Earlier Use of Inhaled Nitric Oxide in Term and Near-Term Neonates With Hypoxic Respiratory Failure (HRF) and Pulmonary Hypertension (PH)
Disclosure Information

This program is sponsored by Ikaria®, manufacturer of INOMAX® (nitric oxide) for inhalation.
Outline

• Acute Hypoxic Respiratory Failure (HRF) in Newborns: The Clinical Problem

• Physiologic Approach to HRF

• Earlier Use of Inhaled Nitric Oxide (iNO) in the Treatment of HRF
HRF in the Newborn: A Definition

A relative deficiency of oxygen in arterial blood, often associated with insufficient ventilation.¹

This deficiency can be reflected by progressive respiratory and metabolic acidosis and remains a persistent challenge in the management of some newborns.

Question 1

In an average month how many term/near-term infants (>34 weeks gestation) with hypoxic respiratory failure (HRF)/persistent pulmonary hypertension of the neonate (PPHN) does your unit treat?

A. 0–5
B. 6–10
C. ≥10
Epidemiology of Neonatal HRF

HRF in Newborns: Some Commonly Occurring Diseases

- **Idiopathic PPHN**
  - No underlying lung disease

- **Respiratory Distress Syndrome**
  - Acute lung injury
  - Surfactant deficiency or inactivation
  - Pulmonary edema, volume loss

- **Meconium Aspiration Syndrome**
  - Airway obstruction with gas trapping
  - Surfactant inactivation
  - Pneumonitis

- **Congenital Diaphragmatic Hernia**
  - Lung hypoplasia
  - Decreased vascular surface area
  - Increased pulmonary artery musculature

Images courtesy of John P. Kinsella, MD, and Steven H. Abman, MD.
Pathophysiology of HRF: The Cardiopulmonary Triad$^{1,2}$

Lung disease
- Low and high lung volumes
- Regional gas trapping, hyperinflation

Cardiac disease
- Left ventricular dysfunction
- High right ventricular pressure

Pulmonary vascular disease
- Increased vascular tone and reactivity
- Decreased vascular growth (lung hypoplasia)
- Hypertensive vascular remodeling

Cardiopulmonary Interactions in Neonatal HRF

- High vascular tone
- Altered reactivity
- Structural disease

Hypoxia, hypercapnia, acidosis

- Hypovolemia
- RV pressure overload
- LV dysfunction

Right-to-left shunting at PDA or FO

- Lung volume
- Compliance
- Intrapulmonary shunt

**HRF in Newborns: Pathophysiology**

- **Intrapulmonary shunt**: pulmonary arterial blood reaches the pulmonary venous side without passing through ventilated areas of the lung.

- **Extrapulmonary shunt (PPHN)**: right-to-left shunting of blood bypasses the lung through fetal channels (ductus arteriosus and/or foramen ovale).

- **Ventilation–perfusion (V/Q) mismatch**: imbalance between ventilation and perfusion; alveolar hypoxia, increased dead-space ventilation.

Intrapulmonary Shunting

PA = pulmonary artery; PV = pulmonary vein.
HRF in Newborns: Pathophysiology


- **Intrapulmonary shunt**: pulmonary arterial blood reaches the pulmonary venous side without passing through ventilated areas of the lung

- **Extrapulmonary shunt (PPHN)**: right-to-left shunting of blood bypasses the lung through fetal channels (ductus arteriosus and/or foramen ovale)

- **Ventilation–perfusion (V/Q) mismatch**: imbalance between ventilation and perfusion; alveolar hypoxia, increased dead-space ventilation
Extrapulmonary Shunting

Right Atrium

Foramen Ovale

Right Ventricle

Normal Blood Flow to the Lungs

Ductus Arteriosus: Some Blood Bypasses the Lungs

To Body

Left Ventricle

Normal Blood Flow to the Lungs

Left Atrium

Normal Blood Flow to the Lungs

Blood Flow to Body

Some Blood Bypasses the Lungs

To Lungs

To Body

RBC [Oxygenated]

RBC [Oxygeanated]

RBC [Deoxygenated]

RBC [Low Oxygenation]

RBC, red blood cell.

HRF in Newborns: Pathophysiology

- **Intrapulmonary shunt**: pulmonary arterial blood reaches the pulmonary venous side without passing through ventilated areas of the lung.
- **Extrapulmonary shunt (PPHN)**: right-to-left shunting of blood bypasses the lung through fetal channels (ductus arteriosus and/or foramen ovale).
- **Ventilation–perfusion (V/Q) mismatch**: imbalance between ventilation and perfusion; alveolar hypoxia, increased dead-space ventilation.

