Hypoxic Respiratory Failure in Term and Near-Term Neonates

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Disclosure Information

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

SPEAKER: THIS SLIDE MUST BE SHOWN.
This program will discuss 3 topics: the clinical problem of acute hypoxic respiratory failure (HRF) in newborns, a physiologic approach to understanding and treating HRF, and the role of inhaled nitric oxide in the treatment of HRF.
HRF in the Newborn: A Persistent Challenge

• Definition: A relative deficiency of oxygen, often associated with insufficient ventilation. This deficiency can be reflected by progressive respiratory and metabolic acidosis and remains a persistent challenge in the management of some newborns.

• Epidemiology\(^1\):
  - 18 per 1000 for all live births\(^*\)
  - Higher rates in males and blacks

• Mortality\(^1\): 9.9% to 14.5%

• Morbidities include neurodevelopmental abnormalities, cognitive delay, and a high rate of chronic childhood diseases, learning disabilities, and sensorineural hearing loss\(^2,3\).

\(^*\)As measured by overall rate of mechanical ventilation.

HRF can be defined as a relative deficiency of oxygen, often associated with insufficient ventilation. This deficiency can be reflected by progressive respiratory and metabolic acidosis and remains a persistent challenge in the management of some newborns.

The overall scope of the problem was described in a large cohort study by Angus et al, who found that the overall incidence of HRF in very low, low, and normal birth weight infants, as measured by the overall rate of mechanical ventilation, was 18 per 1000 live births. This rate was 100-fold greater in very low birth weight infants (700 to 800 g at birth) and was also greater in males and blacks (20 and 29 per 1000, respectively).\(^1\)

Overall mortality rates ranged from approximately 10% to 15% at lower and higher level hospitals, respectively. The higher rates observed at higher level hospitals reflect a patient population that typically has more severe illness, as reflected by higher rates of infection, major congenital abnormalities, and hospital mortality.\(^1\)

In a separate study, HRF patients were found at follow-up at 5 to 11 years of age to have a higher frequency of learning disabilities, require more remedial help, and have higher rates of sensorineural hearing loss than a matched control group.\(^2\)

References

## Differential Diagnosis of PPHN

<table>
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<th>Pulmonary</th>
<th>Cardiac</th>
<th>Other conditions</th>
</tr>
</thead>
<tbody>
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<td>Anomalous Pulmonary venous return:Complete or Partial</td>
<td>Surfactant Protein-B Deficiency</td>
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<td>RDS</td>
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<tr>
<td>Pulmonary Hypoplasia</td>
<td><em>RV Dysfunction</em></td>
<td>Chronic Asphyxia</td>
</tr>
<tr>
<td>Pulmonary Sequestration</td>
<td><em>LV outlet obstruction</em></td>
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*RV Dysfunction* and *LV outlet obstruction* indicate specific types of cardiovascular malformations.
Workup of NB with Hypoxic Respiratory failure

• History and Physical exam
• Hyperoxia test (pre and post-ductal PaO₂ &/or SaO₂)
• ? Hyperoxia - Hyperventilation test
• Echocardiogram: R/O cyanotic CHD, assess cardiac function
• CBC with differential & platelet counts, CRP, Blood culture
• Blood sugar, serum calcium, electrolytes
• X-ray chest
HRF is a clinical syndrome that occurs in diverse settings that can include a wide spectrum of diseases, including but not limited to these 4 examples.

HRF can occur in infants with meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS), idiopathic persistent pulmonary hypertension of the newborn (PPHN), and congenital diaphragmatic hernia.1-4

<table>
<thead>
<tr>
<th>Meconium Aspiration Syndrome</th>
<th>Respiratory Distress Syndrome</th>
<th>Idiopathic PPHN</th>
<th>Congenital Diaphragmatic Hernia</th>
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<tr>
<td>Airway obstruction with gas trapping</td>
<td>Acute lung injury</td>
<td>No underlying lung disease</td>
<td>Lung hypoplasia</td>
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<tr>
<td>Surfactant inactivation</td>
<td>Surfactant deficiency or inactivation</td>
<td></td>
<td>Decreased vascular surface area</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Pulmonary edema, volume loss</td>
<td></td>
<td>Increased pulmonary artery muscularity</td>
</tr>
</tbody>
</table>

PPHN = persistent pulmonary hypertension of the newborn.

