The Forgotten Fragile—Oxygen Toxicity in the Term Infant

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The speaker has signed a disclosure form and indicated he has no significant financial interest or relationship with the companies or the manufacturer(s) of any commercial product and/or service that will be discussed as part of this presentation.

Session Summary

Often times, clinicians are less concerned about the risks of high FiO2 in term neonates. Evidence supports more aggressive management at an earlier point in the clinical case.

Session Objectives

Upon completion of this presentation, the participant will be able to:

- discuss the clinical problem of acute hypoxic respiratory failure (HRF) in newborns;
- describe treatment of HRF from a physiologic approach;
- describe the role of inhaled nitric oxide in the treatment of HRF.

References


**Session Outline**

See presentation handout on the following pages.
Oxygen Toxicity and Hypoxic Respiratory Failure in Term and Near-Term Neonates

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Outline
• Acute Hypoxic Respiratory Failure (HRF) in Newborns: The Clinical Problem
• Physiology of HRF
• Oxygen Toxicity
• Avoidance of Prolonged High O2 - Mechanical
• Avoidance of Prolonged High O2- Chemical

Changes in PVR and SVR during the last half of gestation and postnatally

Mechanism of endothelium-dependent pulmonary vasodilation at birth
Konduri et al. Advances in the Diagnosis and Management of PPHN. Ped Clin N Am 2009 June;56(3)579-602.

Physiology
• External respiration of room air (0.21%)
  – transfer oxygen molecules from the atmosphere to blood
• Blood oxygen transport
  – movement of oxygen from blood to the site of intracellular utilization
• Internal respiration
  – oxygen consumption
Factors Influence Move Of Oxygen From The Air Into The Blood

- Fraction of inspired oxygen
- Distribution of ventilation
- Alveolar gas exchange
- Mixed venous-oxygen

**Hemoglobin Oxygen Dissociation Curve**

Factors Influencing Oxygen Affinity

- The delivery of oxygen to tissue
- Dependent on
  - Partial pressure of alveolar oxygen (PAO₂)
    - \( F_iO_2(P_{aw}-P_{H_2O}) - P_{ACO_2} \)
  - Lung volume and V/Q matching
  - Cardiac function
    - Output
      - Heart rate
      - Ejection volume
    - \( O_2 \) content = 1.36*Hgb*O₂sat + 0.003*PatO₂

Oxygenation

Hypoxic Respiratory Failure in Term and Near-Term Neonates

Basically, when “non-preterm” babies require supplemental O₂ in the Newborn Period

Important Points

- The antecedents of lung injury begin in utero
  - Inflammation
    - Chorioamnionitis
  - Maternal periodontal disease
  - Mechanical issues
    - Compression (diaphragmatic hernia)
    - Allowed lung fluid (renal problems)
    - Abnormal fetal breathing (neurological problems)
  - Lung immaturity
    - Structural (alveolarization)
    - Mechanical (chest wall)
    - Biochemical (surfactant, proteins, antioxidants)
- Neonatal lung injury begins in the delivery room
- Optimizing cardiopulmonary support reduces lung injury
- Lung injury can alter future lung growth
Pathologic changes in pulmonary circulation in neonatal HRF

![Image](https://example.com/pathologic_changes.png)

Hemodynamic changes in PPHN/HRF

![Image](https://example.com/hemodynamic_changes.png)

**Shunt Physiology**

- Pulmonary shunt is a physiological condition which results when the alveoli of the lung are perfused with blood as normal, but ventilation (the supply of air) fails to supply the perfused region.
- The ventilation/perfusion ratio (the ratio of air reaching the alveoli to blood perfusing them) is zero.
- Pulmonary shunt occurs when the alveoli fill with fluid, causing parts of the lung to be unventilated although they are still perfused.
- Intrapulmonary shunting is the main cause of hypoxemia (inadequate blood oxygen) in pulmonary edema and conditions such as pneumonia in which the lungs become consolidated.

