Inhaled nitric oxide: clinical evidence for use in adults

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Conflict of interest

- Ikaria provided data for 3 trials included in a meta-analysis
- No other support
Objectives

• Review data from randomized trials of inhaled NO, primarily in ARDS

• Consider whether our practice should change
Robert Furchgott  
Louis Ignarro  
Ferid Murad
INHALED NITRIC OXIDE FOR THE ADULT RESPIRATORY DISTRESS SYNDROME

ROLF ROSSAINT, M.D., KONRAD J. FALKE, M.D., FRANK LÓPEZ, B.S., KLAUS SLAMA, M.D., ULRICH PISON, M.D., AND WARREN M. ZAPOL, M.D.

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\[ N = 9 \]
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N=7
Rapid clinical uptake

• Survey of ESICM members, 1997
  – 63% (196/310) used NO
  (95% reported ARDS as an indication)

• Survey of Ontario intensivists, 2003
  – 39% used NO sometimes or always
  – 15% rarely
  – 47% never

Intensive Care Med 24:864-77, Crit Care Med 32:946-54
It’s 2014 – why is anyone still talking about NO?
This is one reason

![Bar chart showing total cost and total patient-hours for different years.](chart)

Sunnybrook HSC, NO utilisation data
We’re not the only ones who use NO

• Mayo Clinic:
  – 7% of ARDS patients
  – 10% of patients with LIS ≥3

• H1N1 pandemic
  – South Korea, 8%
  – Europe, 12%
  – Canada, 14%

Arguments from the bedside

- Mayo Clinic:
  - 7% of ARDS patients
  - 10% of patients with LIS ≥3

- H1N1 pandemic
  - South Korea, 8%
  - Europe, 12%
  - Canada, 14%

Absence of evidence ≠ Evidence of absence

‘Don’t talk to me about trials, my patient is very sick’
NO does not belong in this category

- Intubation or tracheostomy for airway obstruction
- Vasopressors for shock
- Early antibiotics for septic shock
- Insulin for DKA
- Epinephrine for anaphylaxis
- General anaesthesia for surgery

Thus, using GRADE’s definition of quality of evidence, the underlying quality of evidence to support these clinical interventions would be considered high although the evidence comes from observational studies or from unsystematic clinical observations.
The data: meta-analysis of ARDS trials

- Old data! 1997-2004
- Mortality analysis: 9 trials, 1142 patients
  - 2 other eligible trials (lost data; no contact)
- AECC criteria for ARDS (1 trial, ALI)
- Dose
  - Fixed, 4 trials
  - Lowest dose to improve oxygenation, 4 trials
  - Randomized to different doses, 1 trial
- Duration
  - Median 6.5 d (3.5-9)
P/F ratio:

**Short term effect**
PA_{mean}: short term effect

BMJ 2007;334:779
No effect on mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Nitric oxide Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Dellinger et al, 1998</td>
<td>43</td>
<td>158</td>
<td>20</td>
<td>75</td>
<td>12.6%</td>
<td>1.02 [0.65, 1.61]</td>
</tr>
<tr>
<td>Gerlach et al, 2003</td>
<td>3</td>
<td>20</td>
<td>4</td>
<td>20</td>
<td>1.4%</td>
<td>0.75 [0.19, 2.93]</td>
</tr>
<tr>
<td>Lundin et al, 1999</td>
<td>41</td>
<td>93</td>
<td>35</td>
<td>87</td>
<td>21.9%</td>
<td>1.10 [0.78, 1.55]</td>
</tr>
<tr>
<td>Mehta et al, 2001</td>
<td>4</td>
<td>8</td>
<td>3</td>
<td>6</td>
<td>2.3%</td>
<td>1.00 [0.35, 2.88]</td>
</tr>
<tr>
<td>Michael et al, 1998</td>
<td>11</td>
<td>20</td>
<td>9</td>
<td>20</td>
<td>6.6%</td>
<td>1.22 [0.65, 2.29]</td>
</tr>
<tr>
<td>Park et al, 2003</td>
<td>4</td>
<td>11</td>
<td>2</td>
<td>6</td>
<td>1.4%</td>
<td>1.09 [0.28, 4.32]</td>
</tr>
<tr>
<td>Payen et al, 1999</td>
<td>48</td>
<td>98</td>
<td>46</td>
<td>105</td>
<td>29.5%</td>
<td>1.12 [0.83, 1.50]</td>
</tr>
<tr>
<td>Taylor et al, 2004</td>
<td>44</td>
<td>192</td>
<td>39</td>
<td>193</td>
<td>17.7%</td>
<td>1.13 [0.77, 1.66]</td>
</tr>
<tr>
<td>Troncy et al, 1998</td>
<td>9</td>
<td>15</td>
<td>8</td>
<td>15</td>
<td>6.6%</td>
<td>1.13 [0.60, 2.11]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>207</td>
<td>615</td>
<td>166</td>
<td>527</td>
<td>100.0%</td>
<td>1.10 [0.94, 1.29]</td>
</tr>
</tbody>
</table>

