Inhaled nitric oxide in acute respiratory failure in adults

J. D. Young, W. J. Brampton, J. D. Knighton and S. R. Finfer

Summary

We have assessed the acute effects of inhaled nitric oxide 8, 32 and 128 volumes per million (vpm) on pulmonary haemodynamics and arterial oxygenation in patients with severe acute respiratory failure. Fourteen patients requiring artificial ventilation with mean pulmonary artery pressures greater than 30 mm Hg were given inhaled nitric oxide; haemodynamic values and blood-gas tensions were measured before and after 10 min of inhalation of nitric oxide. Nitric oxide inhaled at 8, 32 and 128 vpm decreased mean pulmonary artery pressure by 1.7 (SD 2.2), 3.2 (2.6) and 3.3 (3.3) mm Hg, pulmonary vascular resistance by 20 (64), 53 (57) and 66 (54) dyn s cm⁻⁵ and increased arterial oxygen tension by 2.5 (3.6), 3.0 (5.1) and 2.9 (3.9) kPa, respectively. All changes were significant (P < 0.05 or less) except for changes in pulmonary vascular resistance at 8 vpm. The improvement in arterial oxygenation with 128 vpm was related to pulmonary vascular resistance before commencing nitric oxide. The major beneficial effect of nitric oxide in acute respiratory failure would appear to be improvement in oxygenation rather than reduction in pulmonary artery pressure. The degree of improvement in arterial oxygenation with nitric oxide was related directly to pulmonary vascular resistance before treatment. (Br. J. Anaesth. 1994; 73: 499-502)

Key words
Pharmacology, nitric oxide. Lung, pathophysiology

Severe acute respiratory failure is often associated with pulmonary hypertension [1]. Treatment with systemic vasodilators reduces pulmonary artery pressure but causes systemic hypotension and a decrease in arterial oxygenation by worsening of ventilation-perfusion relationships [2,3]. Nitric oxide is an endogenously produced smooth muscle relaxant [4] which when inhaled causes vascular smooth muscle relaxation and hence pulmonary vasodilatation. Nitric oxide reaching the blood in the lumen of pulmonary vessels is bound rapidly to haemoglobin and inactivated, and so does not cause systemic effects [5]. In addition, as inhaled nitric oxide is distributed in the lung in proportion to local ventilation, ventilation-perfusion relationships should be maintained. Inhaled nitric oxide has been shown to be a selective pulmonary vasodilator in idiopathic pulmonary hypertension [6], primary pulmonary hypertension of the newborn [7,8], adult respiratory distress syndrome [9] and pulmonary hypertension secondary to mitral valve disease [10]. This study was performed to determine the cardiorespiratory effects of three concentrations of inhaled nitric oxide which spanned the therapeutic range for nitric oxide established from previous animal experiments [11].

Patients and methods

The study was approved by the local Ethics Committee. Informed written consent was obtained from the patient's nearest relative. Fourteen patients were studied (table 1). All required mechanical ventilation with 50–100% inspired oxygen and positive end-expiratory pressure (PEEP), 13 patients underwent ventilation with controlled mechanical ventilation and one with inspiratory pressure support. Puritan Bennett "7200" series or Engstrom "Erica" ventilators were used and the settings were unchanged during the study. All patients had pulmonary artery balloon flotation catheters in situ. Nitric oxide (BOC Special Gases, Guildford, UK) was added to the inspiratory limb of the ventilation system as nitric oxide in nitrogen 2000 volumes per million (vpm). This concentration allows manageable and easily measured nitric oxide mixture flow rates while avoiding excessive dilution of the inspired gases with nitrogen. The required flow of nitric oxide–nitrogen mixture was calculated from the final desired concentration and the expired minute volume, as measured by the ventilator using the formula:

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\text{Flow of nitric oxide–nitrogen mixture (litre min}^{-1}\text{)} = \frac{\text{Expired minute volume (litre)} \times \text{desired final nitric oxide concentration (vpm)} - \text{Nitric oxide in mixture (vpm)}}{\text{desired final nitric oxide concentration (vpm)}}
\]

This was delivered via two precision flowmeters

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J. D. Young*, BM, FRCA, DM, W. J. Brampton†, MA, MB, BCHIR, FRCA, J. D. Knighton‡, MB, BS, S. R. Finfer§, MB, BS, MRCP, FRCA, Intensive Care Unit, John Radcliffe Hospital, Headington Way, Oxford OX3 9DU and Intensive Care Unit, Gloucestershire Royal Hospital, Great Western Road, Gloucester GL1 3NN. Accepted for publication: April 7, 1994.