**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

  - Mortality\(^1\): 9.9% to 14.5%

  - Morbidities include neurodevelopmental abnormalities, cognitive delay, and a high rate of chronic diseases of the Lung and other organs, learning disabilities, and sensorineural hearing loss\(^2,3\)

**HRF in the Newborn: A Persistent Challenge**

- 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 diseases of the Lung and other organs, learning disabilities, and sensorineural hearing loss\(^2,3\)

\(^1\)As measured by overall rate of mechanical ventilation.
# HRF in the Newborn: A Persistent Challenge

- A clinical condition which challenges us to provide the least risky strategy **PHYSIOLOGICALLY** to improve the relative deficiency of oxygen.
- In the current day, **HOW MANY OF THE OUTCOMES of HRF ARE RELATED TO DECISIONS WE MAKE ABOUT COST OVER CLINICAL CONCERNS.**

## Pathophysiology of HRF: By Etiology—It’s a 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

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### HRF in Term & Near-Term Newborns: Some Commonly Occurring Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meconium Aspiration Syndrome</td>
<td>Acute lung injury and surfactant dysfunction</td>
</tr>
<tr>
<td>Respiratory Distress Syndrome</td>
<td>Surfactant deficiency or inactivation, pneumonia, lung disease</td>
</tr>
<tr>
<td>Idiopathic PPHN</td>
<td>Pulmonary edema, volume loss</td>
</tr>
<tr>
<td>Congenital Diaphragmatic Hernia</td>
<td>Lung hypoplasia, decreased vascular surface area, 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.

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### HRF in Newborns: Deeper Look at the 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 hypoaxia, increased dead-space ventilation

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### Intrapulmonary Shunt and V/Q Mismatch

![Intrapulmonary Shunt and V/Q Mismatch](image-url)
Extrapulmonary Right-to-Left Shunt Driven by High Pulm Vasc Pressures

Extra-Pulmonary (Cardiac) Shunt with even mild Atelectasis = V/Q Mismatch

Cardiopulmonary Interactions in Neonatal HRF- Usually parts of all 3


FO = foramen ovale; LV = left ventricular; PDA = patent ductus arteriosus; PVR = pulmonary vascular resistance; RV = right ventricular; SVR = systemic vascular resistance.
Treatment of Neonatal HRF

• Lung: optimize lung recruitment, ventilation
  – Whether adjusting the Conventional ventilator or changing to High Frequency, remember that these are the tools. They require the knowledgeable carpenter. Also damage can be done if too much of any one thing is pushed.
  – Address the potential co-variable problems or other causes of poor ventilation
  – (eg Fighting the vent, Large airway Obstruction)
• 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


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

• Extremes of lung volume cause damage and contribute to high PVR
• Greenhalgh JM, Kinsella JP. Early Hum Dev. 2008;84:709-716.

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

Mismatched low inflation to perfusion

Mismatched high inflation with low perfusion

Matched inflation/perfusion (V/Q ~ 1)

• Poor ventilation despite perfusion produces hypoxemia
  – Intrapulmonary shunting

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

• Adequate ventilation with perfusion optimizes oxygenation
  – V/Q matching occurs

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

PVR Can Increase at Low and High Lung Volumes

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

- Lung: optimize lung recruitment, ventilation
- Heart: enhance cardiac function (treat acidosis and use inotropes) and increase 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


Caring for the Baby’s Baby Lung

- Baby’s lung sitting on top of a consolidated lung
  - Tidal volumes of 6 to 10 ml/kg based on weight
  - Tidal volumes of 18 to 30 ml/kg based on open lung units

It’s easy to go from Low to High Lung Volumes, so why not Treat PVR Earlier

PVR

Lung Volume

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

Treatment of Neonatal HRF

- Increasing FiO2 has been the accepted standard for so long that many new clinicians have forgotten the Outcomes of Pre-ECMO period where 100% FiO2 was all we had.
- Some survivors had scars from massive ventilation approaches.
- Perhaps more suffered from the effects of >80% FiO2 for 3 Hours or more.


“decision-making schizophrenia”

What else can you try?

This is how it really seems to look!

Underinflation in one Segment—which is about to go to Overinflation in another. Both will Create MORE V/Q Mismatching

Underventilated portion of lung
- Decreased PaO₂
- Increased pulmonary artery pressure and decreased blood flow

If get Overinflation
Will get Decrease O₂
Increased PVR
Decreased Flow

PA = pulmonary artery; PV = pulmonary vein.

