Placebo-controlled study of inhaled nitric oxide to treat hypoxaemia during one-lung ventilation

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The aim of this prospective, placebo-controlled study was to assess if unilaterally inhaled nitric oxide 20 ppm could treat hypoxaemia during one-lung ventilation. Sixty patients undergoing pulmonary resection using a lateral thoracotomy were allocated randomly to a control or nitric oxide group (NO group). During one-lung ventilation in the lateral decubitus position, the lungs were ventilated mechanically with 90% oxygen–10% nitrogen. After randomization, if \( P_{aO_2} \) decreased to less than 9.3 kPa during one-lung ventilation, nitric oxide 20 ppm or nitrogen was added to the inspired gas. The criterion for treatment efficacy was an increase in \( P_{aO_2} \) to greater than 9.3 kPa after gas administration. Eight patients in the control group and eight in group NO experienced hypoxaemia during one-lung ventilation. \( P_{aO_2} \) was not significantly different in the two groups at the time of gas administration (control group mean 8.0 (SD 0.6) kPa; NO group 8.5 (0.5) kPa). The efficacy criterion was reached in two of eight patients in the control and NO groups. The results of this study showed that inhaled nitric oxide 20 ppm, administered in the dependent lung, was not superior to nitrogen in the treatment of hypoxaemia during one-lung ventilation. Nitric oxide should not be recommended as an alternative to conventional management of hypoxaemia in this condition.

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Hypoxaemia is a well described risk during one-lung ventilation. The decrease in \( P_{aO_2} \) is related mainly to venous admixture (\( Qs/Qt \)) in non-ventilated areas, despite hypoxic pulmonary vasoconstriction (HPV).¹ The incidence of hypoxaemia is variable according to the study conditions and definition of hypoxaemia. The profound arterial desaturation may present a major challenge for the anaesthetist. Several methods have been proposed to correct hypoxaemia. However, the only two effective manoeuvres for improving oxygenation caused by a high \( Qs/Qt \) are intermittent double-lung ventilation or continuous positive airway pressure (CPAP) to the non-dependent lung. Both manoeuvres can impair operative exposure, and thus may be difficult to apply during some surgical manipulations.

Experimental and clinical studies have established that inhaled nitric oxide is a potent vasodilator of the pulmonary vascular bed in a variety of pathological conditions associated with pulmonary arterial hypertension.²⁻⁵ Furthermore, it has been shown to improve oxygenation in patients with adult respiratory distress syndrome (ARDS), probably by increasing blood flow to ventilated lung areas, owing to a reduction in intrapulmonary shunting.⁶ During one-lung ventilation, inhalation of nitric oxide was reported to have no significant effect on oxygenation in the absence of hypoxaemia.⁷⁻⁹ However, it was not known if inhaled nitric oxide could be efficacious in hypoxaemic patients with an open chest in the lateral decubitus position. We hypothesized that in these patients, the increase in pulmonary blood flow in the ventilated lung could be submaximal and increased further by inhalation of nitric oxide.

In this prospective, placebo-controlled study, we have evaluated the effect of inhaled nitric oxide on arterial oxygenation in patients who experienced arterial desaturation during one-lung ventilation with an open chest in the lateral decubitus position.

Patients and methods

This study was approved by our Local Human Investigation Committee and written informed consent was obtained from all patients. We studied patients undergoing pulmonary resection via a lateral thoracotomy requiring one-lung ventilation, and who had a right to left pulmonary blood flow ratio of 45–55% on preoperative nuclear perfusion.
Inhaled nitric oxide and one-lung ventilation

Table 1 Preoperative characteristics of patients who experienced hypoxaemia during one-lung ventilation in the control and nitric oxide (NO) groups (mean (SD or range) or number). FEV₁ = Forced expiratory volume in 1 s. No significant differences

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>NO group</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>52 (44–59)</td>
<td>51 (35–64)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66 (8)</td>
<td>64 (12)</td>
</tr>
<tr>
<td>FEV₁ (%)</td>
<td>71 (12)</td>
<td>70 (12)</td>
</tr>
<tr>
<td>Non-dependent lung perfusion (%)</td>
<td>49 (2)</td>
<td>50 (2)</td>
</tr>
<tr>
<td>Non-dependent lung (right/left)</td>
<td>5/3</td>
<td>4/4</td>
</tr>
</tbody>
</table>

