NITRIC OXIDE: 
USE IN THE NICU AND BEYOND

Bobbie Terrell, MSHA, RNC, NNP-BC
Neonatal Nurse Practitioner
VCU Health, CJW, Pediatrix

Kathy Marshall, BS, RRT-NPS
Pediatric Respiratory Therapy Clin. 4/ECMO Specialist
Respiratory Care Services
VCU Health
Richmond, VA

DISCLOSURES

I HAVE NO FINANCIAL TIES TO ANY OF THE PRODUCTS MENTIONED IN THE PRESENTATION
SOME OF THE SLIDES USED WITH PERMISSION WERE FROM MALLINKRODT IKARIA
OBJECTIVES

• PARTICIPANTS WILL BE ABLE TO DEFINE/DESCRIBE WHAT INHALED NITRIC OXIDE (INO) IS AND IT'S MECHANISM OF ACTION
• PARTICIPANTS WILL BE ABLE TO LIST POPULATIONS/DISEASE STATES RESPONSIVE TO INO
• PARTICIPANTS WILL BE ABLE TO DISCUSS INO ADMINISTRATION, DOSING, WEANING, AND ALTERNATIVE/ADJUNCT THERAPIES
• PARTICIPANTS WILL BE ABLE TO IDENTIFY TOXIC EFFECTS AND MONITORING

NITRIC OXIDE

• What is it??
• What it's not.....

• Nitrous oxide
  • Commonly known as laughing gas, nitrous, nitro, or NOS
  • Chemical compound with the formula N2O
  • Oxide of nitrogen
  • AT ROOM TEMPERATURE, IT IS A COLORLESS, NON-FLAMMABLE GAS, WITH A SLIGHTLY SWEET ODOR AND TASTE.
**Medicine vs. Poison**

- Greek word “Pharmakon” means both “medicine” and “poison.”
- ...the right dose differentiates a poison and a remedy. 
  

**What is Nitric Oxide (NO)?**

- NO is an industrial pollutant that exist in the atmosphere in concentrations of 10- 100 ppb
  - Concentrations routinely inhaled by people who smoke cigarettes are in the 400 – 1000 ppm range
- It is a colorless, nonflammable, and toxic gas
- When in contact with air it forms brown fumes
- Assumptions were that it had no useful purpose
Nitric Oxide- not just a noxious gas anymore

• As we learn more about its presence in the human body we find:
  – It is a messenger molecule produced by many types of cells in the human body
    • The common action of nitroprusside and nitroglycerin is due to their release of NO in the blood vessels
  – Some researchers believe that it is the principle regulator of blood pressure, not angiotensin and norepinephrine, as was earlier assumed
  – Some research suggests neuroprotective properties
  – May help prevent formation of thrombi by inhibiting platelet aggregation

NITRIC OXIDE

• Nitric oxide is produced in vascular endothelial cells
• Important in regulating blood pressure and blood flow to the lungs after birth
• Inhaled nitric oxide regulates vascular tone causes selective pulmonary vasodilation
• Studies have shown acute and sustained improvement with PPHN with iNO and a reduction in the need for ECMO in term and near term neonates
• iNO was FDA approved in 1999 for the treatment of hypoxic respiratory failure of newborns > 34 weeks; safety and efficacy in preterm infants has not been proven
• Use in preterm infants and other pediatric populations remains controversial
**Nitric Oxide**

- Nitric oxide and blends are used to promote capillary and pulmonary dilation to treat pulmonary hypertension
- **Mechanism of action:**
  - Relaxes smooth muscle by binding to the heme moiety of cytosolic guanylate cyclase, activating guanylate cyclase and increasing intracellular levels of cyclic-guanosine 3, 5-monophosphate leading to vasodilation
  - With inhaled nitric oxide there is minimal effect on systemic vasculature because of the efficient scavenging by hemoglobin
  - Increases PaO₂ by dilated pulmonary vessels in areas of better ventilated lung, moving away from poorly ventilated, improving ventilation to perfusion (V/Q)
PERSISTENT PULMONARY HYPERTENSION

• Common in neonates with hypoxemic respiratory failure
• Pulmonary hypertension and extrapulmonary right to left shunting across foramen ovale and ductus arteriosus
• ECMO was rescue treatment when conventional treatments failed until development of inhaled nitric oxide
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
Congenital diaphragmatic hernia

- Controlled trials of iNO for CDH have not shown reduction in need for ECMO
- Neonates with CDH have had ongoing pulmonary hypertension despite improvement in respiratory symptoms
- May have some benefit of continued low dose iNO
RESPIRATORY SUPPORT

OXYGEN THERAPY
CONVENTIONAL VENTILATION
HIGH-FREQUENCY VENTILATION
WHEN VENTILATION FAILS, THEN WHAT???