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

- Extremes of lung volume contribute to high PVR
  - High lung volume ventilation overdistends, resulting in volutrauma
  - Low lung volume ventilation tears adhesive surfaces

Primary/Sec Pulm Htn or Heart Dysfunction Creates V/Q Mismatching by Affecting Perfusion

Pulm Vascular Congestion
Inadequate Perfusion from Hrt Pump issue
Increased pulmonary artery pressure and decreased blood flow

With that much to consider, no wonder the first thing people think about is using MORE OXYGEN in Hypoxic Respiratory Failure for Term and Near-Term Neonates

Many times the clinician uses FIO₂ > 80% before really giving consideration to the preceding physiology considerations.
Once Upon a Time...Severe Hypoxic Respiratory Failure in Term and Near-Term Neonates simply meant turn up the FiO2 and do what you could.

If that didn’t work.... Transfer to an ECMO Center

Inhaled Nitric Oxide

In the mid 90’s, a few select centers were granted FDA permission to use iNO in a “compassionate use” indication.

The USF Neonatal Division was one of those centers.

EVERYTHING WAS ABOUT TO CHANGE!

*Please see sales representative to find out if your ventilator is compatible.

Effect of inhaled NO on the pulmonary circulation

Konduri et al. Advances in the Diagnosis and Management of PPHN. Ped Clin N Am 2009 June;56(3)579-602.

Nitric Oxide Reduces V/Q Mismatching by changing Pulm Vasc Tone

INo increases vasodilation
- Decreases pulmonary artery pressure
- Increases PaO2 and blood flow in better ventilated regions
- Improves V/Q ratios in neonates with HRF


Nitric Oxide 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)


Effect of inhaled NO on the pulmonary circulation

Konduri et al. Advances in the Diagnosis and Management of PPHN. Ped Clin N Am 2009 June;56(3)579-602.
Inhaled Nitric Oxide Phase III Studies for Neonatal HRF

<table>
<thead>
<tr>
<th>Objective</th>
<th>CINRGI¹,²</th>
<th>NINOS²,³</th>
<th>I-NO/PPHN²,⁴</th>
</tr>
</thead>
<tbody>
<tr>
<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>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Design</th>
<th>186 term/near-term infants (&gt;34 weeks) with HRF and PPHN</th>
<th>235 term/near-term infants (≥24 weeks) with HRF and PPHN</th>
<th>155 term infants* (≥237 weeks) with HRF and PPHN</th>
</tr>
</thead>
<tbody>
<tr>
<td>iNO Dose</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>


NINOS: Efficacy Outcomes

**Primary Outcome**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (%)</th>
<th>INOMAX (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Secondary Outcome**

<table>
<thead>
<tr>
<th>30-Minute Change From Baseline (mm Hg)</th>
<th>Placebo</th>
<th>INOMAX</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA-aO₂ (A:a gradient)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P=0.014</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


NINOS, NEJM, 1997  
CINRGI, NEJM, 2000  
Davidson, Peds, 1998

Safety Outcomes From Phase III Studies

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


Role of INHALED NITRIC OXIDE in the Treatment of Neonatal HRF

**INDICATION**

- Nitric Oxide 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**

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


The results from the Phase III Studies gave us the approval of Nitric Oxide for Hypoxic Respiratory Failure.

Many experts were recommending initiation at an Oxygenation Index of ≥25 with ECMO @ 40
This left us with the next Question:
When Is the “Right Time” to Initiate Nitric Oxide?

Additional Studies to Address When to Use Nitric Oxide In Infants With HRF


Konduri et al: 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 FiO2 ≥0.80
- Dosing: iNO initiated at 5 ppm or simulated (sham) dose
  - Dose increased to 20 ppm if the increase in PaO2 was ≤20 mm Hg
  - Infants in either group were transitioned to standard iNO if OI increased to ≥25
- Objective: To determine whether earlier iNO administration results in additional reduction of the incidence of ECMO or death. (Primary Outcome)

Konduri et al: Preface to the Results

- Patient Enrollment:
  - The trial was halted by investigators after 3 years because of persistent decline in enrollment.
  - The decline in ECMO patients fell to approximately half of the projected incidence on the basis of the 1997 pilot data.
- The outcomes weren’t known prior to terminating the trial. This was validated by NICHD.

