**CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

Controlled prospective randomised trial on the effects on pulmonary haemodynamics of the ambulatory long term use of nitric oxide and oxygen in patients with severe COPD

K Vonbank, R Ziesche, T W Higenbottam, L Stiebellehner, V Petkov, P Schenk, P Germann, L H Block

**Background:** Pulmonary hypertension is a frequent complication of severe chronic obstructive pulmonary disease (COPD) and a major cause of morbidity and mortality in this condition. Based on the improved survival of these patients due to long term oxygen therapy and the potent and selective pulmonary vasodilation by inhaled nitric oxide, the safety and effectiveness of the combined inhalation of these two gases over a 3 month period was assessed.

**Methods:** Forty patients with secondary pulmonary hypertension due to COPD were randomly assigned to receive either oxygen alone or “pulsed” inhalation of nitric oxide with oxygen over a period of 3 months. “Pulsed” inhalation of nitric oxide was used to reduce pulmonary ventilation-perfusion mismatch and formation of toxic reaction products of nitric oxide and oxygen.

**Results:** Compared with oxygen alone, the combined inhalation of nitric oxide and oxygen caused a significant decrease in mean (SE) pulmonary artery pressure (from 27.6 (4.4) mm Hg to 20.6 (4.9) mm Hg, p<0.001) and pulmonary vascular resistance index (from 569.7 (208.1) to 351.3 (159.9) dyne.s.cm⁻².m⁻², p<0.001) without decreasing arterial oxygenation. Cardiac output increased by 0.5 litres (from 5.6 (1.3) l/min to 6.1 (1.0) l/min, p=0.025). Systemic haemodynamics and left heart function remained unchanged during this period and no increase in toxic reaction products of nitric oxide was observed.

**Conclusions:** This is the first controlled trial indicating that the “pulsed” inhalation of nitric oxide together with oxygen may be safely and effectively used for the long term treatment of severe COPD.

Chronic obstructive pulmonary disease (COPD) is the sixth most common cause of death worldwide. Severe COPD is frequently complicated by pulmonary hypertension, which decreases the 4 year survival rate of patients with COPD from 79% to 46%. Attempts to use vasodilator therapy to reverse pulmonary hypertension in patients with COPD have included calcium channel blockers, dipryridamole, and hydralazine. These drugs lower both pulmonary and systemic vascular resistance causing systemic hypotension and worsen the mismatch between ventilation and perfusion in the lung. Long term oxygen therapy (LTOT), by contrast, improves survival in patients with secondary pulmonary hypertension due to COPD and reduces their pulmonary vascular resistance. In hypoxic lung disease there is evidence of impaired endothelial cell release of nitric oxide (NO). Thus, replacement of NO by long term NO inhalation may aid the reversal of hypoxia induced pulmonary hypertension in COPD. Inhaled NO is a significantly better pulmonary vasodilator than oxygen in COPD, but when used alone it can reduce arterial oxygen tension. We therefore combined long term oxygen and NO therapy in patients with severe COPD. To allow mobility and easy use at home, oxygen and NO were provided by a novel portable inspiratory pulsing device using small storage cylinders for inhaled NO in combination with conventional devices for liquid oxygen therapy.

**METHODS**

**Patients**

Patients were included in the study if they had evidence of COPD according to the criteria of the American Thoracic Society. All patients were at home and had received supplemental oxygen (LTOT) for more than 15 hours per day for over 6 months. None had suffered acute exacerbations of COPD or any active infection for at least 3 months before entering the study. The prescription of LTOT was made in accordance with the recommendations of the Austrian Society for Pneumology with an arterial oxygen tension (PaO₂) at rest and breathing room air of 7.3 kPa (55 mm Hg) or less on three separate measurements. All had a mean pulmonary artery pressure (PAP) of at least 25 mm Hg as diagnosed by right heart catheterisation. During the study period all patients continued their regular medication which consisted of inhaled bronchodilators and steroids, some patients received theophylline, and a few were on low dose oral steroids. There was no change in the medication during the whole study period, and no patients received any new treatment at the beginning of the study.

