INO, there were approximately 1,400 ECMO runs in term/near-term neonates per year.\textsuperscript{24} Based on the ECMO rate of 59\% in the placebo arms of two RCTs,\textsuperscript{12,13} there are approximately 2,400 babies per year (1,400/59\%) who would meet the RCT entry criteria. Our study suggested that INO remains better than $100,000 per QALY with dilution of the RCT population by between 55\% and 85\% (depending on the types of babies who dilute the trial population). This translates into a national estimate of 5,300–16,000 babies per year who can receive INO with a cost-effectiveness profile nationwide of < $100,000 per QALY and a decrease in ECMO runs by one third to approximately 900. If the acquisition cost of INO decreases significantly, the number of neonates who could be administered INO could increase in the same proportion without jeopardizing cost-effectiveness, assuming conservatively that none of the neonates in the expanded population benefits from INO. Without more information regarding the benefits of INO over a longer time horizon or in other patient populations, one would be concerned that INO use in a larger population than this might be increasingly cost-ineffective.

**Summary**

INO appears to offer a cost-effective alternative to traditional care paradigms in the treatment of term or near-term infants with hypoxic respiratory failure. The cost-effectiveness will degenerate if use is too indiscriminant. Subsequent study to better understand the long-term effects of perinatal INO, as well as the consequences of receiving or avoiding ECMO, will be crucial if we are to fully understand the societal consequences of this therapy.

**References**

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The questions for each session in the proceedings are found in pages 36-39.
Inhaled Nitric Oxide in the Hypoxic Newborn: A Review of the Evidence
Timothy R Myers BS RRT-NPS

Objectives

• State the labeled indication for inhaled nitric oxide (INO).
• Explain the rationale for INO in the hypoxic newborn.
• Discuss the evidence for INO in the hypoxic newborn.
• Discuss the advantages of combining high-frequency oscillation ventilation with INO.

Questions

1. Which of the following was not significantly demonstrated with the implementation of INO in any of the clinical trials described in this manuscript?
   A. Increase in $P_{aO_2}$
   B. Decrease in oxygenation index
   C. Decrease in the need for ECMO
   D. Decrease in mortality rate

2. In a trial by Davidson et al, published in Pediatrics in 1998, the most common reason for exclusion from participation in the clinical trial was:
   A. Surfactant administration
   B. High-frequency oscillatory ventilation
   C. Oxygenation status
   D. Gestational age ≤ 37 weeks
   E. No documented evidence of PPHN

3. In the Neonatal Inhaled Nitric Oxide Study (NINOS), full-term infants needed to have which oxygenation index value to qualify for enrollment and randomization?
   A. ≥ 25
   B. ≥ 15
   C. ≤ 20
   D. ≤ 35
   E. ≥ 50

4. Kinsella et al found that INO combined with what other treatment modality produced better clinical outcomes?
   A. Hyperventilation
   B. High-frequency oscillatory ventilation
   C. Surfactant administration
   D. Sedation and paralysis
Inhaled Nitric Oxide in the Hypoxic Newborn: Patient Selection, Dosage, Monitoring Response, and Weaning

Peter Betit RRT-NPS FAARC

Objectives

• Describe patient selection criteria for administering INO to newborns with hypoxic respiratory failure, including pre-treatment considerations.
• Describe dosing of inhaled nitric oxide, evaluation of response, and identification of non-responders.
• Describe the potential adverse effects of INO, and associated monitoring.
• Describe approaches to weaning INO, managing weaning failure, and potential rebound pulmonary hypertension.

Questions

5. Which of the following are considered criteria for initiating INO therapy in a newborn with hypoxic respiratory failure?
   A. Oxygenation index ≥ 25
   B. Difference between pre-ductal and post-ductal oxygen saturation, measured via pulse oximetry (SpO₂)
   C. Gestational age > 34 weeks
   D. All of the above

6. Which of the following best describes a response to INO therapy?
   A. Improved inflation on chest x-ray
   B. 20 mm Hg improvement in PaO₂
   C. Decrease in FIO₂ by 5%
   D. pH > 7.45

7. Which of the following should be monitored during INO therapy?
   A. NO₂
   B. NO
   C. metHb
   D. All of the above

8. Which of the following should be done before discontinuing INO therapy?
   A. Suction the endotracheal tube
   B. Increase the FIO₂
   C. Obtain a chest x-ray
   D. Decrease the mean airway pressure
Delivery of Inhaled Nitric Oxide
Richard D Branson MSc RRT FAARC

Objectives

• List the critical components of a system for delivery of INO.
• List the important variables for continuous monitoring during INO delivery.
• List factors that lead to nitrogen dioxide production and how to alleviate them.
• Explain the setup of the INOVent with a mechanical ventilator, a manual resuscitator, and a low-flow oxygen-delivery system.

Questions

9. The INOvent can be used with
   A. Ventilator
   B. Face mask
   C. Nasal cannula
   D. All of the above

10. The NO concentration in the cylinders used with the INOvent is
    A. 40 ppm
    B. 80 ppm
    C. 400 ppm
    D. 800 ppm

11. The INOvent monitors which of the following?
    A. Oxygen concentration
    B. Nitric oxide concentration
    C. Nitrogen dioxide concentration
    D. All of the above

12. The purpose of the purge procedure with the INOvent is to
    A. Remove nitrogen dioxide from the delivery system
    B. Calibrate the oxygen sensor
    C. Test the alarm system
    D. Check the microprocessor
Cost-Effectiveness of Inhaled Nitric Oxide in the Hypoxemic Newborn

R Scott Watson MD MPH
Derek C Angus MD MPH

Objectives

• Define cost-effectiveness analysis.
• Explain why cost-effectiveness analysis is important.
• Discuss the cost-effectiveness of INO in the treatment of neonatal respiratory failure.
• Discuss the limitations of cost-effectiveness analysis.

Questions

13. A cost-effectiveness ratio is defined as
   A. The relative net cost of an intervention compared to other interventions
   B. The incremental change in costs divided by the incremental change in effects of
      an intervention
   C. The cost of an intervention plus the effects of an intervention
   D. The cost of an intervention divided by the cost of lives saved by the
      intervention

14. The difference between cost-effectiveness and cost-efficacy is that
   A. Cost-effectiveness is cost per quality-adjusted life year (QALY) and cost-efficacy
      is cost per life saved
   B. Cost-effectiveness ratios are more precise
   C. Cost-efficacy represents an intervention’s use under ideal conditions and cost-
      effectiveness is more reflective of use in actual practice
   D. Cost-efficacy is a better reflection of what insurance companies would be willing
      to pay for a therapy

15. The US Public Health Service Panel on Cost-Effectiveness in Health and Medicine
    (PCEHM) recommends that cost-effectiveness analyses should be conducted from
    which perspective?
    A. Society’s
    B. The Federal Government’s
    C. The patient’s
    D. The insurer’s

16. Which of the following statements is TRUE?
   A. One advantage of calculating a cost-effectiveness ratio, versus determining
      costs alone, is that the time period over which costs and effects are measured
      does not have a substantial impact on it
   B. The primary reason to perform a cost-effectiveness analysis is to decrease health
      care spending
   C. Quality-adjusted life years (QALYs) are the recommended unit of effects
      because they are easy and straightforward to measure
   D. When performing a cost-effectiveness analysis as a part of a randomized
      controlled trial, only those costs that behave differently between study arms
      affect the ratio
Proceedings from a special symposium on

**Use of Inhaled Nitric Oxide in the Hypoxic Newborn**

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