---

When Is the “Right Time” to Initiate Inhaled NO?¹,²

- 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

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

[Example: FiO₂, 0.60; MAP, 15; PaO₂, 50 torr = (0.60 × 15 × 100)/50 = 18 OI]

---

Mild | Moderate | Severe | Very Severe
--- | --- | --- | ---
0 | 15 | 25 | 40
### Inhaled NO Phase III Studies for Neonatal HRF

<table>
<thead>
<tr>
<th>Objective</th>
<th>CINRGI(^{1,2})</th>
<th>NINOS(^{2,3})</th>
<th>I-NO/PPHN(^{2,4})</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 bronchopulmonary dysplasia (BPD)</td>
<td></td>
</tr>
<tr>
<td>Design</td>
<td>186 term/near-term infants (≥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>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>

### Golombek et al: Study Design\(^1\)

**Objectives**

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

**Methods**

- A retrospective pooled analysis of all subjects receiving 20 ppm iNO in the CINRGI, NINOS, and I-NO/PPHN Phase III trials
- No censoring based on underlying diagnosis or baseline characteristics
Golombek et al: Oxygenation Results

Inhaled NO causes rapid improvement (at 30 min) in oxygenation

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

- NINOS (N=227)
- I-NO/PPHN (N=75)
- CINRG (N=186)
- All Studies (N=493)

P<0.001  P<0.001  P<0.001  P<0.001

Golombek et al: Oxygenation Results

Inhaled NO improves oxygenation even in mild and moderate HRF

Change in mean PaO₂ at 30 Minutes by Baseline OI (mmHg [kPa])

- Baseline OI = ≤15 (n=40)
- >15 to ≤25 (n=91)
- >25 to ≤40 (n=170)
- >40 (n=186)
**González et al: Study Design**

- **Objective:** to evaluate whether early treatment with iNO can prevent infants with moderate respiratory failure from developing severe HRF (OI ≥40)
- **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

---

**González et al: OI Outcomes**

*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

**Graph:**

- **Y-axis:** Oxygenation Index (10 to 40)
- **X-axis:** Time (hours: 0, 4, 12, 24, 48)
- **Legend:**
  - Early iNO
  - Control
- **Statistical Note:** *P<0.01
González et al: Treatment Failure Outcomes

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

- Placebo: 61% (n=28)
- iNO: 25% (n=28)

Treatment Failure (OI >40 within 48 hours)

P<0.05

González et al: Days on Oxygen Therapy

Early iNO significantly reduced the median time on oxygen therapy (11.5 days vs 18 days, P<0.03)

Survival plot of the probability of oxygen therapy requirement after enrollment in the trial.
INO DELIVERY SYSTEM

- INOMAX DS IR
- DELIVERS NITRIC OXIDE GAS INTO VENTILATOR BREATHING CIRCUIT IN CONSTANT CONCENTRATIONS
- PROVIDES CONTINUOUS MONITORING OF INSPIRED O2, NO2, AND NO
  - ALARMS INTEGRATED INTO SYSTEM
- BATTERY BACKUP FOR UP TO 6 HOURS
- PROVIDES 2 BACKUP DELIVERY SYSTEMS

INO DELIVERY SYSTEM

- CAN BE USED WITH 63 DIFFERENT VENTILATORS
  - CONVENTIONAL
  - INVASIVE AND NON-INVASIVE
  - HFJV
  - HFOV
  - ANESTHESIA DEVICES
INJECTOR MODULE

• WHERE THE MAGIC HAPPENS

THE REST OF IT

• A PUMP

• A BUNCH OF SENSORS
How to transition off iNO

• Once iNO is initiated and oxygenation improves, iNO is decreased gradually so that endogenous nitric oxide
• Can have rebound effects
• May need to add adjunct therapies to successfully transition off iNO
  • Sildenafil
  • Bosentan
TOXICITY