Table 2 Intraoperative respiratory variables of patients who experienced hypoxaemia during one-lung ventilation (1-LV) (P<sub>O₂</sub> 90%) (mean (SD)). No significant differences

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>NO group</th>
</tr>
</thead>
<tbody>
<tr>
<td>P&lt;sub&gt;A&lt;/sub&gt;O₂ (kPa)</td>
<td>2-LV</td>
<td>1-LV inc</td>
</tr>
<tr>
<td></td>
<td>52.4 (4.4)</td>
<td>8.0 (0.6)</td>
</tr>
<tr>
<td>P&lt;sub&gt;A&lt;/sub&gt;CO₂ (kPa)</td>
<td>2-LV</td>
<td>1-LV inc</td>
</tr>
<tr>
<td></td>
<td>5.9 (0.6)</td>
<td>6.2 (0.6)</td>
</tr>
<tr>
<td>pH</td>
<td>2-LV</td>
<td>1-LV inc</td>
</tr>
<tr>
<td></td>
<td>7.39 (0.01)</td>
<td>7.37 (0.03)</td>
</tr>
<tr>
<td>Duration 1-LV to 1-LV inc (min)</td>
<td>14 (5)</td>
<td>13 (3)</td>
</tr>
</tbody>
</table>

No. of patients requiring re-ventilation of non-dependent lung

<table>
<thead>
<tr>
<th></th>
<th>At 1-LV&lt;sub&gt;5&lt;/sub&gt;</th>
<th>At 1-LV&lt;sub&gt;10&lt;/sub&gt;</th>
<th>At 1-LV&lt;sub&gt;15&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

lung scans. Patients with a medical history of respiratory insufficiency, those with a forced expiratory volume in 1 s (FEV₁) of less than 50% of predicted value, and those receiving vasodilators or β-blockers were excluded. The selected patients were allocated randomly before operation to one of two groups to receive nitric oxide (NO group) or nitrogen (control group) if hypoxaemia occurred during one-lung ventilation. All preoperative medications were continued until the morning of surgery, and patients received hydroxyzine 1 mg kg<sup>−1</sup> as premedication. Patient monitoring included pulse oximetry, continuous electrocardiogram, capnography, oesophageal temperature and a 20-gauge radial artery catheter. After placement of a warm pulsed air blanket and a 5-min period of preoxygenation, anaesthesia was induced with fentanyl 3–5 µg kg<sup>−1</sup> and thiopental 3–5 mg kg<sup>−1</sup>. Orotracheal intubation with a left-sided double-lumen tube with carinal hook was facilitated with vecuronium 0.1 mg kg<sup>−1</sup>. The correct position of the tracheal tube was assessed before and after placement of the patient in the lateral decubitus position, by physical examination and fiberoptic bronchoscopy. Anaesthesia was maintained with 0.3–1% isoflurane and bolus doses of fentanyl, as indicated clinically, and the patient received no vasodilator or inotropic agent throughout the study.

Ventilatory variables

During double-lung ventilation (2-LV) in the lateral decubitus position, the lungs were ventilated at a tidal volume of 10 ml kg<sup>−1</sup> and a ventilatory frequency of 12 bpm, breathing a mixture of 90% oxygen–10% nitrogen (open circuit, Siemens 710 ventilator, Sweden). After a 10-min period of equilibration (2-LV<sub>Cont</sub>), ventilatory variables were adjusted to obtain a P<sub>A</sub>CO₂ of 4.6–6.0 kPa. End-expiratory pressure was maintained at zero for both lungs during the study. These ventilatory variables were not modified during one-lung ventilation with the chest open.