Konduri et al: 1° Outcome- Death/ECMO

- “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.”
- “iNO improved 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.”
Konduri et al: \(O_2\) 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 (OI &gt;25)</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>
</tr>
</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 \(PaO_2\) in response to study gas initiation compared with the control group \((P<0.001)\):
  - 73% of early \(iNO\) infants
  - 37% of control infants


Konduri et al: Safety

- None of the study infants had study gas weaned or discontinued because of elevated methemoglobin or NO\(_2\) 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%) \((P=0.68)\)


Golombek et al: Study Design (Pooled Data)

- **Methods**
  - A retrospective pooled analysis of all subjects receiving 20 ppm inhaled nitric oxide in the CINRGI, NINOS, and I-NO/PPHN Phase III trials
  - No censoring based on underlying diagnosis or baseline characteristics
- **Objectives**
  - To analyze the effects of Nitric Oxide on measures of oxygenation
  - To analyze the effects of Nitric Oxide across a range of illness severity strata
  - To analyze the effects of Nitric Oxide on the duration of mechanical ventilation


Golombek et al: Oxygenation Results

- Nitric Oxide causes rapid improvement (at 30 min) in oxygenation


- Nitric Oxide improves oxygenation even in mild and moderate HRF

Golombek et al: Time on Vent Results

- Nitric Oxide 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 INOT 01/02 (P=0.24). Outliers are removed for visual purposes.


Konduri et al. Advances in the Diagnosis and Management of PPHN. Ped Clin N Am 2009 June;56(3)579-602.


3rd New Study (ECMO required a Transfer): González et al: Study Design

- Prospective, randomized, controlled, open-label, multicenter 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)


Effect of OI at initiation of INO on incidence of ECMO and death

González et al: Treatment Failure Outcomes

- INO significantly decreased the probability of developing severe disease as shown by the primary endpoint, treatment failure

González et al: OI Outcomes

- INO significantly reduced OI over time in infants with mild to moderate HRF

González et al: Safety

- Patients treated with iNO did not have elevated blood levels of methemoglobin or high levels of NO₂ 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

Nitric Oxide Dosage and Administration

- Recommended starting dose = 20 ppm
  - Risk of methemoglobinemia and elevated NO₂ levels increases significantly at doses >20 ppm
  - Clinical trials dosing (CINRGI):
    - If oxygenation improved at 20 ppm, dose reduced to 5 ppm as tolerated at end of 4 hours of treatment
  - Clinical trial dosing (NINOS):
    - Dose increase to 80 ppm permitted if no improvement at 20 ppm, however, no improvement was seen at 80 ppm
- Infants who cannot be weaned from Nitric Oxide by 4 days should undergo careful diagnostic workup for other diseases
- When FiO₂ is <60% and PaO₂ is >60, support can be safely weaned if there is no increase in FiO₂ of >15%

Important Safety Information When Using Nitric Oxide—Contraindication

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

Important Safety Information When Using Nitric Oxide—Precautions

- Rebound
  - Abrupt discontinuation may lead to worsening oxygenation and increasing pulmonary artery pressure (PAP)
- Methemoglobinemia
  - Increases with dose of Nitric Oxide
- Elevated NO₂ levels
  - Increase with Nitric Oxide dose and FiO₂
  - Inspired NO and NO₂ levels should be monitored using a device with an alarm
  - The delivery system used to provide Nitric Oxide:
    - Should allow operator-determined, constant concentration of NO in the breathing gas
    - Should not cause excessive generation of inhaled NO₃
- Pre-existing left ventricular dysfunction
  - Nitric Oxide may increase pulmonary capillary wedge pressure leading to pulmonary edema

Methemoglobin Levels

- Nitric Oxide (ppm): 80 20 5.0 Control

Common Causes of Response Failure to iNO.

Question:
Where have subsequent discussions led us?

Konduri discussed his Results when asked at a dinner meeting in 2011.

- “iNO improved oxygenation but did 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.”

- The group consensus was to look harder at the Subgroup Analysis of the 04 paper.

Konduri et al: 1° Outcome- Death/ECMO in the FIRST paper.

