Inhaled Nitric Oxide or Prostacyclin in Acute Respiratory Failure: Efficacy, Safety, and Cost

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Why Should Inhaled Vasodilators Be Considered in ARDS?

• Acute PAH is a common finding
• Disseminated arterial /microvascular embolization is prominent feature
• Incidence of Cor-Pulmonale: 22-25% in ARDS
• 50% in severe ARDS
• Some Degree of PFO found ~20% of ARDS cases
Mortality Impact of PAH-RV Dysfunction in ARDS

- **Greene (1981):** 88% mortality w/ pulm vasc obstruction vs 50% with elevated PVR w/o obstruction.
- **Villar (1989):** Mortality w/ PAH (79%) vs. PAH Absent (44%)
- **Monchi (1998):** RAP > PAOP $\rightarrow$ 5x ↑ mortality risk
- **Squarra (1998):** ↑ R:L SWI ratio highly predictive for mortality.
- **Bull (2010):** ↑ transpulmonary gradient (PAP-PAOP $\geq$ 12 mmHg) assoc w/ higher mortality (30% vs. 19%).
- **Boissier (2013):** ARDS (P/F < 200) despite LPV, ACP assoc w/ signif ↑ hospital mortality (67% vs. 49%).
Therapeutic Context: Management

- Some LPV strategies potentiate PAH (e.g. permissive hypercapnia/acidosis, permissive hypoxemia and higher PEEP).
- **Schmitt (2001):** Despite LPV, moderate PEEP (13cmH₂O) impairs RV function (potentiated by acidosis: PEEP ~ 11)
- **L’heritier / Vieillard-Baron (2013):** PaCO₂ > 60 mmHg, associated with a nearly 4-fold ↑risk for ACP.
- **Puybasset (1994):** despite mean PaCO₂ 65 mmHg, INO of 2ppm ↓PVR & MPAP towards levels found during normocapnia (unrelated to PaO₂)
- **Flexibility:Issue** RH Protective Ventilation Goals (Pplat < 27; Pplat-PEEP < 17 cmH₂O) not always feasible.
**INO Mechanism of Action**

**iNO** diffuses across alveolar capillary membrane & penetrates vascular smooth muscle.

Stimulates conversion of guanosine-5-triphosphate to Cyclic Guanosine Monophosphate (cGMP) → Intracellular [Ca$^{+}$] in vascular smooth muscle.

Smooth Muscle Relaxation / Vasodilation
Prostacyclin Mechanism of Action

PGI$_2$ diffuses across alveolar capillary membrane & penetrates vascular smooth muscle

Activates enzyme adenylyl cyclase → $\uparrow$ Cyclic Adenosine Monophosphate (cAMP) → $\downarrow$ Intracellular [Ca$^+$] in vascular smooth muscle

Smooth Muscle Relaxation / Vasodilation
Nitric Oxide

• Potent vasodilator
• Inhibits neutrophil & platelet aggregation
• Anti-inflammatory properties (severe malaria)
• Antimicrobial properties
• FDA-approved: PAH-associated hypoxia, term/near term neonates (≥ 34 wk).
• Dosing: 5-20ppm (max of 40)
Prostacyclin (Flolan)

- Analog of endogenous PGI$_2$
- Potent vasodilator
- Inhibits platelet aggregation
- Potent inhibitor of growth factor release from platelets and leukocytes, ($\downarrow$ smooth muscle cell proliferation & vascular remodeling).
- $\uparrow$ LV Contractility via $\uparrow$cAMP
- FDA-approved: IV for PAH (Aerosolized “off-label”)
- Aero-dose range: 10-50 ng/kg/min
Comparability: Improvements in Oxygenation Not Significantly Different

Combined N = 28 prospective cross-over; N = 105 retrospective (T study)
Comparable Reductions in MPAP
INO vs. Aero-PGI$_2$

Haraldsson 1998: 11% ↑ in CO w/ PGI2
97 ARDS Patients Receiving Aero PGI-2 w/ paired ABG’s and No Other Intervention

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>47 ± 17</td>
</tr>
<tr>
<td>Lung Injury Score</td>
<td>3.0 ± 0.6</td>
</tr>
<tr>
<td>APACHE II</td>
<td>26 ± 9</td>
</tr>
<tr>
<td>SAPS II</td>
<td>52 ± 18</td>
</tr>
<tr>
<td>$C_{RS} \text{mL/cmH}_2\text{O}$</td>
<td>29 ± 9</td>
</tr>
<tr>
<td>$P_aO_2/FiO_2$</td>
<td>99 ± 52</td>
</tr>
<tr>
<td>Oxygenation Index</td>
<td>25 ± 16</td>
</tr>
<tr>
<td>$V_D/V_T$</td>
<td>0.69 ± .13</td>
</tr>
<tr>
<td>ARDS Days to Rx Start</td>
<td>1.1 ± 2.0</td>
</tr>
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</table>

Since 2002: 221/1802 (12%) ARDS pts received aero-PGI$_2$ (~250 since 1998)
Clinically Positive Effect of Aerosolized Prostacyclin According to Degree of Initial Hypoxemia