Overall effect: p=0.24; Heterogeneity: $I^2=0\%$
No effect on mortality regardless of P/F ratio

Crit Care Med 2014; 42:404–412
Unlike proning...
More AKI

- these trials represent 72% of randomized patients
- variable definitions (new RRT in Lundin, Payen)
- mechanism?

BMJ 2007;334:779
Why was NO ineffective? (1)

• Oxygenation may be the wrong target
  – ARDS network trial
  – OSCILLATE
  – Only 13-19% die from respiratory failure
• Benefit overwhelmed by injurious MV
• NO does not decrease VILI

Why was NO ineffective? (2)

• Accumulated toxicity over time

Am J Respir Crit Care Med 2003;167:1008-15
A Randomized Trial of Inhaled Nitric Oxide to Prevent Ischemia–Reperfusion Injury after Lung Transplantation

Maureen O. Meade, John T. Granton, Andrea Matte-Martyn, Karen McRae, Bruce Weaver, Paula Cripps, Shaf H. Keshavjee, and the Toronto Lung Transplant Program

- 84 patients undergoing lung transplantation
- Randomised to
  - NO 20 ppm or nitrogen
  - Started 10 mins after start of reperfusion, for ≥6 hours
  - Median duration 10.5 hr (NO) vs. 9.6 hr ($N_2$)
  - Criteria for unblinded NO
  - Criteria for weaning

Am J Respir Crit Care Med 2003;167:1483
A Randomized Trial of Inhaled Nitric Oxide to Prevent Ischemia–Reperfusion Injury after Lung Transplantation

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<table>
<thead>
<tr>
<th></th>
<th>NO Group</th>
<th>Control Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 42)</td>
<td>(n = 42)</td>
<td></td>
</tr>
<tr>
<td>( \text{Pa}_2/\text{Fi}_2 &lt; 150 ) in first 48 h</td>
<td>9 (22.0%)</td>
<td>8 (19.0%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Unblinded NO initiated in ICU</td>
<td>2 (4.9%)</td>
<td>1 (2.4%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Time to unassisted breathing, h</td>
<td>25.7 (10.8–75.3)</td>
<td>27.3 (12.9–267.1)</td>
<td>0.76</td>
</tr>
<tr>
<td>Time to successful extubation, h</td>
<td>28.5 (15.8–135.0)</td>
<td>35.3 (18.5–130.5)</td>
<td>0.86</td>
</tr>
<tr>
<td>Time to ICU discharge, d</td>
<td>3.0 (3.0–7.5)</td>
<td>3.0 (3.0–16.5)</td>
<td>0.90</td>
</tr>
<tr>
<td>Time to hospital discharge, d</td>
<td>26.8 (21.5–37.7)</td>
<td>29.3 (19.8–46.6)</td>
<td>0.56</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In operating room</td>
<td>1/42 (2.4%)</td>
<td>0/42 (0.0%)</td>
<td>1.00</td>
</tr>
<tr>
<td>In ICU before first extubation</td>
<td>3/41 (7.3%)</td>
<td>3/42 (7.1%)</td>
<td>1.00</td>
</tr>
<tr>
<td>In ICU after first extubation</td>
<td>1/38 (2.6%)</td>
<td>1/39 (2.6%)</td>
<td>1.00</td>
</tr>
<tr>
<td>In hospital after ICU discharge</td>
<td>0/37 (0.0%)</td>
<td>2/38 (5.3%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Total</td>
<td>5/42 (11.9%)</td>
<td>6/42 (14.3%)</td>
<td>0.75</td>
</tr>
<tr>
<td>30-d postoperative mortality</td>
<td>4/42 (9.5%)</td>
<td>5/42 (11.9%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Mitral valve surgery