“iNO improved oxygenation but does not reduce the incidence of ECMO/mortality when initiated at an OI of 15-25 compared with initiation at >25 in term and near-term neonates with respiratory failure.”

Konduri et al: 1° Outcome- Death/ECMO Subgroup Analysis

*The primary outcome observed in the EARLY group with inhaled Nitric Oxide started at 15-19.9 had a 41% reduction in Need for ECMO or Death

Konduri Subgroup Analysis

- For babies enrolled at OI>20, early INO decreased progression to OI>30 or death/ECMO (early INO 29%, controls 56%, p<0.01).
- Stepwise log regression analysis showed that OI at enrollment >20 (OR 1.89, CI 1.02-3.54), diagnosis of PPHN relative to RDS (OR 3.92, CI: 1.19-17.81) and no surfactant therapy (OR 1.85, CI 0.99-3.47) were independently associated with death/ECMO.

NINOS: FDA Wasn’t Looking For Less O2

?? Inflammation and O2 Toxicity ??

Secondary Outcome

The FDA was Primarily interested in prevention of Death as an Outcome

*Primary outcomes.
2. The Neonatal Inhaled Nitric Oxide Study Group; Pediatrics. 1997;91:597-604

A3b: OXYGEN TOXICITY IN THE TERM INFANT
**Question?**

What is known about the impact of early iNO on Oxidative Stress?

That requires that we understand Oxidative Stress and Oxygen Toxicity in Hypoxic Respiratory Failure in Term and Near-Term Neonates

Certainly, much has been made of the same concerns in PRETERM INFANTS

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**Factors Influencing Oxygen Affinity**

![Graph showing factors influencing oxygen affinity](image1)

**Oxygenation**

- The delivery of oxygen to tissue
- Dependent on
  - Partial pressure of alveolar oxygen (PAO₂)
  - \( \text{FiO}_2 \) (\( P_{\text{atm}} - P_{\text{H}_2\text{O}} \)) - PACO₂
  - Lung volume and V/Q matching
  - Cardiac function
    - Output
      - Heart rate
      - Ejection volume
    - \( O_2 \) content = 1.36*Hgb*O₂sat + 0.003*PaO₂

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**Oxygen Toxicity**

- Even short-term exposure to a high FiO2 can generate reactive oxygen and nitrogen species
GSSG/GSH ratio × 100 in cord blood on days 1 and day 3 in ELGANs resuscitated with initial FiO2 of 90% (high-oxygen [Hox] group) or 30% (low-oxygen [Lox] group).

TNF-α (A) and IL-8 (B) levels in plasma, as determined through flow cytometry, during weeks 1, 2, 3, and 5 after birth in ELGANs initially resuscitated with FiO2 of 90% (high-oxygen [Hox] group) or 30% (low-oxygen [Lox] group).

Study Design

- Patients: 60 Term infants (>37 weeks gestation) with HRF who were ALL TREATED WITH NITRIC OXIDE for Echo proven PPHN

  | FiO2 Tx 1: | 45% | Variable Vent Settings |
  | FiO2 Tx 2: | 80% | Variable Vent Settings |

Outcome:

Measured Inflammatory Indices
### Methods

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>20ppm iNO @ 45%</td>
<td>20ppm iNO @ 80%</td>
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</table>

Blood drawn at:
- Start (Time 0), 1 day, and 3 days

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### Results

#### Ox Index

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (low O2)</th>
<th>Group 2 (high O2)</th>
<th>p</th>
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<tbody>
<tr>
<td>T 0-</td>
<td>40</td>
<td>42</td>
<td>NS</td>
</tr>
<tr>
<td>1 d</td>
<td>24.3</td>
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<tr>
<td>2 d</td>
<td>14.3</td>
<td>18.5</td>
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Both had OI improvement

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#### IL-6

<table>
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<tr>
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<th>Group 1 (low O2)</th>
<th>Group 2 (high O2)</th>
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<tr>
<td>T 0-</td>
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Decrease | Increase
Both p < .001

