Inhaled Nitric Oxide
Beyond the Evidence- Children

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Nitric Oxide and Bob Dylan
Swedish scientists reveal 17 year competition to slip Bob Dylan quotes into research papers

- Contest started with a paper called 'Nitric Oxide and Inflammation: The answer is blowing in the wind'
- The winner will be the researcher who quotes Bob Dylan in the most scientific articles before they retire

By MARK PRIDDY FOR MAILONLINE
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Scientists sneak Bob Dylan lyrics into articles

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Five Swedish scientists have confessed that they have been quoting Bob Dylan lyrics in research articles and are running a wager on who can squeeze the most in before retirement.

REVIEW

Nature Medicine, 3, 30-31 (1997)
doi:10.1038/nm0197-30

**Nitric oxide and inflammation: The answer is blowing in the wind**

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Detection of mucosal inflammation by a novel, minimally invasive technique.
Furchgott, Zawadzki 1980 Nature
Inhaled nitric oxide as a cause of selective pulmonary vasodilatation in pulmonary hypertension

JOANNA PEPKE-ZABA
TIMOTHY W. HIGENBOTTAM
A. TUAN DINH-XUAN   DAVID STONE
JOHN WALLWORK

The acute effects of inhaled nitric oxide (NO) (40 ppm in air) on pulmonary (PVR) and systemic

In 10 normal volunteers, \( \dot{Q} \) was measured non-invasively with a transthoracic impedance method (NCCOM-3 Bomed Medical Manufacturing, Irvine, California, USA). Mean SAP was measured with a sphygmomanometer.

The effects of inhaled NO (40 ppm in air) and infused prostacyclin (PGL\(_2\)) (24 \( \mu \)g/h) were investigated in patients with pulmonary hypertension, whereas only inhaled NO was studied in the cardiac and volunteer groups. The mixture of NO (about 40 ppm) in air was made from 5 litres of 1000 ppm NO in nitrogen (Air Products, Walton on Thames, UK), and added to 120 litres of air in a Douglas bag. The NO/air mixture was made 15 min before use, the concentration of NO being measured immediately before and after each study (chemiluminescence analyser, Chemlab, Hornchurch, UK). Each subject, wearing a nose clip, breathed through a mouthpiece connected to a two-way valve and a switch to two Douglas bags, one containing air and the other the NO/air
Haemodynamic effects of infused PGI$_2$ and inhaled NO

Inhaled nitric oxide: a magic bullet?

T. Higenbottam

DOI: http://dx.doi.org/login.ezproxy.library.ualberta.ca/ 555-558 First published online: 1 September 1993

Quarterly Journal of Medicine, 1993; 86:555–558

Editorial

Inhaled nitric oxide: a magic bullet?

The reactive gas nitric oxide (NO) has excited widespread interest amongst biological scientists. It has been identified as a unique mediator between cells, in the vasculature and central nervous system.\(^1\) When produced in nM quantities it appears to be responsible for cytotoxic properties of inflammatory cells such as macrophages.\(^2\) The enzyme which produces NO, NO synthase, has been found in a number of isoforms. Its substrates are L-arginine and molecular oxygen.\(^3\) Use of specific inhibitors has led to the discovery that continuous basal release from endothelial cells regulates resting vascular tone.\(^4\) Nitric oxide has been shown to be a powerful, long-lasting, gaseous mediator that mediates many physiological functions, including regulation of vascular tone and blood pressure.\(^5\) Nitric oxide is synthesized in a pH-dependent reaction of L-arginine to yield L-citrulline, NO and urea.\(^6\) Nitric oxide appears to be the most potent vasodilator known, acting on smooth muscle in a rapid, concentration-dependent manner, with half-maximal relaxation occurring at 2.5 μM.\(^7\) These effects are long-lasting, with half-lives of 2.5 to 5 minutes in the absence of scavengers.\(^8\) The most important scavenger of NO is the reactive nitrogen oxide species NO.\(^9\) Its half-life of 150 μM is several times longer than that of NO.\(^10\) For all these reasons, nitric oxide appears to be an ideal candidate for use in clinical settings.
Inhaled Nitric Oxide

- Decreases (selectively) Pulmonary Artery Pressure
- Improves Oxygenation
- Rapid Onset/Offset
- Inexpensive
- Favorable risk/benefit ratio

Various intentional and unintentional factors influence beliefs beyond what scientific evidence justifies.
Beyond the evidence

- Strength of the belief exceeds the strength of the evidence
- Beliefs
  - Low saturations are bad for patients
  - Increased pulmonary aretry pressures are bad for patients
  - Treating either or both is beneficial to patient outcomes
Prolonged Therapy with Inhaled NO Pulmonary Artery Pressure

Current Values
Time: 10:41 a.m.
Left axis:
PA (mmHg)
Sys = 25
Mean = 15
Dia = 10

Courtesy David Wessel
Inhaled vasodilators are directed preferentially to high $V_A$ areas.
Effect of inhaled NO on PA pressure and $Q_s/Qt$