Present addresses:
*Neuffield Department of Anaesthetics, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE.
†Cheltenham General Hospital, Sandford Road, Cheltenham GL53 7AN.
‡Department of Anaesthetics, Southampton General Hospital, Tremona Road, Southampton SO9 4XY.
§Intensive Therapy Unit, Royal North Shore Hospital, St Leonards, NSW 2065, Australia.
Correspondence to J. D. Y.
Nitric oxide caused a small but statistically significant reduction in mean pulmonary artery pressure at each dose and a very modest reduction in central venous pressures with 128 vpm, all other measured pressures and cardiac output were unchanged (table 2). As a result, the calculated pulmonary vascular resistance decreased at each dose; this was statistically significant only at doses of 32 and 128 vpm. Arterial $P_{O_2}$ increased at each dose and as a result the calculated venous admixture decreased. Although the mean results showed a statistically significant improvement in arterial oxygenation, this did not occur in all patients. Figure 1 shows that only patients with increased pulmonary vascular resistance had an increase in arterial oxygenation with nitric oxide 128 vpm; there appeared to be little improvement in oxygenation if the patient's initial pulmonary vascular resistance was less than 300 dyn s cm$^{-5}$. Similar results were obtained with nitric oxide 8 and 32 vpm. In patients with increased pulmonary vascular resistance, improvement in arterial oxygenation was often dramatic; in one patient, $P_{A_{O_2}}$ increased from 9.2 to 28.9 kPa when nitric oxide was first added at 32 vpm. Mean pulmonary artery pressure decreased more with nitric oxide 32 and 128 vpm than with 8 vpm (paired t tests), but no benefit could be shown when nitric oxide increased from 32 to 128 vpm. Arterial oxygen tensions in these patients were not stable during the study, in spite of unchanged inspired oxygen tensions and so the values for $P_{A_{O_2}}$ before administration of nitric oxide are different. The difference in $P_{A_{O_2}}$ values before and after nitric oxide was therefore examined, rather than the absolute value, to determine any dose-dependent effects. No difference was found.

Methaemoglobin concentrations did not exceed 3.7% in any patient during the study. Inhaled nitrogen dioxide concentrations in the last two patients reached a maximum of 6 vpm when nitric oxide 128 vpm was inhaled.
Discussion

The use of nitric oxide in the adult respiratory distress syndrome was reported recently by Rossaint and co-workers [9]. Their results were similar to those presented here; nitric oxide 36 vpm reduced mean pulmonary artery pressure by 7 mm Hg and pulmonary vascular resistance by 78 dyn s cm⁻⁵. They also reported a mean improvement in the \( P_AO_2 / P_FO_2 \) ratio of 4.5 kPa attributed to improvement in the distribution of ventilation-perfusion ratios determined by the multiple inert gas technique. The patients in their study had very severe respiratory failure; six of the patients had venous admixtures of greater than 0.45 and required venovenous extra-corpooreal membrane oxygenation. This may have masked some of the effects of nitric oxide, as venovenous extra-corpooreal membrane oxygenation may also be expected to cause some pulmonary vasodilation by increasing pulmonary arterial \( P_AO_2 \) [12]. The maximum dose of nitric oxide used by Rossaint and colleagues [9] was 36 vpm which is less than the dose for maximum effect determined from animal studies, which is probably 80–100 vpm [11].

Inhaled nitric oxide was proposed originally as a treatment for pulmonary hypertension to reduce right-to-left extrapulmonary shunts in infants [7, 8] or right ventricular afterload in adults [6, 10]. The small reduction in pulmonary artery pressure observed in our study is probably clinically insignificant, although the reduction in central venous pressure with 128 vpm might suggest improvement in right ventricular function as a result of reduced afterload. In a patient with severe pulmonary hypertension, a marked improvement in right ventricular function after treatment with nitric oxide was reported [13]. In our study, patients with higher transpulmonary pressure gradients had a more marked reduction in pulmonary artery pressure after nitric oxide, both in absolute terms and as a fraction of baseline pulmonary artery pressure. This is not surprising as nitric oxide has no effect on basal pulmonary vascular tone, and would be expected to have an effect in proportion to the degree of pulmonary vasoconstriction [14].

Although the mean values for change in arterial \( P_AO_2 \) were 2.5–3 kPa, some patients showed dramatic improvements in \( P_AO_2 \), with a maximum recorded increase of 19.7 kPa. This was probably caused by improvement in the ventilation-perfusion relationship noted by Rossaint and colleagues [9]. Nitric oxide only dilates pulmonary vasculature in areas that are ventilated and thus tends to divert pulmonary blood flow towards ventilated areas. In contrast, i.v. vasodilators are transported by the circulation to all parts of the lung and they dilate all pulmonary vessels, including those in areas without alveolar ventilation. As a result, i.v. pulmonary vasodilators decrease \( P_AO_2 \) [2, 9], whereas nitric oxide increases \( P_AO_2 \). The improvement in arterial oxygenation with inhaled nitric oxide was related to pulmonary vascular resistance before treatment. The higher the pulmonary vascular resistance, the greater the improvement in oxygenation, although the reason for this is unknown.