Optimal Oxygenation Requires Matching Ventilation and Perfusion (V/Q)\(^1\)

**MISMATCHED**
Low inflation to perfusion

- Poor ventilation despite perfusion produces hypoxemia
- Intrapulmonary shunting

**MISMATCHED**
High inflation with low perfusion

- Inflation recruits the lung, but with low blood flow
- Hypoxemia persists

**MATCHED**
Inflation/perfusion (V/Q \(~ 1\))

- Adequate ventilation with perfusion optimizes oxygenation
- V/Q matching occurs

Adequately Recruiting the Lung: Optimizing Lung Volume Is the First Step

Overdistention and underinflation contribute to high PVR

High lung volume ventilation overdistends, resulting in volutrauma

Low lung volume ventilation tears adhesive surfaces

Figure reprinted from Froese AB. *Crit Care Med.* 1997;25:906-908. Copyright 2009, with permission from Society of Critical Care Medicine.
PVR Can Increase at Low or High Lung Volumes

Images courtesy of John P Kinsella, MD, and Steven H. Abman, MD.
Treatment of Neonatal HRF\textsuperscript{1,2}

Lung
- Optimize lung volume and ventilation

Heart
- Enhance cardiac function and systemic blood pressure

Pulmonary vascular disease
- Lower PVR
- Improve ventilation–perfusion mismatch by redirecting blood from poorly aerated or diseased lung regions to better aerated distal air spaces

Indication

- INOMAX is a vasodilator, which, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks gestation) 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.

- Utilize additional therapies to maximize oxygen delivery with validated ventilation systems.

Important Safety Information When Using INOMAX-- Contraindication¹

Inhaled nitric oxide must not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood.

In the CINRGI Study, Clinical Evidence of PPHN Was Defined as One of the Following:

A

Differential Oxygenation

- Differential oxygenation in preductal and postductal areas (ie, 5% difference in preductal and postductal saturations by pulse oximetry or arterial blood gases)

B

>2 Desaturation Events in 12 hours

- Marked clinical lability in oxygenation despite optimized treatment of the neonate’s lung disease
- Marked clinical lability is defined as more than 2 desaturation (\( \text{SaO}_2 <85\% \)) events occurring within a 12-hour period

---

a The attending physician must attribute the desaturation events to PPHN and not to changes in lung disease or ventilator strategy. \( \text{SaO}_2 \), arterial oxygen saturation.

Inhaled Nitric Oxide Causes Selective Pulmonary Vasodilation

Underinflation Creates V/Q Mismatching¹

Underventilated portion of lung

- Decreased PaO₂
- Increased pulmonary artery pressure and decreased blood flow

PA = pulmonary artery; PV = pulmonary vein.

Inhaled Nitric Oxide (iNO) Reduces V/Q Mismatching¹

Inhaled NO increases vasodilation
- Decreases pulmonary artery pressure
- Increases PaO₂ and blood flow in better ventilated regions
- Improves V/Q ratios in neonates with HRF

PA = pulmonary artery;
PV = pulmonary vein;
NO = nitric oxide.

An Inhaled Vasodilator

Inhalation of NO offers selective activity
• The only FDA-approved drug that selectively dilates the pulmonary vasculature\(^1\)
• Targeted delivery to the pulmonary bed\(^1\)

Inhalation of NO offers rapid onset
• Clinical responses seen in as little as 30 minutes\(^1\)
• Inhaled nitric oxide causes vasodilation in the pulmonary vasculature\(^1\)

Inhalation of NO offers rapid clearance
• Rapid inactivation by hemoglobin minimizes systemic effects\(^1,2\)
• Nitrate, the predominant metabolite of nitric oxide, is rapidly cleared by the kidneys\(^1\)

## Inhaled Nitric Oxide Phase III Studies for Neonatal HRF

<table>
<thead>
<tr>
<th></th>
<th>CINRGI$^{1,2}$</th>
<th>NINOS$^{2,3}$</th>
<th>I-NO/PPHN$^{2,4}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>to reduce the need for ECMO</td>
<td>to reduce mortality and/or the need for ECMO</td>
<td>to reduce the incidence of death, ECMO, neurologic injury, or BPD</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>186 term/near-term infants (&gt;34 weeks) with HRF and PPHN</td>
<td>235 term/near-term infants (≥34 weeks) with HRF and PPHN</td>
<td>155 term infants* (≥37 weeks) with HRF and PPHN</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>*Trial halted due to slow enrollment</td>
</tr>
<tr>
<td><strong>iNO Dose</strong></td>
<td>20 ppm, weaned to 5 ppm</td>
<td>20 ppm, with possible increase to 80 ppm</td>
<td>5, 20, or 80 ppm</td>
</tr>
</tbody>
</table>