Patients were excluded from the study if they had any of the following: acute left heart disease, pulmonary wedge pressure >13 mm Hg, atrial fibrillation or flutter, significant coronary artery disease, and myocardial infarction or stroke during the 6 month period before the study.

**Nitric oxide delivery system**

Nitric oxide (900 parts per million (ppm) in nitrogen; Messer Austria, Gumpoldskirchen, Austria) was mixed with nitrogen by a gas blender and delivered via a novel device (NOXXI; Messer Austria). The gas mixture was introduced via a nasal cannula connected to the NOXXI inhalation control system in
order to shorten the time that NO and oxygen spent in the breathing circuit and to reduce the accumulation of the oxidative products of NO such as nitrogen dioxide. This was achieved by delivering a small volume (“pulsed”) of NO in nitrogen 40 ms after the start of inhalation. The amount of NO delivered was the result of the concentration of the gas within the cylinder, the gas flow, and the length of time for which the solenoid valve was open. To achieve a pulse of 50 ml oxygen +20 ppm NO, oxygen flow was adjusted to 4000 ml/min and NO flow to 220 ml/min. Opening the valve for 750 ms for oxygen and 390 ms for NO in nitrogen resulted in a delivery of 2089 µmol oxygen, 59.65 µmol nitrogen, and 53.7 nmol NO. The fall in intrathoracic pressure during early inspiration triggered the delivery of NO and oxygen. Using this method, the maximum contact time for NO and oxygen in the breathing circuit was less than 1 s. The flow of NO and oxygen in the NOXXI system was volumetrically calibrated and verified by an NO/NO₂ chemiluminescence analyser (CLD 700 AL; ECO Physics, Zurich, Switzerland). Inhaled concentrations of oxygen, NO, and its oxidative products were continuously measured by electrochemical cells (Cytec Technology, Hants, UK) during the whole study period. The concentration of nitrogen dioxide did not exceed 1 ppm. The duration of gas delivery was assessed by an internal control system which sensed the opening time of the gas valves. This system permitted precise concentrations of NO to be delivered with low levels of oxidative products.

**Study protocol, lung function, and haemodynamic measurements**

The effect of inhaled oxygen plus NO and that of oxygen therapy alone on pulmonary haemodynamics and pulmonary gas exchange was assessed by a randomised controlled prospective open study. The study protocol was approved by the local ethics committee and informed consent was given by each patient at the time of entry into the study. After the first right heart catheterisation, each patient was randomised by a telephone call to the randomisation centre to receive either oxygen therapy alone or a combination of oxygen and NO (block randomisation technique, block size n=4). The primary end point was the influence of a “pulsed” inhalation of NO in combination with oxygen on the pulmonary vascular resistance index (PVRI) after 3 months of treatment compared with inhaled oxygen alone. During the whole study period all patients inhaled either oxygen and NO or oxygen alone during a 24 hour regimen.

Right heart catheterisation and complete lung function tests were performed at baseline and after 3 months of treatment. Spirometric tests and body plethysmography were performed using the Autobox DL 6200 (SensorMedics, Vienna, Austria). Predicted normal values were derived from the reference values of the Austrian Society of Pulmonary Medicine. Each value represents the better of at least two attempts. Blood gas pressures were determined with an ABL 510 gas analyser (Radiometer, Copenhagen, Denmark).