• 28 patients with MS and pulmonary HTN for MV repair or replacement
  – $P_{A_{sys}} > 60$ mmHg and NYHA ≥2

• Randomised, unblinded
  – NO 10 ppm vs oxygen from end of CPB to up to 48 hours
  – Via ETT and sealed mask after extubation

Am J Cardiol 2011;107:1040–1045
Mitral valve surgery

Am J Cardiol 2011;107:1040–1045
• 11 patients with LVAD with $\text{PA}_{\text{mean}} > 25$ mmHg and CI $< 2.5$ L/min/m$^2$ at end of CPB

LVAD implantation: clinical

• 150 patients undergoing LVAD, with PVR $\geq 200$ dyne/s/cm$^{-5}$
  – Excluded: current or planned BiVAD or ECLS
• Randomised to
  – NO 40 ppm or placebo starting 5 mins before CPB wean, continued for up to 48 hrs
• Main outcome – RV dysfunction

J Heart Lung Transplant 2011;30:870–8
## LVAD Implantation: Clinical

<table>
<thead>
<tr>
<th></th>
<th>NO</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open-label NO</td>
<td>21%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>RV dysfunction</td>
<td>9.6%</td>
<td>15.6%</td>
<td>0.33</td>
</tr>
<tr>
<td>28-day mortality</td>
<td>11.3%</td>
<td>11.4%</td>
<td>0.92</td>
</tr>
<tr>
<td>28-day RVAD</td>
<td>5.6%</td>
<td>10.0%</td>
<td>0.47</td>
</tr>
<tr>
<td>RRT</td>
<td>14.1%</td>
<td>11.4%</td>
<td>0.64</td>
</tr>
</tbody>
</table>

- 18/35 crossovers BEFORE study defined criteria
  - 15/18 from 1 centre

J Heart Lung Transplant 2011;30:870–8
Possible responses to the data

• ‘I don’t believe the results’
  – Wrong patients
  – Not enough patients
  – Wrong design
  – Wrong outcome
  – Wrong treatment specifics

• ‘I may still use NO sometimes, with appropriate humility about my convictions’

• ‘We need a total crackdown on NO prescription’
Conclusions

• Physiologic mechanism of NO makes it an attractive therapy for several conditions

• RCTs support time-limited modest physiological effects

• RCTs in ARDS
  – No effect on mortality regardless of hypoxemia
  – Increased AKI – mechanism unclear
Conclusions

• Use of NO is highly likely to continue
  – In short term: limited harm and modest benefit –
    • more dramatic benefit in some
  – Rule of rescue (clinicians’ thresholds differ)
  – Temporising strategy
  – Easy to administer
  – Clinicians insensitive to costs at point of care

• Protocols may force early reassessment and stopping when physiologic goals not met
Conclusion:
In summary, the discovery of and research on the many positive effects of iNO has improved care of critically ill patients worldwide. It is a noble effort to continue on this path.

Conflicts of interest: None.
thank you
neill.adhikari@sunnybrook.ca
What is NO?