- iNO combines with oxygen to produce NO2 which is a toxic gas
- Methemoglobin is formed when NO reacts with hemoglobin
  - Methemoglobin is incapable of transporting oxygen
  - Premature infants are more susceptible to methemoglobinemia due to low levels of methemoglobin reductase
- Platelet dysfunction and bleeding problems are theoretical as iNO may affect platelet aggregation and thrombus formation

INHALED NITRIC OXIDE
BEYOND NICU

KATHY MARSHALL, BS, RRT-NPS
PEDIATRIC RESPIRATORY THERAPY CLIN. 4/ECMO SPECIALIST
RESPIRATORY CARE SERVICES
VCU MEDICAL CENTER
RICHMOND, VA
DISCLOSURES

• ALTHOUGH I WILL BE REFERENCING A PARTICULAR INHALED NITRIC OXIDE DELIVERY SYSTEM, I HAVE NO FINANCIAL TIES TO THE COMPANY AND RECEIVE ABSOLUTELY NOTHING FROM THEM.

• THIS IS THE SYSTEM I AM FAMILIAR WITH AND I PLAY THE HAND I AM DEALT

• I WILL BE DISCUSSING OFF LABEL USES
Nitric Oxide- not just a noxious gas anymore

- Cancer research suggest that it can defend against tumors
- There is promising research that NO can improve Sickle-Cell HbO2 binding lessening the severity of sickle cell crisis
- We are all aware of what NO has done of the field of erectile dysfunction

iNO

- In 1999, iNO was approved by the FDA for the treatment of hypoxic respiratory failure (HRF) of the term and near-term (>34 weeks) newborn
  - To date, this is the ONLY FDA approved use of this therapy
  - All other uses are off label
    - Has been investigated for use in primary pulmonary hypertension, sickle cell disease, heart and lung transplantation, diagnostic testing of pulmonary vascular reactivity, and for use in premature infants with RDS
AREAS OF INTEREST BEYOND NICU

- ARDS
- SICKLE CELL DISEASE
- DIAGNOSTIC USES
- TREATMENT OF PERIOPERATIVE PULMONARY HYPERTENSION
  - CONGENITAL HEART DISEASE
  - CARDIAC TRANSPLANTATION
  - LVAD INSERTION
ARDS (ACUTE RESPIRATORY DISTRESS SYNDROME)

- ACUTE ON SET RESPIRATORY FAILURE
- CXR WITH BILATERAL OPACITIES
- NON CARDIOGENIC PULMONARY EDEMA
- OXYGENATION
  - MILD: PAO2/FIO2 <300 MMHG WITH PEEP>5 CMS
    - MORTALITY 27%
  - MODERATE: PAO2/FIO2 <200 WITH PEEP>5
    - MORTALITY 32%
  - SEVERE: PAO2/FIO2 <100 WITH PEEP>5
    - MORTALITY 45%

Use of iNO in Patients with ARDS

- Multicenter, randomized, placebo-controlled study conducted in ICU's of 46 hospitals in the United States with patient enrollment between March 1996 and September 1999.
- 385 patients with moderately severe acute lung injury, with PaO2 to FiO2 ratio of <250
- Sepsis was not the cause of lung injury
- No significant nonpulmonary organ system dysfunction
iNO in ARDS

- Outcome measures was days alive off assisted breathing
- Secondary outcomes included mortality, days alive and meeting oxygenation criteria for extubation, and days alive following successful unassisted ventilation

iNO in ARDS

- Conclusion showed short-term oxygenation improvement but no substantial impact on the duration of ventilator support or mortality

JAMA, April 7, 2004
WHY???

• Patients with ARDS do not die of refractory hypoxemia but of multi-organ failure
  • The actions of ino are beneficial on oxygenation and are not expected to improve MOF
• ARDS is a heterogeneous condition with diverse causes
  • Specific interventions are required to affect outcomes

SICKLE CELL DISEASE (SCD)

• Autosomal-recessive disorder of the beta globin gene
• Mutant hemoglobin S polymerizes red cells
• Occludes small blood vessels
• Results in painful vaso-occlusive crisis (VOC)
  • Causes organ damage
  • About 2 hospitals admissions per year
  • About 20% go on to develop acute chest syndrome (ACS)
INO