CINRGI: Efficacy Outcomes¹,²

*Primary outcome.
CINRGI: Retrospective Analysis

Inhaled nitric oxide shortens median time on oxygen therapy (17 vs 34 days)

Time on oxygen therapy shown in a Kaplan-Meier analysis of retrospective data from the CINRGI phase III study. Median oxygen time is defined as the day at which 50% of patients went off oxygen therapy. Patients who died or received extracorporeal membrane oxygenation are censored. Total length of hospital stay was not different between study groups. CINRGI was not sufficiently powered to show significance in this endpoint.

NINOS: Efficacy Outcomes\textsuperscript{1,2}

**Primary Outcome**

- **Death and/or ECMO**
  - Placebo: 64, iNO: 46, \( P = 0.006 \)
  - \( N = 235 \)
- **Death**
  - Placebo: 17, iNO: 14, \( P = 0.60 \)
- **ECMO**
  - Placebo: 55, iNO: 39, \( P = 0.014 \)

**Secondary Outcome**

- **PA-aO\textsubscript{2} (A-a gradient)**
  - Placebo: \(-60\)
  - iNO: \(-6.7\), \( P < 0.001 \)

\*Primary outcome.

Results from NINOS and CINRGI studies¹

- Combined mortality: placebo (11%); inhaled NO (9%)
- In CINRGI, the only adverse reaction (>2% higher incidence on INOmax than placebo) was hypotension (14% vs. 11%)
- Treatment groups were similar with respect to incidence and severity of intracranial hemorrhage, periventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, and pulmonary or gastrointestinal hemorrhage
- 6-month follow-up: inhaled NO (n=278); control (n=212)
  - No differences in pulmonary disease or neurological sequelae, or in the need for rehospitalization or special medical services

Question 2

What is the most important parameter you use to classify the severity of HRF/PPHN of the term/near-term newborn?

A. Oxygenation Index (OI)
B. Partial pressure of arterial $O_2$ ($PaO_2$)
C. Level of PEEP
D. Level of mean airway pressure ($P_{aw}$)
E. A-a Gradient or A-aDO$_2$
F. None of the above
Question 3

What is your typical Oxygenation Index (OI) threshold for the initiation of inhaled NO in a term/near-term infant with HRF associated with pulmonary hypertension?

A. <15
B. 15 - 19
C. 20–24
D. >25
E. Do not use OI for initiation
When Is the “Right Time” to Initiate Inhaled Nitric Oxide?

Use of Oxygenation Index (OI) in term and near-term neonatal HRF

• Compares the level of ventilator support (FiO₂ and mean airway pressure [MAP]) with the resultant systemic arterial oxygen levels

\[
\text{OI} = \frac{\text{FiO}_2 \times \text{mean airway pressure} \times 100}{\text{postductal PaO}_2}
\]

[Example: \(\text{FiO}_2, 0.60; \text{MAP}, 15; \text{PaO}_2, 50 \text{ torr} = \frac{(0.60 \times 15 \times 100)}{50} = 18 \text{ OI}\)]

Additional Publications to Address Earlier Use of iNO in Infants With HRF


Konduri et al 2004: Study Design

- **Prospective, randomized, controlled, double-masked, multicenter trial**

- **Patients:** 299 infants (≥34 weeks gestation) with respiratory failure that needed assisted ventilation
  - OI ≥15 and <25 (mild to moderate severity) on FiO\(_2\) ≥0.80

- **Dosing:** iNO initiated at 5 ppm or simulated (sham) dose
  - Dose increased to 20 ppm if the increase in PaO\(_2\) was ≤20 mm Hg
  - Infants in either group were transitioned to standard iNO if OI increased to ≥25

- **Objective:** To determine whether early iNO administration results in additional reduction of the incidence of ECMO or death

The primary outcome incidence observed in the control group (19.5%) is approximately half of the projected incidence on the basis of our 1997 pilot data.

The mean OI at enrollment in study infants was nearly 20, and a lack of a clear separation between early and standard iNO groups may have contributed to the lack of treatment effect in our study.

iNO improves oxygenation but does not reduce the incidence of ECMO/mortality when initiated at an OI of 15 to 25 compared with initiation at >25 in term and near-term neonates with respiratory failure.
More infants in the early iNO group had >20 mm Hg increase in PaO$_2$ in response to study gas initiation compared with the control group ($P<0.001$)

- 73% of early iNO infants
- 37% of control infants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early iNO group (n=150)</th>
<th>Control group (n=149)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of study gas administration*</td>
<td>57 ± 48 hours</td>
<td>39 ± 38 hours</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Initiation of standard iNO therapy (OI ≥ 25)</td>
<td>61 (41%)</td>
<td>81 (54%)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Progression of OI &gt;40</td>
<td>11 (7%)</td>
<td>21 (14%)</td>
<td>0.056</td>
</tr>
</tbody>
</table>

*Mean ± standard deviation.