Images courtesy of John P. Kinsella, MD, and Steven H. Abman, MD.

References
Pathophysiology of HRF: The Cardiopulmonary Triad

- Lung disease
  - Low 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

Kinsella JP. *Early Hum Dev.* 2008;84:709-716.

Whatever the specific disease, HRF can involve the following 3 distinct but overlapping areas of pathophysiology:

- Airway and pulmonary parenchymal abnormalities
- Cardiac dysfunction
- Pulmonary vascular disorders

While some cases of HRF are attributable to just one area of dysfunction—cardiac, lung, or pulmonary vascular disease—most cases of hypoxemia will involve an interplay of these mechanisms at any given time. Moreover, the contribution of each of these mechanisms may change over time. Therefore, clinicians should continually reassess the underlying pathophysiology and adjust treatment accordingly.

References
HRF in Newborns: Pathophysiology

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

Features of HRF may include:

- Intrapulmonary shunting, in which arterial blood reaches the pulmonary venous side without passing through ventilated areas of the lung
- Extrapulmonary shunting, typically seen in PPHN, in which blood bypasses the lung through so-called fetal channels of the ductus arteriosus and/or the foramen ovale
- Ventilation–perfusion (V/Q) mismatch, which can occur in both situations and involves an imbalance between ventilation and perfusion, such as when there is alveolar hypoxia and increased dead-space ventilation

As noted earlier, patients may have more than 1 contributing cause to their HRF.

Reference
This slide illustrates the complex relationship between the lung, the heart, and the pulmonary vasculature in hypoxic respiratory failure, and how they are interrelated.¹

Disturbances in hypovolemia, cardiac performance, and increased vascular resistance may compromise the balance between pulmonary and systemic circulation.¹

For example, in an infant with lung disease, hypoxia and resultant acidosis may have negative effects on the pulmonary vasculature as well as on the heart. In combination, this can worsen the relationship of pulmonary vascular resistance (PVR) to systemic vascular resistance (SVR), leading to extrapulmonary right-to-left shunting at the patent ductus arteriosus (PDA) or the foramen ovale (FO). Similarly, a poorly functioning heart can lead to acidosis, vasoconstriction, and altered shunting.²

Reference
Treatment of Neonatal HRF

• Lung: optimize lung recruitment, 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

References

There are 3 pathophysiologic components that can play a role in the development of HRF—lung, cardiac, and pulmonary vasculature disorders—so treatment should be targeted at correcting the underlying disorder.
While optimizing lung volume is the first step in recruiting the lung, care must be taken to achieve atelectasis reversal without causing overdistention. Indeed, extremes of overinflation and underinflation must be avoided, as they alter autonomic tone and increase PVR.

Increases in PVR and pulmonary artery pressure associated with hyperinflation impede right ventricular ejection. Moreover, in what has been called the zone of overdistention, lung injury can occur as a result of edema from fluid accumulation, surfactant degradation, high oxygen exposure, and mechanical disruption.

Reduction in lung volume precipitates hypoxia and stimulates increased vasomotor tone by hypoxic pulmonary vasoconstriction. Additionally, lung injury can result from direct trauma of repeated closure and reexpansion of airways and alveoli, stimulation of the lung’s inflammatory response, inhibition of surfactant, and the effects of local hypoxemia and compensatory overexpansion of the rest of the lung as the lung “shrinks.”

References
1. Froese AB. High frequency oscillatory ventilation for adult respiratory distress syndrome: let’s get it right this time! Crit Care Med. 1997;25:906-908.
The bottom line is that PVR can increase at both low and high lung volumes and thus ventilator strategies should seek to avoid these extremes. Both conditions can lead to progressive lung injury that arises not from the disease itself but from well-intentioned interventions.

References
1. Froese AB. High frequency oscillatory ventilation for adult respiratory distress syndrome: let’s get it right this time! *Crit Care Med.* 1997;25:906-908.
Role of INOMAX® (nitric oxide) for Inhalation in the Treatment of Neonatal HRF

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.