For right heart catheterisation the patients were admitted to an intensive care unit. During the period of observation no signs of severe stress were observed by changes in blood pressure, heart rate, or respiratory rate. After local anaesthesia a pulmonary artery catheter (REF-Sat; Baxter, Irvine, CA, USA) was inserted via the cubital or jugular vein and guided into the pulmonary artery under permanent electrocardiographic monitoring. The catheter position was confirmed by chest radiography. The pressure transducers were zeroed to the level of the right atrium. A polyethylene catheter (Viggo, Spectramed, Helsingborg, Sweden) was then introduced into the radial artery for direct measurement of Pao₂ and methaemoglobin pressure, and a cannula was inserted into a peripheral arm vein for venous blood sampling. During measurement the patients were controlled online by ECG, invasive measurement of Pao₂, and determination of peripheral oxygen saturation (Hewlett Packard, Böblingen, Germany). Cardiac output (CO) was measured using the thermodilution technique. Each value was the mean of at least five measurements. Haemodynamic measurements were always performed by the same investigator. Pulmonary vascular resistance (PVR) was calculated according to the standard formula. Arterial oxygen tension and methaemoglobin concentrations were repeatedly measured during the last 5 minutes of each inhalation interval using an AVL 912 and AVL 995-Hb spectrophotometer, respectively (AVL, Graz, Austria).

Measurement of baseline conditions was performed during inhalation of 50 ml oxygen per breath. Nitric oxide was then added in concentrations of 10, 15, 20, 25, 30, and 35 ppm as measured at the nasal tube. Each inhalation step lasted 25 minutes. During the last 10 minutes of each step, complete haemodynamic assessment was performed and blood samples were taken from the pulmonary and radial arteries for analysis of blood gas concentrations. In each patient the individual most effective NO concentration (NOₓ) was then determined. NO₃⁻ was defined as the individual concentration that resulted in the largest decrease in PVR without a significant change in Pao₂. This individually determined concentration was later used for NO inhalation therapy. After determination of NOₓ, the patient was randomly assigned to receive either oxygen therapy alone or a combination of inhaled NOₓ and oxygen for a period of 3 months including the second right heart catheterisation. During the study period other treatments such as theophylline and β₂ adrenoceptor agonists continued unchanged.

**Statistical analysis**

After generation of the database, data were collected by the double entry technique. The data were analysed descriptively using the IDV-module report 6.1.05 (IDV-Data Analysis and Study Planning, Report 6.1.05, Munich, 1999). The primary target criterion (PVRI) was compared between treatment groups by analysis of covariance taking the baseline as a covariate. All other tests were performed exploratively by this method or using the Wilcoxon-Mann-Whitney U test, the Mantel-Haenszel test, or the χ² test. Titration results were analysed for within-group comparison using the Wilcoxon-Pratt test. The statistical methods used were the IDV-module testimate 5.2a (IDV-Data Analysis and Study Planning, Testimate 5.2a, Munich, 1996).

**RESULTS**

**Patient characteristics**

Forty patients (13 women, table 1) with severe COPD and secondary pulmonary hypertension who had received LTOT for more than 6 months were examined between July 1998 and January 2000. Mean forced expiratory volume in 1 second (FEV₁) was 1.19 (0.6) l and the ratio of FEV₁ to forced vital capacity (FVC) was 45.1 (13.1%). On acute testing the airflow limitation was irreversible with inhalation of a β₂ agonist. Thirty one patients completed the study. One patient in the control group died as a result of right heart failure during an exacerbation of COPD. Two patients in both treatment groups dropped out because of acute bronchitis during the first 2 weeks after the start of inhalation treatment. One patient in each group was excluded because of previously undetected coronary heart disease during the second spirometric tests, and two patients were excluded for not complying with the 24 hour inhalation regimen. No significant differences were detected between the control group receiving oxygen therapy alone and the group treated with the combination of inhaled NO and oxygen.

**Short term effects of inhaled NO**

During the acute test the combination of inhaled NOₓ and oxygen significantly decreased PVR, PVRI, and mean PAP, and
increased CO and cardiac index (CI) in all patients (table 2). Mean NO concentration was 20 ppm (range 15–25) as measured at the nasal cannula. Pulmonary capillary wedge pressure (PCWP) did not change.

