Minimizing the Inhaled Dose of NO With Breath-by-Breath Delivery of Spikes of Concentrated Gases

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Background—Pulmonary vasodilatation with a 100 ppm concentration of NO given as a short burst of a few milliliters at the beginning of each breath (NO\textsubscript{min}) was compared with conventionally inhaled NO, in which a full breath of 40 ppm of NO was inhaled (NO\textsubscript{CD}).

Methods and Results—NO\textsubscript{min} was studied in 16 patients with severe pulmonary hypertension and in 16 isolated porcine lungs with experimentally induced pulmonary hypertension. We compared volumes of 8 to 38 mL of 100 ppm NO in N\textsubscript{2} injected at the beginning of each breath with conventional inhalation of 40 ppm NO in air. NO\textsubscript{CD} and NO\textsubscript{min} were studied in 4 pigs after inhibition of NO synthase with \textit{N}\textsuperscript{G}-nitro-L-arginine methyl ester (1 to 2 mg/kg IV) had raised the pulmonary vascular resistance index (PVRI) from 4.4±0.8 to 10.0±1.6 mm Hg · L\textsuperscript{-1} · min\textsuperscript{-1} · kg\textsuperscript{-1}. A similar comparison was made in 7 isolated porcine lungs after the thromboxane analogue U46619 (10 pmol · L\textsuperscript{-1} · min\textsuperscript{-1}) increased the mean PVRI from 4.6±0.8 to 12.2±1.3 mm Hg · L\textsuperscript{-1} · min\textsuperscript{-1} · kg\textsuperscript{-1}. Patients’ mean PVRI was reduced from 29.2±3.7 to 24.0±3.1 with NO\textsubscript{min} and 24.5±3.3 mm Hg · L\textsuperscript{-1} · min\textsuperscript{-1} · m\textsuperscript{-2} (mean±SEM) with NO\textsubscript{CD}. In isolated porcine lungs, there was the same reduction of PVRI for NO\textsubscript{min} and NO\textsubscript{CD} between 12.7% and 34.8%.

Conclusions—A small volume of NO inhaled at the beginning of the breath was equally effective as NO\textsubscript{CD} but reduced the dose of NO per breath by 40-fold, which ranged from 1.2×10\textsuperscript{-3} (0.4 \mu g) to 1.6×10\textsuperscript{-7} mol/L (4.8 \mu g) compared with 5.3×10\textsuperscript{-7} (16 \mu g) to 1.2×10\textsuperscript{-8} mol/L (36 \mu g) per breath with NO\textsubscript{CD}. (Circulation. 1998;98:2429-2432.)

Key Words: hypertension, pulmonary \(\text{II lung \text{II vasodilation}

Inhaled NO is a selective pulmonary vasodilator,\textsuperscript{1,2} and in acute respiratory distress syndrome (ARDS), it improves gas exchange.\textsuperscript{3} Current methods of administration of NO are complicated and not without hazard.\textsuperscript{4}

NO is stored in concentrations of 100 to 10 000 ppm, with N\textsubscript{2}. Safe and effective concentrations of inhaled NO range from 1 to 40 ppm,\textsuperscript{5} which are achieved by mixing NO with respiratory gases. The flow rate of the mixed gases is carefully matched to the rate of ventilation, preventing buildup of NO\textsubscript{2}.\textsuperscript{6} While straightforward for ventilated patients, ambulatory patients who vary their rate of ventilation renders delivery difficult. A new method of delivery is needed for them because inhaled NO can be used to treat pulmonary hypertension.\textsuperscript{7}

Higher doses of inhaled NO are needed to reduce pulmonary hypertension than to improve gas exchange in ARDS.\textsuperscript{5} Conventional delivery (NO\textsubscript{CD}), which distributes inhaled NO throughout the lungs, can, however, worsen gas exchange in patients with chronic obstructive pulmonary disease (COPD).\textsuperscript{9,10} Selective delivery of NO to fast-ventilated regions of the lungs could reduce this problem.