Konduri et al 2004: Safety\textsuperscript{1}

- None of the study infants had study gas weaned or discontinued because of elevated methemoglobin or NO\textsubscript{2} levels
- 1 iNO infant and 2 control infants developed severe (grade 3-4) intraventricular hemorrhage and periventricular leukomalacia
- Seizures occurred in 14 iNO infants (9.4\%) and 11 control infants (7.4\%) (\(P=0.68\))

\textsuperscript{1} Konduri GG, et al. \textit{Pediatrics}. 2004;113(3 pt 1):559-564.
Konduri et al 2013: Risk of ECMO/death by OI at enrollment\(^1\)*

- Early iNO: OI = 15 to <20
- Early iNO: OI =20 to ≤ 25

\[ p = 0.02 \]

- 60% relative reduction in ECMO/death

*Post-hoc, subgroup analysis of prospectively collected data from the early iNO RCT to identify factors associated with ECMO/death and progression of HRF.

Konduri et al 2013: Risk of ECMO/death by treatment assignment and OI at enrollment

*Post-hoc, subgroup analysis of prospectively collected data from the early iNO RCT to identify factors associated with ECMO/death and progression of HRF.

†The control group was eligible to receive iNO if their HRF progressed to an OI > 25
Konduri et al 2013: Progression of HRF*

*Post-hoc, subgroup analysis of prospectively collected data from the early iNO RCT to identify factors associated with ECMO/death and progression of HRF.

†The control group was eligible to receive iNO if their HRF progressed to an OI ≥ 25

Question 4

What would you consider to be a maximal (amount) of FiO\textsubscript{2} to obtain adequate oxygenation (PaO\textsubscript{2} ≥ 60 mmHg) for a term/near-term infant with HRF/PPHN?

A. ≤ .30
B. ≤ .60
C. ≤ .80
D. ≤ .90
E. 1.0
Question 5

Assuming a less than optimal response in oxygenation, how long would you maintain a patient on a FiO₂ of 1.0 prior to iNO initiation with a term/near-term infant with HRF/PPHN?

A. 0
B. >0 but <1 hour
C. 1 hour
D. >1 hour
Golombek et al: Study Design

**Objectives**

- To analyze the effects of inhaled nitric oxide on measures of oxygenation
- To analyze the effects of inhaled nitric oxide across a range of illness severity strata
- To analyze the effects of inhaled nitric oxide on the duration of mechanical ventilation

**Methods**

- A retrospective pooled analysis of all subjects receiving 20 ppm inhaled nitric oxide in the CINRG1, NINOS, and I-NO/PPHN Phase III trials
- No censoring based on underlying diagnosis or baseline characteristics

Inhaled nitric oxide causes rapid improvement (at 30 min) in oxygenation.

Change in mean PaO2 at 30 Minutes (mm Hg [kPa])

- **Baseline**
  - NINOS (N=227) 8.85
  - I-NO/PPHN (N=75) 17.95
  - CINRGI (N=186) 19.08
  - All Studies (N=493) 14.15

- **Ventilation**
  - P<0.001

- **Ventilation + iNO**
  - P=0.046
  - P<0.001
  - P<0.001

Inhaled NO improves oxygenation in severe and very severe HRF

Change in mean $\text{PaO}_2$ at 30 Minutes by Baseline OI (mm Hg [kPa])

<table>
<thead>
<tr>
<th>Baseline OI</th>
<th>&gt;25 to ≤40 (n=170)</th>
<th>&gt;40 (n=186)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{PaO}_2$</td>
<td>13.95 (P&lt;0.001)</td>
<td>18.66 (P&lt;0.001)</td>
</tr>
</tbody>
</table>

Golombek et al: Oxygenation Results

Inhaled NO improves oxygenation even in mild and moderate HRF

![Graph showing change in mean PaO2 at 30 Minutes by Baseline OI (mm Hg [kPa])]

Baseline OI:
- ≤15 (n=40)
- >15 to ≤25 (n=91)
- >25 to ≤40 (n=170)
- >40 (n=186)