### Long term effects of inhaled NO

After 3 months of treatment the combination of inhaled NO and oxygen caused a significant reduction in PVRI from 569.7 (208.1) to 332.8 (159.9) dyne-s/cm−5 (difference 236.9, 95% CI 180.2 to 373.6, p<0.001) and in PVR from 276.9 (96.6) to 173.1 (87.9) dyne-s/cm−5.m−2 (difference 103.8, 95% CI 87.9 to 120.3, p<0.001). Although not reaching statistical significance, CI increased significantly by 0.5 l/min from 2.7 (0.6) l/min/m to 3.0 (0.4) l/min/m, (difference 0.3, 95% CI –0.1 to 0.7, p=0.889). Mean NO eff was 20 ppm (range 15–25) as measured at the beginning of the study (table 2). Oxygen uptake during spiroergometric tests increased from 896.8 (406.7) ml/min at baseline to 1005.0 (326.3) ml/min after 3 months in the group given NO and oxygen compared with 883.3 (303.5) ml/min (baseline) and 842.7 (232.6) ml/min at 3 months in the control group.

The patients in both treatment groups did not differ in terms of pulmonary ventilation parameters (table 4), with no significant differences in FEV1, total lung capacity (TLC), or residual volume (RV) before and after 3 months of treatment. Comparable results were obtained for arterial oxygenisation: PaO2 did not differ between the treatment groups after 3 months of treatment (from 11.4 (4.2) kPa to 10.6 (1.9) kPa in the oxygen group, difference 0.8, 95% CI –0.8 to 3.4; and from 10.5 (1.8) kPa to 10.1 (1.6) kPa in the group receiving NO+oxygen, difference 0.3, 95% CI –1.0 to 0.4; p=0.037). In contrast, PaCO2 decreased significantly in the patients treated with a combination of NO and oxygen (from 7.4 (1.4) to 6.7 (1.1) kPa, difference 0.8, 95% CI 1.4 to 0.2, p=0.037), which may indicate an improved perfusion of better ventilated areas of the lung. This is strengthened by the finding that PaO2 increased slightly in this group of patients when measured without previous oxygen therapy, although this increase was not significant. Moreover, during acute testing when titrating for the optimum dose of NO, PaO2 also increased. The arterial methaemoglobin concentration did not differ between the two groups of patients (p=0.614). Using a standardised four step

### Table 1 Characteristics of patients at baseline

<table>
<thead>
<tr>
<th></th>
<th>Oxygen alone (n=20)</th>
<th>Oxygen + NO (n=20)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.2 (8.7)</td>
<td>62.0 (7.6)</td>
<td>0.882</td>
</tr>
<tr>
<td>F:M</td>
<td>6:14</td>
<td>7:13</td>
<td>1.000</td>
</tr>
<tr>
<td>Non-smoker at entry</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83.7 (19.3)</td>
<td>87.1 (18.8)</td>
<td>0.516</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.2 (7.9)</td>
<td>169.1 (6.6)</td>
<td>0.578</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>10.1 (1.2)</td>
<td>7.9 (4.1)</td>
<td>0.125</td>
</tr>
<tr>
<td>Duration of LTOT (weeks)</td>
<td>99.1</td>
<td>108.5</td>
<td>0.576</td>
</tr>
</tbody>
</table>

Values are mean (SD). LTOT=long-term oxygen therapy.
Table 4 Parameters of lung function before and after inhalation therapy

<table>
<thead>
<tr>
<th></th>
<th>Oxygen alone (n=17)</th>
<th>Oxygen + NO (n=15)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 3 months</td>
<td>Baseline 3 months</td>
<td></td>
</tr>
<tr>
<td>FEV1 (l)</td>
<td>1.29 (0.7)</td>
<td>1.09 (0.4)</td>
<td>0.742</td>
</tr>
<tr>
<td>FEV1%FVC (%)</td>
<td>45.6 (13.6)</td>
<td>44.5 (13.0)</td>
<td>0.797</td>
</tr>
<tr>
<td>TLC (l)</td>
<td>7.0 (1.4)</td>
<td>6.2 (2.4)</td>
<td>0.836</td>
</tr>
<tr>
<td>RV (l)</td>
<td>4.2 (1.3)</td>
<td>4.2 (1.5)</td>
<td>0.797</td>
</tr>
<tr>
<td>RV/TLC (%)</td>
<td>59.4 (14.8)</td>
<td>59.4 (14.8)</td>
<td>0.138</td>
</tr>
<tr>
<td>Pao2 (kPa)</td>
<td>11.4 (2.4)</td>
<td>10.5 (1.8)</td>
<td>0.739</td>
</tr>
<tr>
<td>PacO2 (kPa)</td>
<td>7.4 (1.4)</td>
<td>7.4 (1.4)</td>
<td>0.037</td>
</tr>
<tr>
<td>PaO2 (kPa)</td>
<td>5.5 (0.6)</td>
<td>5.7 (0.4)</td>
<td>0.512</td>
</tr>
<tr>
<td>Met Hb [mm Hg]</td>
<td>0.4 (0.2)</td>
<td>0.4 (0.1)</td>
<td>0.614</td>
</tr>
</tbody>
</table>

