Use of nitric oxide inhalation in chronic obstructive pulmonary disease

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Abstract

Background—Inhalation of nitric oxide with oxygen could be a promising treatment in patients with chronic obstructive pulmonary disease (COPD) and pulmonary hypertension. However, the current methods of delivery of NO are cumbersome and unsuitable for long term use. The present study was undertaken to investigate the safety and efficacy of a mixture of nitric oxide (NO) and oxygen administered via a nasal cannula for 24 hours in patients with oxygen dependent COPD.

Methods—Twenty five parts per million (ppm) of NO was administered by inhalation combined with supplemental oxygen at a flow rate of 2 l/min via a nasal cannula for 24 hours to 11 ambulatory men with stable, oxygen dependent COPD. Room air with supplemental oxygen at 2 l/min was administered in an identical manner for another 24 hours as control therapy in a randomised, double blind, crossover fashion to all patients. Pulmonary function tests, exercise tolerance, dyspnoea and minute ventilation were measured at baseline, 24, and 48 hours. Pulmonary artery pressure (PAP), cardiac output (CO), pulmonary vascular resistance (PVR), arterial blood gas tensions, and minute ventilation were measured at baseline, after 30 minutes and 24 hours of breathing NO and oxygen. Venous admixture ratio (Qs/Qt) and dead space ratio (Vd/Vt) were also calculated. Concentrations of nitrogen dioxide (NO₂) and NO in the inhaled and ambient air were monitored continuously. Differences in pulmonary function, arterial blood gas tensions, pulmonary haemodynamics, exercise tolerance, and dyspnoea between oxygen and NO breathing periods were analysed for significance using paired t tests.

Results—A significant (p<0.05) fall was observed in PVR (183.1 (116.05) and 137.2 (108.4) dynes.s.cm⁻⁵ before and after breathing NO for 24 hours, respectively) with NO administration without significant changes in symptoms, pulmonary function, arterial oxygen tension, or exercise tolerance.

Conclusions—NO at a concentration of 25 ppm blended with oxygen can be safely administered by nasal cannula for 24 hours without significant adverse effects and lowers PVR in stable patients with COPD receiving long term oxygen therapy.
MEASUREMENTS

Complete pulmonary function tests including flow-volume loops and lung volume determination by body plethysmography were obtained. Patients then performed a symptom limited stepwise incremental work load exercise on a treadmill with work load beginning at 0 watts and increasing by 10 watts every minute.17 Heart rate, oxygen saturation by pulse oximetry (SpO₂), and respiratory rate were continuously monitored and recorded at one minute intervals and at the breaking point of exercise. The total exercise time and sensation of dyspnoea on a modified Borg’s dyspnoea scale19 were recorded every day before and after exercise.

After a rest period of three hours the patients were transported to the cardiac catheterisation laboratory and lay supine on the table in a relaxed position. A pulmonary artery balloon flotation catheter (Argon Maxum, Athens, Texas, USA) was then introduced into the pulmonary artery via the antecubital vein and secured in place. PAP was measured using a pressure transducer-oscilloscope system connected to the PA catheter. Expired air was collected for five minutes and carbon dioxide output (VCO₂) and dead space/tidal volume ratio (Vd/Vt) were measured. After three minutes of collecting expired air arterial blood was obtained by arterial punctures using a 22 gauge needle and simultaneously mixed venous blood was obtained from the pulmonary arterial line. Cardiac output (CO) was determined by the carbon dioxide Fick equation using VCO₂ from analysis of mixed expired air and calculations of arterial and mixed venous carbon dioxide contents from directly measured mixed venous and arterial oxygen and carbon dioxide tensions (PO₂ and PCO₂) based on McHardy’s equations20 as discussed by Jones.21 These measurements were validated using the thermodilution technique in 24 samples obtained simultaneously from four patients; a good correlation was obtained (r = 0.6; p<0.01) and the individual values agreed within one litre of each other. Furthermore, values of PVR obtained by the two methods had excellent correlation (r = 0.96).