Unlike the reduction in pulmonary artery pressure, the improvement in arterial oxygenation appeared to be independent of the dose of nitric oxide used. In animal studies the changes in pulmonary vascular resistance and arterial oxygenation occurred in parallel, but a recent study has suggested that inhaled nitric oxide in concentrations as low as 0.06 vpm (60 parts per billion) improved arterial oxygenation without changing pulmonary artery pressures [15, 16]. In human ARDS, the dose-response for the increase in arterial oxygenation with nitric oxide may not parallel the changes in pulmonary artery pressure and the doses used in our study may have elicited a maximum response. Thus there is little need to exceed a dose of nitric oxide 32 vpm for treatment as maximum effects are seen at this dose.

Table 2  Mean (sd) cardiorespiratory variables before and after each dose of nitric oxide (NO) (abbreviations as in table 1). *P < 0.05 compared with corresponding baseline value (paired t tests)

<table>
<thead>
<tr>
<th>Nitric oxide</th>
<th>Mean AP (mm Hg)</th>
<th>Mean PAP (mm Hg)</th>
<th>CVP (mm Hg)</th>
<th>PCWP (mm Hg)</th>
<th>Cardiac output (litre min⁻¹)</th>
<th>( P_AO_2 ) (kPa)</th>
<th>PVR (dyn s cm⁻⁵)</th>
<th>SVR (dyn s cm⁻⁵)</th>
<th>( QVA/QT )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre NO 8 vpm</td>
<td>74.7 (11.4)</td>
<td>37.6 (5.3)</td>
<td>12.8 (3.5)</td>
<td>16.5 (4.7)</td>
<td>6.1 (1.8)</td>
<td>12.2 (8.0)</td>
<td>308 (138)</td>
<td>874 (313)</td>
<td>0.18 (0.13)</td>
</tr>
<tr>
<td>NO 8 vpm</td>
<td>73.6 (10.9)</td>
<td>35.9 (5.9)*</td>
<td>12.9 (3.5)</td>
<td>15.4 (5.3)</td>
<td>6.3 (1.9)</td>
<td>14.7 (10.8)*</td>
<td>288 (119)</td>
<td>845 (350)</td>
<td>0.14 (0.11)*</td>
</tr>
<tr>
<td>Pre NO 32 vpm</td>
<td>72.5 (11.5)</td>
<td>38.1 (4.8)</td>
<td>12.6 (3.3)</td>
<td>16.2 (5.0)</td>
<td>6.2 (1.9)</td>
<td>10.7 (4.1)</td>
<td>315 (120)</td>
<td>847 (363)</td>
<td>0.20 (0.14)</td>
</tr>
<tr>
<td>NO 32 vpm</td>
<td>74 (13.7)</td>
<td>34.9 (5.2)*</td>
<td>11.9 (3.1)</td>
<td>15.4 (5.4)</td>
<td>6.4 (1.7)</td>
<td>13.7 (6.5)*</td>
<td>262 (105)*</td>
<td>833 (335)</td>
<td>0.15 (0.11)</td>
</tr>
<tr>
<td>Pre NO 128 vpm</td>
<td>71.2 (12.2)</td>
<td>37.6 (5.6)</td>
<td>12.2 (3.0)</td>
<td>15.5 (4.8)</td>
<td>6.3 (2.0)</td>
<td>9.3 (2.2)</td>
<td>309 (124)</td>
<td>811 (341)</td>
<td>0.20 (0.11)</td>
</tr>
<tr>
<td>NO 128 vpm</td>
<td>73.1 (12.8)</td>
<td>34.3 (5.3)*</td>
<td>11.4 (2.9)*</td>
<td>16.1 (4.6)</td>
<td>6.6 (1.9)</td>
<td>12.2 (4.6)*</td>
<td>243 (103)*</td>
<td>813 (348)</td>
<td>0.16 (0.12)*</td>
</tr>
</tbody>
</table>

Figure 1  Changes in arterial oxygenation (\( P_AO_2 \)) with nitric oxide 128 vpm in relation to pulmonary vascular resistance (PVR).
Higher concentrations of nitric oxide may cause problems, notably formation of greater quantities of methaemoglobin and nitrogen dioxide. Nitrogen dioxide formation is proportional to oxygen concentration and the square of the nitric oxide concentration, and thus increasing the concentration of nitric oxide from 32 to 128 vpm would cause a 16-fold increase in the rate of formation of nitrogen dioxide. The National Institute of Occupational Safety and Health (NIOSH) recommends a maximum inhaled nitrogen dioxide concentration of 5 vpm and a preferred level of 1 vpm. The maximum nitrogen dioxide concentration recorded in two patients where monitoring was available was 6 vpm, suggesting that the use of nitric oxide 128 vpm would result in excessive exposure to nitrogen dioxide.

Acknowledgements
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References