---

#### IL-8

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (low O2)</th>
<th>Group 2 (high O2)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>T 0-</td>
<td>115</td>
<td>98</td>
<td>NS</td>
</tr>
<tr>
<td>1 d</td>
<td>86</td>
<td>266</td>
<td></td>
</tr>
<tr>
<td>2 d</td>
<td>56</td>
<td>672</td>
<td></td>
</tr>
<tr>
<td>3 d</td>
<td>32</td>
<td>1168</td>
<td></td>
</tr>
</tbody>
</table>

Decrease | Increase
Both p < .001

---

#### TNF alpha

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (low O2)</th>
<th>Group 2 (high O2)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>T 0-</td>
<td>14.2</td>
<td>12.0</td>
<td>NS</td>
</tr>
<tr>
<td>1 d</td>
<td>8.7</td>
<td>25.2</td>
<td></td>
</tr>
<tr>
<td>2 d</td>
<td>4.3</td>
<td>40.0</td>
<td></td>
</tr>
<tr>
<td>3 d</td>
<td>1.1</td>
<td>61.4</td>
<td></td>
</tr>
</tbody>
</table>

Decrease | Increase
Both p < .001

---

### Speculation

Never getting to FiO2 80% is better.

Inhaled Nitric Oxide may modulate pulmonary inflammatory response by downregulating the production of inflammatory cytokines and by reducing lung neutrophil accumulation.

This was previously also seen in adults when iNO studied by Chollet-Martin in Am J Respir Crit Care Med, 1996
Cardiopulmonary Targets of O2 Toxicity in Neonatal HRF- Usually parts of all 3

- High vascular tone
- Altered reactivity
- Structural disease

Lung volume
Compliance
Intrapulmonary shunt

Hypoxemia
RV pressure overload
LV dysfunction

FO = foramen ovale; LV = left ventricular; PDA = patent ductus arteriosus; PVR = pulmonary vascular resistance; RV = right ventricular; SVR = systemic vascular resistance.


HRF in the Newborn: A Persistent Challenge

- Definition: A clinical condition which challenges us to provide the least risky strategy (Vent & O2) PHYSIOLOGICALLY to improve the relative deficiency of oxygen.
- In the current day, HOW MANY OF THE OUTCOMES of HRF ARE RELATED TO DECISIONS WE MAKE ABOUT COST OVER CLINICAL CONCERNS.

Toxicity of Excess O2 in HRF in the Newborn:

- Definite effects of FiO2 > 50% are continuously recognized in animal and Adult RDS research.
- NICU directions currently challenge us to MINIMIZE exposure to more O2 than absolutely necessary for ANY Preterm Infant.
- Caspase 2 and Mitochondrial mechanisms cause Apoptosis (Brain and other cell death) as a response to O2
- VEGF incr and Oxygen free radicals kill cells

Questions?

What do surveys say about the current practice of Neo’s and NNP’s?

Survey: Oxygenation Index at which iNO should be started

<table>
<thead>
<tr>
<th>Year</th>
<th>Neo’s</th>
<th>NNP’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>29</td>
<td>-</td>
</tr>
<tr>
<td>2010</td>
<td>20</td>
<td>41</td>
</tr>
<tr>
<td>2011</td>
<td>20</td>
<td>37</td>
</tr>
</tbody>
</table>

100% FiO2- How long before trying something else?

<table>
<thead>
<tr>
<th>Time</th>
<th>Neo</th>
<th>NNP’s</th>
<th>Neo Nurses</th>
<th>RT’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 hrs</td>
<td></td>
<td>1-3hrs</td>
<td>&gt;3hrs</td>
<td></td>
</tr>
</tbody>
</table>

### 100% FiO2 - How long?

<table>
<thead>
<tr>
<th></th>
<th>Never - 1 hrs</th>
<th>1-3hrs</th>
<th>&gt;3hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neo</td>
<td>52%</td>
<td>25%</td>
<td>23%</td>
</tr>
<tr>
<td>NNP’s</td>
<td></td>
<td></td>
<td>Avg 6hrs</td>
</tr>
<tr>
<td>Neo Nurses</td>
<td></td>
<td>Avg 13hrs</td>
<td></td>
</tr>
<tr>
<td>RT’s</td>
<td></td>
<td>Avg 2.5hrs</td>
<td></td>
</tr>
</tbody>
</table>

THANK YOU