<table>
<thead>
<tr>
<th>Change in mean PaO2 at 30 Minutes by Baseline OI (mm Hg [kPa])</th>
<th>Ventilation</th>
<th>Ventilation + iNO</th>
</tr>
</thead>
<tbody>
<tr>
<td>P=0.003</td>
<td>-23.03</td>
<td>62.39</td>
</tr>
<tr>
<td>P=0.004</td>
<td>18.28</td>
<td>52.93</td>
</tr>
<tr>
<td>P&lt;0.001</td>
<td>13.95</td>
<td>62.07</td>
</tr>
<tr>
<td>P&lt;0.001</td>
<td>18.66</td>
<td>45.17</td>
</tr>
</tbody>
</table>

Inhaled NO reduces median days on mechanical ventilation (11 vs. 14 days)

This is a Kaplan-Meier analysis of pooled data from 3 independent controlled studies, NINOS, CINRGI, and I-NO/PPHN (N=243). Outliers are removed for visual purposes.

González et al: Study Design\textsuperscript{1}

- Prospective, randomized, controlled, open-label, two-center trial
- **Patients:** 56 term/near-term infants (≥35 weeks gestation) with HRF and PPHN
  - OI between 10 and 30 (mild to moderate severity)
- **Dosing:** 20 ppm, weaned to 5 ppm
- **Objective:** to evaluate whether early treatment with iNO can prevent infants with moderate respiratory failure from developing severe HRF (OI ≥40)

Early iNO significantly decreased the probability of developing severe disease as shown by the primary endpoint, treatment failure.

<table>
<thead>
<tr>
<th>Placebo</th>
<th>iNO</th>
</tr>
</thead>
<tbody>
<tr>
<td>61% (17/28)</td>
<td>25% (7/28)</td>
</tr>
</tbody>
</table>

Treatment Failure (OI >40 within 48 hours)
Early iNO significantly reduced OI over time in infants with mild to moderate HRF.

17 of the 28 control infants reached an OI >40 and were switched to iNO.

*P<0.01

Early iNO significantly reduced the median time on oxygen therapy (11.5 days vs 18 days, $P<0.03$)
González et al: Safety

- Patients treated with iNO did not have elevated blood levels of methemoglobin or high levels of NO$_2$ in the ventilatory circuit
- There were no differences between groups in the incidence of other neonatal complications such as bleeding and/or coagulation disorders, hypotension, or infections

INOMax® DS_{IR}®

- Compatible with most neonatal ventilators and modes of ventilation*

*Please see sales representative to find out if your ventilator is compatible.
Guidelines for Weaning Patients Off iNO

• iNO should be maintained up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from iNO therapy

• Abrupt discontinuation of iNO may lead to increasing pulmonary artery pressure and worsening oxygenation even in neonates with no apparent response to NO for inhalation

• To wean iNO, down titrate in several steps, pausing several hours at each step to monitor for hypoxemia

• If rebound pulmonary hypertension occurs, reinstate iNO therapy immediately
Important Safety Information When Using Inhaled Nitric Oxide-- Contraindication

Inhaled nitric oxide must not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood.

Important Safety Information When Using Inhaled Nitric Oxide

Rebound

- Abrupt discontinuation of INOmax may lead to increasing pulmonary artery pressure and worsening oxygenation even in neonates with no apparent response to nitric oxide for inhalation.

Methemoglobinemia and NO\textsubscript{2} levels

- Increases with dose of iNO
- Nitric oxide donor compounds may have an additive effect with INOmax on the risk of developing methemoglobinemia
- Nitrogen dioxide may cause airway inflammation and damage to lung tissues
- Monitor for PaO\textsubscript{2}, methemoglobin, and inspired NO\textsubscript{2} during INOmax administration.

Pre-existing left ventricular dysfunction

- Inhaled NO may increase pulmonary capillary wedge pressure leading to pulmonary edema

Use only with an INOmax DS\textsubscript{IR}®, INOmax® DS, or INOvent® operated by trained personnel

Methemoglobin Levels\textsuperscript{1}

![Methemoglobin Levels Graph]

Inhaled nitric oxide (ppm): 80, 20, 5.0, Control

Key Takeaways

• HRF continues to be a therapeutic challenge

• Inhaled nitric oxide, combined with adequate ventilation, can improve oxygenation in neonates with HRF at all levels of disease severity

• Earlier use of inhaled nitric oxide in neonates with respiratory failure may improve oxygenation\(^1\) and decrease the probability of developing severe HRF\(^2\)

• Inhaled nitric oxide is well tolerated. Adverse reactions, rebound pulmonary hypertension, methemoglobinemia, and increased NO\(_2\) are manageable and dose related\(^3\)