Values are mean (SD).

Oxygen alone (n=17) Oxygen + NO (n=15) p value

FEV1, forced expiratory volume in 1 second; FEV1%FVC, forced expiratory volume in 1 second as a percentage of forced expiratory vital capacity; TLC, total lung capacity; RV, residual volume; RV/TLC, residual volume as a percentage of total lung capacity; Pao2, arterial oxygen tension; PacO2, arterial carbon dioxide tension; PaO2, central venous oxygen tension; Met Hb, partial arterial methaemoglobin pressure.

questionnaire, 38.5% of the patients who received the combination of inhaled NO and oxygen reported an improvement in physical performance after 3 months of treatment compared with only 12.5% of the patients treated with oxygen alone (p=0.047).

**DISCUSSION**

In chronic pulmonary hypertension due to COPD, treatment for 3 months with combined inhalation of NO and oxygen caused a significant improvement in pulmonary haemodynamics together with normal arterial oxygenation which exceeded that of LTOT alone. Moreover, in patients who received combination therapy the vasodilator response to NO after 3 months was larger than that observed during acute testing. Since this effect was not observed in the control group, our data indicate that chronic inhaled NO has a greater effect than oxygen on the pulmonary vasculature.

Nitric oxide is an important contributor to the regulation of pulmonary vascular tone in humans. In hypoxic lung disease the pulmonary endothelium appears to be less able to release NO than normal, probably as a result of reduced expression of constitutive nitric oxide synthase and a concomitant increase in growth mediators such as endothelin-1. Supplementation with inhaled NO is of benefit in the management of pulmonary hypertension of the neonate and a registered treatment of this condition. In pulmonary hypertension of the adult, NO is a selective pulmonary vasodilator which is used for the testing of pulmonary vasoreactivity in primary pulmonary hypertension.

We and others have shown that short term use of NO can improve the pulmonary haemodynamics in patients with COPD. One fundamental problem with inhaled NO is how to apply the gas safely to spontaneously breathing ambulatory patients because inhaled NO can cause formation of pulmonary artery pressure in chronic obstructive pulmonary disease. Thorax 1981;36:752–8.


References


LUNG ALERT

Manufacturing defects in bronchoscopes can lead to nosocomial infections

This paper describes the investigation of an unexpected rise in the number of bronchoscopic cultures growing *Pseudomonas* and *Serratia* spp in a community hospital. Over a 4 month period 20 of 43 samples tested positive for one or both organisms. All 20 positive cultures were from procedures performed using newly purchased bronchoscopes. Identical organisms were isolated from the biopsy port of the new bronchoscopes and the sink trap in the endoscopy unit. One patient was readmitted with *Pseudomonas* pneumonia. During the same period there were no positive samples from older bronchoscopes used in the department. The biopsy port cap was found to be loose on all four new bronchoscopes. The manufacturer subsequently recalled approximately 14 000 bronchoscopes worldwide for modification. New devices are less likely than drugs to have their safety established clinically before they are marketed. Effective surveillance of marketed medical devices could identify low frequency adverse events including those due to changes in design or manufacture and those resulting from interactions between devices or operators.

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