An alternative to NO\textsubscript{CD} is to inject a small volume of NO, added at the start of each breath. This has been learned from measurement of the gas transfer of carbon monoxide (TLCO) and allows NO to reach the resistance pulmonary arteries.\textsuperscript{11}

Methods

Experimentally Induced Pulmonary Hypertension

Sixteen pathogen-free pigs weighing 36 to 60 kg were studied as previously described.\textsuperscript{12,13} Midazolam (0.3 mg/kg IM) and droperidol (0.5 mg/kg IM) premedication was followed by anesthesia with sodium pentobarbital (25 mg/kg IV). They were ventilated (Manley Ventilator, Blease Medical) with 40% O\textsubscript{2} and 60% N\textsubscript{2}, a tidal volume of 10 to 12 mL/kg, and a maximum airway pressure of 10 mm Hg.

In Vivo Porcine Studies

In supine animals, pulmonary artery pressure (PAP), pulmonary wedge pressure (PWP), and right atrial pressure (RAP) in 9 animals, together with right carotid artery pressure (SAP), were measured. Euthanasia was effected immediately at the end with intravenous (10 mL of 1 mol/L) potassium chloride.

Isolated, Perfused Porcine Lung Studies

Isolated, salt-perfused lungs were prepared as previously described\textsuperscript{13} through a median sternotomy in 7 pigs. Euthanasia was undertaken by exsanguination. Pulmonary blood flow (Q) was measured with a Doppler flow probe and meter (model 16SB185 and model T101D,
Methods of NO Delivery
For the NO\textsubscript{max}, a device\textsuperscript{a} delivered a range of volumes of a mixture of 100 ppm NO/N\textsubscript{2}, at the beginning of each breath. With a solenoid valve (M8B-3E2C-6DC, Valeader Engineering Ltd), NO/N\textsubscript{2} was released at a flow rate of 12 L/min. The volume of gas and hence the dose delivered depended on the duration of opening times, which ranged from 10 to 1000 ms. This was calibrated before each study with a water spirometer. The valve was manual or automatic and ranged from 10 to 1000 ms. This was calibrated before each study with an automatic function triggered from the airway pressure transducer.

With NO\textsubscript{CD}, NO was delivered in a gas mixture of 79% N\textsubscript{2} and 21% O\textsubscript{2} (5% CO\textsubscript{2} was added for the isolated lungs) at a concentration of 40 ppm diluted (Pneumopac Ltd) from a mixture of 10 000 ppm NO/O\textsubscript{2}.

**Protocol**
Endothelial NO synthase was inhibited with N\textsuperscript{G}-nitro-L-arginine methyl ester (L-NAME). A stable rise of pulmonary vascular resistance index (PVRI) and systemic vascular resistance index (SVRI) occurred 20 to 30 minutes after injection. In the isolated lung studies, to achieve a stable elevation of PVRI after 10 to 15 minutes, the thromboxane analogue U46619 (10 pmol \textsuperscript{1} \textsuperscript{L} \textsuperscript{-1} \textsuperscript{min} \textsuperscript{-1}, Sigma Chemical Company Ltd) was infused into the isolated lung perfusate. The experiments undertook in 4 animals. Concentrations of 10, 40, and 80 ppm of NO\textsubscript{CD} were delivered in a gas mixture of 100 ppm NO/N\textsubscript{2} at the beginning of each breath. With a solenoid valve (M8B-3E2C-6DC, Valeader Engineering Ltd), NO/N\textsubscript{2} was released at a flow rate of 12 L/min. The volume of gas and hence the dose delivered depended on the duration of opening times, which ranged from 10 to 1000 ms. This was calibrated before each study with a water spirometer. The valve was manual or automatic and ranged from 10 to 1000 ms. This was calibrated before each study with an automatic function triggered from the airway pressure transducer.