INTERVENTIONS

The patients then breathed either the control gas or NO in the following manner. NO in concentrations of 200 ppm in nitrogen was stored in tanks (MG Industries, Liverpool, NY, USA) fitted with regulators (high purity regulator, model 98202-2, MG Industries) allowing precise delivery of NO. Patients breathed oxygen by a nasal cannula from tanks containing 100% oxygen at a rate of 2 l/min to which NO was added via a Y connector at a rate of 2 l/min to yield 25 ppm of NO in the inspired air; its actual concentration at the nares was measured and displayed by an electrochemical NO/NO₂ analyser (Pulmonox II, Research & Development Corp, Tofield, Alberta, Canada). The patients were kept in a single room with no special exhaust or air exchange devices. The concentrations of nitrogen dioxide (NO₂) in the inspired and room air were also monitored continuously and recorded by the same device. A similar looking set up was used for delivering oxygen in which the NO tank was shut off and the patient received only supplemental oxygen with air. The flow rate of supplemental oxygen was kept at the patient’s usual rate which was 2 l/min in most cases. A designated respiratory therapist checked on the NO and NO₂ readings every 1–2 hours and recorded them in a log book under the supervision of one of the co-investigators (DS) who administered the gas mixtures and made the switches between the control gas (oxygen/air) and NO (NO/oxygen/air) and ensured the specified delivery of appropriate gas mixtures to the patients. The NO/NO₂ display and the log book were not revealed to the patients. No other investigator was privy to the NO/NO₂ readings or was informed of the identity of the gas mixtures breathed by the patients. The investigator (DS) in charge of the administration and monitoring of the gas mixtures did not participate in the evaluation of patients in any fashion. Thus, neither the patients nor the investigators responsible for making the measurements were aware of the identity of the gas mixture. Control gas and NO were each delivered for 24 hours in a randomised, double blind, crossover fashion. Each subject therefore received 25 ppm NO for 24 hours and oxygen/air for another 24 hours in a randomised order and each served as his or her own control. All measurements were repeated at 30 minutes after the switch in the inhaled gases and at 24 and 48 hours of the study in the same order as previously described for day 1. The concentration of methaemoglobin in the venous blood was also measured at 24 and 48 hours of the study.

STATISTICAL ANALYSIS

The measurements made upon breathing NO for 30 minutes and 24 hours were compared with the baseline values. As all patients received long term oxygen therapy for their COPD, the baseline values were taken to be the measurements breathing oxygen immediately before the switch to NO. These were obtained while breathing the control gas mixture (oxygen/air) for 24 hours for the patients randomised to receive control gas in the first part of the crossover study and the initial measurements, also breathing oxygen/air at the same flow rate were also monitored continuously and recorded by the same device. A similar looking set up was used for delivering oxygen in which the NO tank was shut off and the patient received only supplemental oxygen with air. The flow rate of supplemental oxygen was kept at the patient’s usual rate which was 2 l/min in most cases. A designated respiratory therapist checked on the NO and NO₂ readings every 1–2 hours and recorded them in a log book under the supervision of one of the co-investigators (DS) who administered the gas mixtures and made the switches between the control gas (oxygen/air) and NO (NO/oxygen/air) and ensured the specified delivery of appropriate gas mixtures to the patients. The NO/NO₂ display and the log book were not revealed to the patients. No other investigator was privy to the NO/NO₂ readings or was informed of the identity of the gas mixtures breathed by the patients. The investigator (DS) in charge of the administration and monitoring of the gas mixtures did not participate in the evaluation of patients in any fashion. Thus, neither the patients nor the investigators responsible for making the measurements were aware of the identity of the gas mixture. Control gas and NO were each delivered for 24 hours in a randomised, double blind, crossover fashion. Each subject therefore received 25 ppm NO for 24 hours and oxygen/air for another 24 hours in a randomised order and each served as his or her own control. All measurements were repeated at 30 minutes after the switch in the inhaled gases and at 24 and 48 hours of the study in the same order as previously described for day 1. The concentration of methaemoglobin in the venous blood was also measured at 24 and 48 hours of the study.