- < 50%: 71%
- 50-59%: 52%
- 60-79%: 62%
- 80-99%: 67%
- > 100%: 89%
- Overall: 65%
Response to Aerosolized Prostacyclin by Degree of Hypoxemia (as a Signifier for FRC)

PaO2 (mm Hg)

<table>
<thead>
<tr>
<th>Initial Oxygenation Category</th>
<th>DPaO2</th>
<th>PaO2-Post</th>
<th>PaO2-Pre</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 100</td>
<td>54</td>
<td>135</td>
<td>190</td>
</tr>
<tr>
<td>80-99</td>
<td>23</td>
<td>111</td>
<td></td>
</tr>
<tr>
<td>60-79</td>
<td>46</td>
<td>115</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>13</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>21</td>
<td>64</td>
<td></td>
</tr>
</tbody>
</table>
Safety Issues: INO

- INO: vigorously studied
  - NO $\rightarrow$ N$_2$O (2-10 ppm $\rightarrow$ ARDS): 14 RCTs: No ↑ risk
  - Abrupt d/c or Rapid Weaning: Rebound PAH / hypoxemia
    - 48% rebound hypoxemia
    - 26% hemodynamic instability
  - Met-Hb: very rare complication (doses ~80 ppm)*
  - Coagulation issues: No ↑ risk*
  - Nephrotoxicity: Small ↑ risk in ARDS*

* Based on Cochrane Database Studies
Met-Hb as a Mortality Risk factor in ARDS?

- Rolley (2011): 5yr retrospective audit
- N = 215 (80% ARDS; 20% chron pulmonary)
- Independent risk factors for mortality:
  - Worsening
    - SOFA w/in 24h of iNO Rx (OR: 1.07)
    - Charlson Comorbidity (OR: 1.49)
  - Peak Met-Hb during iNO Rx (OR: 2.67) independent of illness of severity
- Median peak Met-Hb 1.5%; > 3% in 5 pts (<5% innocuous)
- INO Dose: 20 ppm [19.8-22.2]; Highest: 43 ppm
- Interpretation: uncertain
Safety Issues: Aero-PGI$_2$

- Only PGI$_2$ monotherapy for primary PAH assoc w/ significant ↑ in long-term survival (3–5 years) in RCTs.
- IV Dosing 20ngm/kg/min no toxicity, toxicity found in some subjects at IV dosing 50 ngm/kg/min
- Very little data to evaluate safety for aero-PGI$_2$
- Primary concern: platelet function
- Vibrating mesh nebs: 60% nominal dosing (AB’s): ~ equivalent to IV dosing of 30 ngm/kg/min at maximal dose
- Glycine Diluent: pH ~ 10.5
- 200 ng/kg/min (4x clinical dose): mild acute tracheitis after 8h
- 28 ng/kg/min: no toxic effects after 8h
Mortality: ≥ 10 days Rx (50%) < than entire group (57%).
Pts who required 51 days was a survivors
## Comparing Delivery Systems

<table>
<thead>
<tr>
<th></th>
<th>INO</th>
<th>Aero-PGI₂</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delivery System</strong></td>
<td>Only 1: Universal Compatibility</td>
<td>Jet or Vibrating Mesh &amp; IV Pumps</td>
</tr>
<tr>
<td><strong>Safety Features/alarms</strong></td>
<td>Good</td>
<td>Only IV pump alarms, Nothing for nebulizers</td>
</tr>
<tr>
<td><strong>Dose Control/Delivery</strong></td>
<td>Precise dose delivery based on vent flow signal</td>
<td>Dependent on nebulizer performance Drug mixing &amp; titration</td>
</tr>
<tr>
<td><strong>Impaction/rain-out /lung distribution issues</strong></td>
<td>None: Gas</td>
<td>Impaction &amp; rainout is a well-known limitation</td>
</tr>
</tbody>
</table>
Comparability: Cost

**Historical Billing**

Cost/day

<table>
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<tr>
<th></th>
<th>iNO</th>
<th>PGI-2</th>
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<tbody>
<tr>
<td></td>
<td>$3,500</td>
<td>$300</td>
</tr>
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</table>

**Torbic (2013)**

Total Cost Rx (3.5 days)

<table>
<thead>
<tr>
<th></th>
<th>iNO</th>
<th>PGI-2</th>
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<tr>
<td></td>
<td>$3,930</td>
<td>$840</td>
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Conclusion INO

• vigorous studied

• good safety profile

• highly effective as a selective pulmonary vasodilator to \( \downarrow \text{PAH} \) & \( \uparrow \text{Pa}_O_2 \)

• requires high-tech delivery system

• 4 x the cost of PGI\(_2\)
Conclusion: Aero-PGI$_2$

- Not vigorously studied in comparison to INO
- Established effective dose range despite uncertainty of actual delivered dose
- **Comparable effectiveness in $\downarrow$PAH & $\uparrow$Pa$_{O2}$**
- Very low-tech delivery system
- $1/4$th the cost of INO
- No evidence of significant AE ~ 20 yrs
- Inferior delivery system in terms of safety
- Requires heightened clinician vigilance