• Atmospheric gas, 10 ppb to 1.5 ppm
• Rapidly inactivated when inhaled

• Airway epithelium:
  – NO$_2$
  – reactive oxygen and nitrogen species

• Blood:
  – Methemoglobin
  – S-nitrosothiols → vasodilation, platelet inhibitor
Effects of NO from RCTs

• Several multicentre RCTs found no mortality benefit
  – Lundin, 1999, n=180
  – Payen, 1999, n=203
  – Taylor, 2004, n=385

• Meta-analysis (2003) pooled data from 2 trials: RR 0.98 (0.66-1.44)

• Additional data since previous review

• 43 centres in Europe
• Concealed, not blinded, 10/87 crossovers, ITT, complete f/u
• Stopped early (planned n=600)
• N=180 (responders randomized)
  – Unilateral or bilateral infiltrates, P/F ≤165, PEEP ≥5, Paw ≥10
  – Lowest effective dose (mean 9 ppm, SD 8)
  – Up to 30d (mean 9, SD 6)

<table>
<thead>
<tr>
<th></th>
<th>NO  n=93</th>
<th>control n=87</th>
</tr>
</thead>
<tbody>
<tr>
<td>30d mortality</td>
<td>44.1%</td>
<td>40.2%</td>
</tr>
<tr>
<td>90d mortality</td>
<td>51.6</td>
<td>43.7</td>
</tr>
<tr>
<td>Reversal ALI</td>
<td>61.3</td>
<td>54.0</td>
</tr>
<tr>
<td>Severe resp fail</td>
<td>2.2</td>
<td>10.3 p=0.04</td>
</tr>
<tr>
<td>New RRT or creat &gt;300</td>
<td>35.0</td>
<td>16.2 p=0.01</td>
</tr>
</tbody>
</table>
Payen et al, 1999 Intensive Care Med 25(Suppl. 1):S166

• 23 centres in France
• Concealed, blinded, 19/105 crossovers to NO, ITT, complete f/u
• N=203
  – AECC criteria and LIS 2-3 after 24h optimisation
  – 10 ppm
  – Up to 28d (median 5d)
Payen et al, 1999 Intensive Care Med 25(Suppl. 1):S166

<table>
<thead>
<tr>
<th>Metric</th>
<th>NO n=98</th>
<th>control n=105</th>
</tr>
</thead>
<tbody>
<tr>
<td>28d mortality</td>
<td>49.0%</td>
<td>43.8%</td>
</tr>
<tr>
<td>Hosp DC 90d</td>
<td>45.9</td>
<td>49.5</td>
</tr>
<tr>
<td>New RRT</td>
<td>37.1</td>
<td>28.9</td>
</tr>
</tbody>
</table>
Taylor et al, 2004 JAMA 291:1603-9

- 46 centres in USA
- Concealed, blinded, no crossovers, ITT, complete f/u
- Stopped early, planned N=516
- N=385
  - AECC (ALI), P/F ≤250, PEEP ≥8
  - 5 ppm
  - Max 28 d (mean ?)
Taylor et al, 2004  JAMA 291:1603-9

- 28d mortality  NO $n=192$  control $n=193$
  - 22.9%  20.2%
- VFD (28d)  10.7d  10.6d
- ↑ creat  6.2%  4.1%
Observations from these RCTs

- Slightly higher mortality in NO arm
- Slightly more renal dysfunction in NO arm
- The trial restricted to responders (Lundin) did not show benefit either
Objective: current meta-analysis

- evaluate the effects of NO in patients with established ALI and ARDS on
  - pulmonary physiology ($P_aO_2/F_iO_2$, OI, mean PA pressure)
  - clinical outcomes (mortality and duration of ventilation)
  - Adverse events
Methods

• Search of MEDLINE, EMBASE, CINAHL, CENTRAL (to Oct 2006)
• Proceedings ATS, SCCM, ESICM, Chest (1994-2006)
• Bibliographies
• Contact with trial authors / experts
Methods

• Inclusion
  – Parallel group RCTs
  – NO used for treatment
  – ≥ 80% ALI/ARDS or separately reported subgroup
  – ALI/ARDS using authors’ definitions
  – Adults and children (not neonates)

• Duplicate data abstraction
Methods

• Outcomes
  – Mortality
  – Duration MV, VFD
  – Pulmonary physiology (days 1, 2, 3, 4)
  – Adverse events
Methods

• Analysis
  – Random-effects
  – RCTs with <50% crossovers included in clinical outcomes analyses
  – Data from multiple-dose groups combined
  – Binary outcomes: RR
  – Continuous outcomes: ratio of means, weighted mean difference
  – Heterogeneity considered: dose, duration, ALI vs ARDS
OI: short term effect