| Table 1 Selected mean (SD) clinical data on the study patients |
|-----------------|-----------------|
| No. of patients | 11              |
| Age (years)     | 63 (10.6)       |
| FEV₁ (%)        | 0.89 (0.37)     |
| FEV₁ (%) predicted | 25.8 (9.4)    |
| FVC (%)         | 2.10 (0.75)     |
| FEV₁/FVC (%)    | 43 (8.5)        |
| Haemoglobin (%) | 14.8 (1.1)      |
| TGV (%)         | 231 (90.2)      |
| Dyspnoea (grade)| 4.78 (2.17)     |
| Peak work rate (watts) | 23.5 (22.9) |
| Exercise time (s) | 165 (95)      |
| Duration of COPD (years) | 12 (4)        |
| Smoking history (pack years) | 21 (8)        |

FEV₁ = forced expiratory volume in one second; FVC = forced vital capacity; TGV = thoracic gas volume at functional residual capacity.
Results

The patients were all male veterans with severe COPD who met the criteria for prescription of long term home oxygen and had been clinically stable for at least three months before the study. Selected demographic and clinical characteristics of the patients are given in table 1. The major findings of this study are that the use of NO inhalation in patients with COPD has been previously reported by a number of investigators. NO has been administered via endotracheal tubes in intubated, mechanically ventilated, and non-rebreathing circuits with absorbers, and non-rebreathing circuits with reservoirs. To the best of our knowledge, ours is the first study to show that NO inhalation is safe, generally well tolerated, and not associated with clinically significant increases in methaemoglobin which stayed below 1% throughout the study.

Discussion

The major findings of this study are that the administration of 25 ppm NO with supplemental oxygen at a rate of 2 l/min for 24 hours via a nasal cannula is safe, generally well tolerated, and does not result in a rise in blood concentrations of methaemoglobin or an accumulation of NO in the inhaled gas or ambient air. Furthermore, NO administered in this manner significantly lowers PVR without significant changes in PaO2 or pulmonary function.

Current methods of administration of NO require cumbersome apparatus, closed systems, continuous suction, and absorbers in various combinations. NO has been administered via endotracheal tubes in intubated, mechanically ventilated, frequently paralysed and sedated patients. A workshop on the use of NO recommended continuous scavenging of all exhaust gases in the breathing circuit. Even short term administration of NO for a few minutes during an exercise test has required a closed non-rebreathing circuit in some studies.

The use of NO inhalation in patients with COPD has been previously reported by a number of investigators. However, all of these studies were conducted for short periods lasting from a few minutes to hours only. Furthermore, the methods of NO delivery in these studies included tight fitting face masks, demand valves with wall suction, soda lime absorbers, and non-rebreathing circuits with reservoirs. To the best of our knowledge, ours is

Table 2

Selected measurements on breathing oxygen and NO/oxygen

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (Mean (SE))</th>
<th>NO (Mean (SE))</th>
<th>After NO (Mean (SE))</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2 (kPa)</td>
<td>11.3 (0.6)</td>
<td>11.5 (0.6)</td>
<td>11.5 (0.6)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>PacO2 (kPa)</td>
<td>6.2 (0.5)</td>
<td>6.2 (0.4)</td>
<td>6.2 (0.4)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>PAP (torr)</td>
<td>26.1 (2.5)</td>
<td>25.1 (2.8)</td>
<td>25.1 (2.8)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Systolic PAP (torr)</td>
<td>35.5 (3.5)</td>
<td>36.0 (4.3)</td>
<td>36.0 (4.3)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>P wedge (torr)</td>
<td>13.8 (1.7)</td>
<td>14.3 (1.4)</td>
<td>14.3 (1.4)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>5.9 (0.4)</td>
<td>8.2 (1.1)</td>
<td>8.2 (1.1)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>PVR (dyne.s.cm–3)</td>
<td>183.1 (36.7)</td>
<td>137.2 (34.2)</td>
<td>137.2 (34.2)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Vd/Vt (%)</td>
<td>50.1 (2.5)</td>
<td>52.6 (1.9)</td>
<td>52.6 (1.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>Qs/Qt (%)</td>
<td>7.5 (1.7)</td>
<td>10.9 (0.9)</td>
<td>10.9 (0.9)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*Statistically significant difference.

Baseline = measurements breathing supplemental oxygen with air alone prior to administration of NO; NO = values obtained after 24 hours of breathing NO; difference = values on NO minus baseline values; PaO2, PacO2 = arterial oxygen and carbon dioxide tensions; PAP = pulmonary artery pressure; P wedge = pulmonary wedge pressure; CO = cardiac output; PVR = pulmonary vascular resistance; Vd/Vt = dead space/tidal volume ratio; Qs/Qt = venous admixture ratio.