- In early animal studies of SCD, INO was shown to:
  - Reduce polymerization of red cells
  - Improve perfusion
  - Prevent platelet aggregation
  - Reduce VOC
  - Reduce lung injury

EVIDENCE

- Prospective, multicenter, placebo-controlled, randomized, phase 2 study of patients with SCD presenting in VOC
- 1078 SCD patients were evaluated, 150 were enrolled
- All participants received INO or placebo via face mask at an FIO2 of .24
- Main outcome measure was time to resolution of painful crisis
- Secondary outcomes included:
  - Length of hospitalization
  - Pain scale scores
  - Opioid use
  - Rate of ACS
RESULTS

• NO SIGNIFICANT DIFFERENCE IN MEDIAN TIME TO RESOLUTION OF CRISIS
• NO SIGNIFICANT DIFFERENCES IN SECONDARY OUTCOMES

DIAGNOSTIC USES

• PULMONARY VASOREACTIVITY TESTING IN CARDIAC CATH LAB
• STUDIES INDICATE INO SAFELY AND EFFECTIVELY ASSESS THE CAPACITY FOR PULMONARY VASODILATION AND PREDICTS RESPONSIVENESS TO MEDICAL VASODILATOR THERAPY
  • >20% DECREASE IN PA PRESSURE PREDICTS A RESPONSE TO ORAL VASODILATORS
  • HELPFUL IN SELECTION OF CHD PATIENTS FOR CORRECTIVE SURGERY AND THE TIMING OF CORRECTIVE SURGERY
TREATMENT OF PERIOPERATIVE PULMONARY HYPERTENSION

- SUDDEN PULMONARY HYPERTENSIVE CRISIS ARE SEEN IN THE POST-OPERATIVE COURSE OF CARDIAC SURGERY
- ASSOCIATED WITH SIGNIFICANT MORBIDITY AND MORTALITY
- IT HAS BEEN SHOWN THAT PULMONARY ENDOTHELIAL DYSFUNCTION IS PRESENT AFTER CARDIOPULMONARY BYPASS (CPB)
  - MOST LIKELY RELATED TO REDUCED ENDOGENOUS NITRIC OXIDE RELEASE

CONGENITAL REPAIRS AT HIGH RISK

- MITRAL VALVE STENOSIS
- TOTAL ANOMALOUS PULMONARY VENOUS RETURN
- BIDIRECTIONAL GLENN ANASTOMOSIS
- FONTAN CIRCULATION
RESULTS

• INO HAS BEEN SHOWN TO DECREASE POSTOPERATIVE PULMONARY HYPERTENSION IN CHD AND TO DECREASE POSTOPERATIVE NEED FOR ECMO
• IN A RANDOMIZED DOUBLE-BLINDED PLACEBO CONTROLLED STUDY IT WAS FOUND THAT HIGH RISK INFANTS GIVEN 10PPM INO UNTIL JUST BEFORE EXTUBATION HAD FEWER PULMONARY HYPERTENSIVE CRISES AND SHORTER TIMES TO ELIGIBILITY FOR EXTUBATION

STUDY

• INO AT 20 PPM STARTED BEFORE COMING OFF CPB AND CONTINUING UNTIL PRIOR TO EXTUBATION
• PA PRESSURES AND CVP MONITORED AND ECHOCARDIOGRAPHIC FINDINGS IN TRANSPLANTATION PATIENTS
• STUDY GROUP COMPARED TO HISTORICAL COHORT GROUP
RESULTS

• INO REDUCED INCIDENCE OF RV DYSFUNCTION
• INO REDUCED PVR AND ENHANCED RV STROKE WORK

INO WITH L-VAD PLACEMENT

• RV DYSFUNCTION OCCURS IN 20-50% OF PATIENTS AFTER INSERTION OF A LEFT VENTRICULAR ASSIST DEVICE (L-VAD)
• PVR IS USUALLY ELEVATED IN PATIENTS WITH LONG STANDING CONGESTIVE HEART FAILURE
• CPB CAN FURTHER INCREASE RV DYSFUNCTION
STUDY RESULTS

• RANDOMIZED, DOUBLE-BLINDED TRIAL DEMONSTRATED HEMODYNAMIC BENEFITS OF INO
• DECREASED PA PRESSURES AND INCREASED L-VAD FLOW
• INO IS RECOMMENDED BEFORE IMPLANTATION OF AN R-VAD