CONTRAINDICATION

• INOMAX should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood.


SPEAKER: THIS SLIDE MUST BE SHOWN.

In neonates with persistent hypoxemia, INOMAX® can play a therapeutic role. INOMAX for inhalation, 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 (HRF) associated with clinical or echocardiographic evidence of pulmonary hypertension (PHT). The use of INOMAX in this setting improves oxygenation and reduces the need for extracorporeal membrane oxygenation (ECMO).

INOMAX should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood.

Reference
Inhaled Nitric Oxide Causes Selective Pulmonary Vasodilation

This slide illustrates how inhaled nitric oxide causes pulmonary vasodilation. Inhaled nitric oxide enters the alveolus with inspired air. Nitric oxide molecules diffuse into the vascular smooth muscle adjacent to pulmonary arterioles where they activate soluble guanylate cyclase (sGC). Because the vasodilatory effects of inhaled nitric oxide are limited to the arterioles adjacent to the alveoli where it has penetrated, it is a selective pulmonary vasodilator without the risk of systemic hypotension.

Note to speaker: Point to the air space between the alveolus and the arteriole when describing the process by which nitric oxide is released from the alveolus and penetrates the smooth muscle cells of the arteriole.

References
INOMAX® Phase III Studies for Neonatal HRF

- Clinical Inhaled Nitric Oxide Research Group (CINRGI)

- Neonatal Inhaled Nitric Oxide Study Group (NINOS)

- I-NO/PPHN Study Group (INOT 01/02)

Speaker: Slides 20-26 must be shown together or not at all.

INOMAX® was studied in 3 Phase III studies in infants with HRF. The following slides discuss the design and results of these studies.

References
CINRGI: Study Design

- Randomized, double-blind, placebo-controlled, multicenter trial\(^1,2\)
- Patients: 186 term/near-term infants (≥34 weeks gestation) with HRF and PPHN\(^1,2\)
- Dosing: 20 ppm, weaned to 5 ppm\(^1,2\)
- Objective: to reduce the need for ECMO\(^1,2\)


Speaker: Slides 20-26 must be shown together or not at all.

The CINRGI trial was a double-blind, randomized, placebo-controlled, multicenter trial in term and near-term neonates with persistent pulmonary hypertension and hypoxic respiratory failure. INOMAX\(^\circledR\) was dosed initially at 20 ppm, and weaned to 5 ppm. The primary objective was to determine whether INOMAX would reduce the need for extracorporeal membrane oxygenation support in these patients. Note: The population of 186 represents the efficacy population that was the basis for approval.

**References**

There was a significant reduction in ECMO in infants treated with INOMAX®, compared with control infants (31% vs 57%, \(P<0.001\)). The incidence of death alone was similar in both groups (3% INOMAX vs 6% placebo).

After the administration of INOMAX, there was a significantly greater decrease in the alveolar/arterial oxygenation gradient compared with infants in the control group (\(P<0.001\)).

References
NINOS: Study Design

• Randomized, double-blind, placebo-controlled, multicenter trial\textsuperscript{1,2}
• Patients: 235 term/near-term infants (>34 weeks gestation) with HRF\textsuperscript{1,2}
• Dosing: 20 ppm, with possible increase to 80 ppm\textsuperscript{1,2}
• Objective: to reduce mortality and/or the need for ECMO\textsuperscript{1,2}


Speaker: Slides 20-26 must be shown together or not at all.

The NINOS trial was a double-blind, placebo-controlled, multicenter study in 235 neonates with HRF who were unresponsive to conventional therapy. INOMAX was dosed at 20 ppm, with a possible increase to 80 ppm. The objective was to determine if inhaled NO therapy would reduce the occurrence of death and/or the initiation of ECMO in term and near-term infants who had HRF that was unresponsive to conventional therapy.