Acetylcholine versus inhaled NO after cardiopulmonary bypass

Transpulmonary cGMP during NO inhalation

- Pulmonary artery
- Left atrium

Baseline, INO, Post NO
Exhaled NO before and after surgical ASD closure

Exhaled NO after ASD closure

* p<0.005

Endothelin and cGMP

Journois, et al JTCVS 1994;107 Inhaled NO after cardiac surgery
Hemodynamic Changes with Inhaled Nitric Oxide in TAPVC

Baseline

HR 149 b/min
CI 2.3 l/m/m²
BP 62 mmHg
SVR 23.5 U m²
mPAP 35.6 mmHg
PVR 11.5 U m²

Mean Percentage Change Compared to Baseline

Wessel, Adatia et al 2009
Withdrawal of NO rebound pulmonary hypertension

Inhaled NO

- Randomized double blind study
- NO group fewer PHTN crises
- Consistently decreased PVRI
- Shorter time to reach extubation criteria

Inhaled NO and hyperventilation

- Inhaled NO and hyperventilation decrease PVRI
- Hypocarbic alkalosis decreases CI and increases SVRI

Inhaled NO

Why does iNO not work?
Proposed natural history of left to right shunts

Reversible

Non reversible
Kulik, Mullen, Adatia. Prog Pediatr Cardiol: 2009:27:25
DuShane et al., in The Child With Congenital Heart Disease After Surgery, Kidd and Rowe, 1976
Acute Vasoreactivity
Long Term Prostanoid Therapy

Prostanoid therapy for pulmonary arterial hypertension


http://dx.doi.org/10.1016/j.jacc.2004.02.036
Right ventricular pressure tracings

Peter Harris Br Heart J 1955:17:173-182
Why do patients with PAH die?
Why do patients with PAH die?
Left Upper Lobe Hematoma

Pleural Defect, LUL
Why do patients with PAH die?
Survival in Pediatric PAH Prior to Availability of Targeted Therapies

Courtesy Robyn Barst
Variability of Improved Survival in Pediatric PAH in the Current Era

Survival vs Years

- 1999 Barst (epo)
- 2010 Ivy
- 2010 Fraisse (France)
- 2009 Haworth IPAH
- 2004 Yung
- 2009 Haworth APAH
- 2010 Moledina
- 2006 Bosentan
- 2010 Barst (REVEAL)
- 2008 Van Loon (prev)
- 2008 Van Loon (inc)
- 2010 Berger
- 2010 Moledina
- 1999 Van Loon
- 1999 Barst (without epo)
- 1999 Barst (NR)
- 1995 Sandoval (Mexico)
- 1993 Houde (Toronto)
- Historical Controls
- 1991 D’Alonzo (NIH)

Courtesy Robyn Barst
Hemodynamic and blood gas response to inhaled NO after BCPA

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
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<th>TPG</th>
<th>Mean</th>
<th>SVC</th>
<th>Art</th>
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<td>mmHg</td>
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<td>mmHg</td>
<td>mmHg</td>
<td>mmHg</td>
<td>minute</td>
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<tr>
<td>PreNO</td>
<td>17±3</td>
<td>7±2</td>
<td>9±5</td>
<td>65±11</td>
<td>33±11</td>
<td>63±7</td>
<td>32±4</td>
<td>38±9</td>
<td>7.46±0.08</td>
<td>143±21</td>
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<tr>
<td>WithNO</td>
<td>15±3*</td>
<td>7±2</td>
<td>7±5</td>
<td>62±9</td>
<td>34±12</td>
<td>65±5</td>
<td>32±4</td>
<td>38±8</td>
<td>7.46±0.07</td>
<td>146±20</td>
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<tr>
<td>PostNO</td>
<td>16±3†</td>
<td>8±2</td>
<td>8±4</td>
<td>63±12</td>
<td>31±7</td>
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<td>32±4</td>
<td>38±8</td>
<td>7.46±0.06</td>
<td>146±18</td>
</tr>
</tbody>
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26 patients

Adatia, Atz, Wessel
J Thorac Cardiovasc Surg 2004
Episodic pulmonary hypertension and increased atrial pressures after heart transplant
Post operative pulmonary hypertensive crises?
Belief beyond the evidence: breakfast, obesity and bias

Inhaled NO –beyond the evidence

• Medical decision-making in individual patients uses the findings of population-based evidence in guidelines, but the recommendations should be translated to an individual patient with unique needs and preferences.

• Moreover, personal experiences and interests of the health care provider and ethical principles together with economic and political considerations influence the ultimate decision. These factors cannot be quantified against each other, as they are difficult to balance.

• The World Health Organisation recognises this dilemma and advises that value judgements should be explicit and be influenced by patients in particular.
Conclusions

• Inhaled nitric oxide
  – reverses acute vasoconstriction
  – Often acutely improves oxygenation
  – Rarely harmful acutely