The use of NO inhalation in patients with COPD has been previously reported by a number of investigators. However, all of these studies were conducted for short periods lasting from a few minutes to hours only. Furthermore, the methods of NO delivery in these studies included tight fitting face masks, demand valves with wall suction, soda lime absorbers, and non-rebreathing circuits with reservoirs. To the best of our knowledge, ours is
the first study of the use of NO for 24 hours using a simple and inexpensive method of delivery in ambulatory patients with COPD performed in a randomised, double blind fashion.

We noted a significant lowering of PVR after 24 hours of NO breathing in all patients, suggesting vasodilation and relaxation of the pulmonary arterial bed. Although the mean and systolic PAP fell slightly, the changes were not significant. Other workers have shown a fall in PAP with administration of NO but their patients had a higher mean PAP than those in our study. We suggest two possible explanations for the absence of a significant fall in PAP in our patients. Firstly, all had received long term oxygen therapy for a long time, were in a stable condition, and had only mildly elevated PAP. None had overt congestive heart failure. We surmise that the PAP could not be lowered any further with NO if these patients had already achieved the maximal reduction in PAP commensurate with their underlying disease with long term oxygen therapy. Alternatively, a rise in CO noted in our study. The rise in CO remains unexplained. However, other workers have also noted a dose dependent rise in CO with the use of NO in patients with ARDS, those undergoing cardiac transplantation, and those with acute right heart syndrome in COPD. Although none of our patients had overt heart failure, they all had severe COPD with an increased likelihood of underlying right ventricular strain or insufficiency. Use of NO could improve CO by reducing the right ventricular afterload in these patients.

Abolition of the hypoxic vasconstrictor reflex could worsen the venous admixture ratio (Qs/Qt) after NO inhalation. However, we noted no significant change in PaO2 or Qs/Qt. The small fall in PaO2 could result from a dilution of oxygen by the inhaled gas mixture during the NO breathing periods. The risks of accumulation of NO in air and significant methaemoglobinemia to the patients seem insignificant with our method of administration. There was no rise in blood concentrations of methaemoglobin or accumulation of NO in the environment or inspired air after administration of NO for 24 hours. This is in agreement with Adatia and colleagues who also showed no rise in NO2 or blood methaemoglobin concentrations after administration of NO in a concentration of 80 ppm for up to 98 hours. No significant adverse effects were noted in our study although four of the 11 subjects complained of cough and a sensation of rawness in the tracheal and substernal areas. In none of them were the symptoms severe enough to withdraw from the study. One of these subjects had underlying reversible airway obstruction suggestive of chronic asthma and possible increased susceptibility to the side effects of NO. It is known that NO has a significant inflammatory effect on the airways and may worsen asthma inflammation.

A formal dose response study of NO was not attempted as it was beyond the scope of the present investigation. We chose to administer 25 ppm of NO based upon the following considerations. A fall in PVR and improvement in oxygenation have been reported with NO concentrations as low as 2 ppm by previous workers. It has also been shown that the maximum haemodynamic response is achieved at concentrations of NO below 1 ppm in patients with ARDS and concentrations of NO higher than 10 ppm are no more effective in improving PaO2 and venous admixture ratios. In another study Katayama et al have shown that a small volume of NO administered at the beginning of each breath was as effective as a vasodilator as a 40 fold higher dose of NO delivered conventionally. On the other hand, inhalation of NO at a concentration of 25 ppm, even for a period as short as 30 minutes, could result in a significant worsening of PaO2 and Va/Q distribution. Therefore, 25 ppm of NO administered by a nasal cannula seemed to be adequate for investigating its therapeutic effects while also being safe.

We conclude that NO in a concentration of 25 ppm can be safely administered to patients with oxygen dependent COPD via nasal cannulae concomitantly with supplemental oxygen for 24 hours without accumulation of NO or a rise in serum levels of methaemoglobin. This method does not require complex apparatus, is well accepted by patients, and seemed to be adequate for investigating its therapeutic effects while also being safe.

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30 Barnes PJ. NO or no NO in asthma. Thorax 1996;51:218–20.