References
There was a significant reduction in death and/or ECMO in infants treated with INOMAX®, compared with control infants (46% vs 64%, \( P=0.006 \)). This significance was driven by the reduction of ECMO. The incidence of death alone was lower in the INOMAX patients, but did not achieve statistical significance.¹

After the administration of INOMAX, there was a significantly greater decrease in the alveolar/arterial oxygenation gradient, compared with infants in the control group (\( P<0.001 \)).²

**References**

**INOT 01/02: Study Design**

- Randomized, double-blind, placebo-controlled, multicenter, dose-ranging trial
- Patients: 155 term infants (≥37 weeks gestation) with HRF and PPHN
- Dosing: 5 ppm, 20 ppm, and 80 ppm
- Objective: to reduce the PPHN Major Sequelae Index (incidence of death, ECMO, neurologic injury or BPD)
- Study was terminated prematurely due to slow enrollment
  - No efficacy conclusions can be drawn


The INOT 01/02 studies were conducted as a randomized, double-blind, placebo-controlled, dose-ranging clinical trial from April 1994 to June 1996. Patients received INOMAX® at doses of 0 (placebo), 5, 20, or 80 ppm. The study was ended prematurely after only 155 patients were enrolled (320 were sought) due to slow enrollment. Because of the early termination, no efficacy conclusions can be drawn. Only the control and 20-ppm treatment groups (n=75) are included for comparison with the 20-ppm groups from the other trials.

**Reference**

Safety Outcomes From Phase III Studies

• Results from NINOS and CINRGI studies:
  – Combined mortality: placebo (11%); INOMAX (9%)
  – 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: INOMAX (n=278); control (n=212)
    • No differences in pulmonary disease or neurological sequelae, or in the need for rehospitalization or special medical services


Speaker: Slides 20-26 must be shown together or not at all.

There were no significant differences between the groups after randomization in the overall incidence or severity of intracranial hemorrhage (total number, 19 in the control group and 18 in the nitric oxide group; grade IV, 8 and 5, respectively).

Neither were there any significant differences between the control group and the nitric oxide group in the occurrence of periventricular leukomalacia (6 vs 3), brain infarction (7 vs 7), seizures requiring anticonvulsant therapy (16 vs 24), and either pulmonary (4 vs 6) or gastrointestinal (1 vs 1) hemorrhage.

When the results from both controlled studies (325 patients on INOMAX® doses of 5 to 80 ppm and 251 patients on placebo) were pooled, combined mortality was 11% for placebo and 9% for INOMAX.

At least 6 months of follow-up are available for 278 patients who received INOMAX and 212 patients who received placebo in the pooled trials. Among these patients, there were no differences in pulmonary disease or neurological sequelae, or in the need for rehospitalization or special medical services.

References
When Is the “Right Time” to Initiate INOMAX®?

Use of oxygenation index (OI) in term and near-term neonatal HRF
• Compares the level of ventilator support (FiO\textsubscript{2} 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} = (0.60 \times 15 \times 100)/50 = 18 \text{ OI}]

The oxygenation index was developed as a prognostic tool to estimate the severity of neonatal pulmonary disease.

References
Additional Studies to Address Earlier INOMAX® Use In Infants With HRF


Three additional studies have recently been published that can shed some light on when to initiate INOMAX®. Golombek et al used pooled data from the INOMAX Phase III trials to compare results across disease severities (measured by OI). González et al and Konduri et al performed randomized controlled trials using INOMAX in infants with mild-to-moderate HRF.
A study published in 2004 also looked at early iNO use and tried to determine whether early iNO administration results in additional reduction of the incidence of ECMO or death. Konduri et al was a prospective, randomized, double-masked, multicenter trial that planned to enroll 400 infants with respiratory failure that needed assisted ventilation. Infants were required to have an OI between 15 and 25 and be on at least 80% oxygen.

After randomization, infants were initiated with 5 ppm of iNO or a simulation. The dose could be increased to 20 ppm if the increase in PaO\textsubscript{2} was less than 20 mm Hg. Nitrogen was used to pressurize the INOvent® in control infants, but was not injected into the breathing circuit. Mock adjustments were made to the INOvent in these infants.

Infants in both groups were transitioned to standard iNO if HRF progressed from moderate to severe (OI reached 25), which means they eventually could receive the benefits of iNO if needed.

iNO as standard therapy is defined as being consistent with practice based on previous randomized trials (prior to July 1998), including initiation of iNO at an OI of 25 or more and dose of 20 ppm.