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**Results**
Porcine Studies
The 10 ppm NO\textsubscript{CD}, was a less effective vasodilator than 40 and 80 ppm of NO\textsubscript{CD} (Figure 1) in 5 animals after L-NAME increased the PVRI by 6.5±1.1 mm Hg \textsuperscript{1} \textsuperscript{L} \textsuperscript{-1} \textsuperscript{min} \textsuperscript{-1} \textsuperscript{kg} \textsuperscript{-1} and in clinical studies to body surface area (mm Hg \textsuperscript{1} \textsuperscript{L} \textsuperscript{-1} \textsuperscript{min} \textsuperscript{-1} \textsuperscript{m} \textsuperscript{2}). The mean values for NO\textsubscript{max} were calculated with standard errors (SEM). ANOVA and Fisher’s test for multiple comparison were undertaken to compare treatments. Paired Student’s t tests were performed to compare baseline and post-L-NAME or post-U46619 PVRI values.

<table>
<thead>
<tr>
<th>Table 1. Reduction of PVR by Spiked NO on Induced Pulmonary Hypertension After L-NAME Infusion in Pigs</th>
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<tbody>
<tr>
<td><strong>Opening Time of Spiked NO, ms</strong></td>
</tr>
<tr>
<td>40</td>
</tr>
<tr>
<td>80</td>
</tr>
<tr>
<td>160</td>
</tr>
<tr>
<td>320</td>
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<td>1000</td>
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* Baseline PVR in response to L-NAME was taken as 100%: reduced PVR is expressed as percentage of this baseline (mean±SEM). All spiked NO reduced PVR significantly (P<0.01).
Clinical Study

The mean PVRI was 29.2 ± 3.7 (mean ± SE) mm Hg · L⁻¹ · min⁻¹ · m⁻², which fell to 24.0 ± 3.1 with NOmin (8 to 38 mL of 100 ppm NO) and to 24.5 ± 3.3 with 40 ppm of NOCD (Table 2). The average tidal volume varied from 320 to 730 mL. PGI₂ caused a comparable fall of mean PVRI to 20.0 ± 2.6 mm Hg · L⁻¹ · min⁻¹ · m⁻². Unlike inhaled NO, PGI₂ also caused a fall in SVRI (Table 2). The volumes of gas delivered by the solenoid valve ranged from 3 to 115 mL (Table 1).

Discussion

A small volume of NO/N₂ of up to 38 mL, delivered at the beginning of the breath, was as effective a vasodilator as a conventional delivery and that lessens potential toxicity as well as offering a safe means of treating ambulatory patients.

In summary, we describe a means of reducing the effective dose per breath of NO by 40-fold when compared with conventional delivery and that lessens potential toxicity as well as offering a safe means of treating ambulatory patients. It should overcome the problems of worsening V/Q inhomogeneity, to allow inhaled NO to be used for COPD.

TABLE 2. Response of Spiked NO, Continuous NO, and PGI₂ Infusion in Patients With Severe Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Condition</th>
<th>PVRI</th>
<th>SVRI</th>
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<tbody>
<tr>
<td>Baseline 1</td>
<td>29.2 ± 3.7</td>
<td>48.4 ± 3.6</td>
</tr>
<tr>
<td>Spike 100 ppm</td>
<td>24.0 ± 3.1*</td>
<td>45.0 ± 3.4</td>
</tr>
<tr>
<td>Continuous 40 ppm</td>
<td>24.5 ± 3.3*</td>
<td>45.4 ± 3.1</td>
</tr>
<tr>
<td>Baseline 2</td>
<td>28.5 ± 3.6</td>
<td>47.0 ± 3.4</td>
</tr>
<tr>
<td>PGI₂</td>
<td>20.0 ± 2.6†</td>
<td>35.7 ± 3.0†</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

Spike of 8 to 38 mL of NO of 100 ppm NO/N₂ at the beginning of the breath achieved the same reduction in PVRI as did a full breath of 320 to 730 mL of 40 ppm of NO. Similar falls in PVRI are seen with PGI₂.

*P < 0.05 compared with baseline 1. †P < 0.01 compared with baseline 2.

References


Acknowledgments

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