Due to slow enrollment, the study was stopped prematurely after 302 infants were enrolled (3 were excluded due to cardiac malformations).

Reference
The primary outcome, death by day 120 or need for ECMO was similar between groups, 19.5% of the control group and 16.7% of the iNO group ($P=0.53$).

There are a few factors that may have contributed to this similarity.

1. Infants were monitored very closely and transitioned to standard iNO therapy rapidly after reaching an OI of 25. This could have happened before the primary endpoint of death or ECMO was reached.

2. The 19.5% incidence in the control group is about half as high as the projected incidence based on the authors’ pilot study in 1997. Also, the overall incidence of the primary outcome was 18.1%, which is lower than all previous randomized trials.

3. The average baseline OI in this study was 19.5.

Reference
## Konduri et al: Additional Outcomes

### Secondary Outcomes

<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</td>
<td>61 (41%)</td>
<td>81 (54%)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Duration of standard iNO therapy†</td>
<td>121 (41-175) hours</td>
<td>100 (56-158) hours</td>
<td>0.52</td>
</tr>
<tr>
<td>Progression of OI &gt;40</td>
<td>11 (7%)</td>
<td>21 (14%)</td>
<td>0.056</td>
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</tbody>
</table>

* Mean ± standard deviation. † Median with first to third quartile ranges in parentheses.

More infants in the early iNO group had >20 mm Hg increase in PaO₂ in response to study gas initiation compared with the control group (P<0.001)
- 73% of early iNO infants
- 37% of control infants

When we look at oxygenation parameters, we see clear separation between the two groups. 73% of infants receiving iNO had at least a 20 mm Hg increase in PaO₂ compared to 37% of control infants (P<0.001).

Also, more than half of control infants (54%) reached an OI of 25 and were transitioned to standard iNO therapy versus 41% of early iNO infants (P<0.02). Infants in the control group progressed to standard iNO therapy and to OI >40 more than early iNO infants (14% vs 7%), although this was not statistically significant, (P=0.056.)

The authors conclude: “Although we were unable to demonstrate a significant decrease in the incidence of ECMO/death with our study design, providing low-dose (5-20 ppm) iNO to neonates earlier in their disease process was apparently safe and effective in improving oxygenation.”

iNO as standard therapy is defined as being consistent with practice based on previous randomized trials (prior to July 1998), including initiation of iNO at an OI of 25 or more and dose of 20 ppm.

### Reference
None of the study infants had study gas weaned or discontinued because of elevated methemoglobin or NO₂ 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%) \((P=0.68)\).

Reference
Since the published literature does not provide conclusive evidence of a relationship between severity of illness and response to INOMAX® therapy, a retrospective pooled analysis of the 3 largest INOMAX clinical trials was undertaken.

The objectives of this analysis were:

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

For the purposes of this analysis, only those subjects who received 20 ppm INOMAX, regardless of the underlying diagnosis, were compared with similar placebo-treated patients.

Reference
By improving perfusion, INOMAX® delivers a rapid increase in oxygenation. The blue bars represent ventilation alone, while the red bars represent ventilation plus INOMAX. In each of these 3 NDA-submitted studies, INOMAX significantly improved PaO$_2$ within 30 minutes versus ventilation alone.

Reference
However, it was interesting to see that there was a similar benefit when the analysis also included infants with mild to moderate HRF (OI ≤25). These data indicate that INOMAX® improves oxygenation across all levels of severity (including mild and moderate) versus ventilation alone.

It has been known for a long time that INOMAX improves oxygenation in neonates with severe HRF, but this retrospective analysis indicates that it also improves oxygenation in neonates with mild and moderate HRF.

Reference
This is a Kaplan-Meier analysis of pooled data from 3 independent controlled studies, NINOS, CINRGI, and INOT 01/02. Adding INOMAX® shortened the median time on ventilation. Within this pooled data, at the point that 50% of patients were off therapy, the INOMAX patients had a savings of 3 ventilator days (11 vs 14 days) \((P=0.003)\).

NOTE: Patients who died or went to extracorporeal membrane oxygenation were excluded from the analysis as their inclusion would have falsely skewed the data in favor of placebo.

Reference