Study procedure

Arterial desaturation during one-lung ventilation (1-LV) was defined as a decrease in S<sub>P<sub>O₂</sub></sub> to less than 95%, lasting at least 30 s. If arterial desaturation occurred, haemodynamic status, double-lumen tube position and the ventilatory system were assessed rapidly. In the absence of an abnormality of one of these variables, a blood-gas sample was obtained and analysed immediately using a blood-gas analyser (Nova Biomedical, Waltham, MA, USA) located in the operating room area. The patient was definitely included (inc) in the study if P<sub>A</sub>O₂ at this time (1-LV<sub>inc</sub>) was less than 9.3 kPa. According to the preoperative randomization, the patient then received either nitric oxide 20 ppm or nitrogen at the same flow rate. S<sub>P<sub>O₂</sub></sub> was recorded every 15 s and blood-gas concentrations were analysed every 5 min for 15 min after the start of gas administration (1-LV<sub>5</sub>, 1-LV<sub>10</sub> and 1-LV<sub>15</sub>). The criterion for treatment efficacy was defined as an increase in P<sub>A</sub>O₂, to greater than 9.3 kPa after gas administration. If S<sub>P<sub>O₂</sub></sub> decreased to less than 90%, gas administration was interrupted and the non-dependent lung was ventilated manually with 100% oxygen. During the 15 min of observation, the surgeon was asked not to clamp the pulmonary vessels or to perform pulmonary resection.

In the NO group, nitric oxide from an external tank (450 ppm balanced in nitrogen) was injected via an injection catheter located in the first 3 cm of the tracheal tube lumen of the ventilated lung. The inhaled concentrations of nitric oxide, nitrogen dioxide and oxygen were monitored continuously at the distal part of the tracheal tube using an online chemiluminescent nitrogen oxides analyser (Eco-Physics, Switzerland) and a fast response oxygen sensor based on the paramagnetic principle (Capnomac Ultima, Datex, Helsinki, Finland), respectively. Both analysers were calibrated before starting each study, according to the manufacturer’s instructions. Nitric oxide and oxygen concentrations, and fresh gas flow rates were set according to predetermined values, and adjusted rapidly to yield an oxygen concentration of 90±2% and an inhaled nitric oxide concentration of 20±2 ppm. This was achieved in all patients in less than 2 min. For patients in the control group, nitrogen from an external tank was also delivered into the inspiratory limb of the breathing system at the same flow rate, and gas flow rates were adjusted to yield an F<sub>I</sub>O₂ of 90±2%.

Statistical analysis

Data are presented as mean (SD). Two sample Student’s t-tests and Fisher’s exact tests were used to test for group
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Fig 1 Individual $P_{aO_2}$ values during one-lung ventilation (1-LV) in the nitric oxide (NO) group (A) and in the control group (B) from the time hypoxaemia occurred (1-LV inc) and after 5, 10 and 15 min of gas administration (1-LV 5, 1-LV 10, 1-LV 15, respectively). The criterion for treatment efficacy was an increase in $P_{aO_2}$ to greater than 9.3 kPa.

equivalencies with respect to physical characteristics and preoperative variables. Variables from each group were compared using Student’s $t$-test for repeated measures. Treatment effect was tested using Fisher’s exact test. $P<0.05$ was considered significant. Statistical analysis was performed using StatView 4.1 software (Abacus Concepts, Inc., LA, CA, USA).

Results

Over an 18-month period, 60 patients met the selection criteria and gave written informed consent to be studied. Sixteen patients (26.6%) experienced hypoxaemia during one-lung ventilation, confirmed by blood-gas analysis (eight in group NO and eight in the control group). None of these arterial desaturations was related to haemodynamic instability, double-lumen tube malposition or failure of the respiratory system. There was no significant difference in patient characteristics between the two groups or in the distribution of pulmonary perfusion on nuclear studies, preoperative lung function tests or the side of surgery (Table 1).

During two-lung ventilation, $P_{aO_2}$ and $P_{aCO_2}$ did not differ between groups (Table 2). At the time of inclusion in the study (1-LV inc), mean $P_{aO_2}$ was not significantly different between groups (8.5 (0.5) kPa in the NO group vs 8.0 (0.6) kPa in the control group). Mean duration of one-lung ventilation before inclusion was not significantly different between groups (Table 2).

Individual values of $P_{aO_2}$ in the two groups are presented in Figure 1. Two patients in group NO and two in the control group reached the criterion of treatment efficacy, with an increase in $P_{aO_2}$ to greater than 9.3 kPa after gas administration. In all four patients, the increase was observed at 1-LV 5 and was sustained at 1-LV 15 (Fig 1A, B) (intergroup difference, ns). $S_{pO_2}$ decreased to less than 90% at 1-LV 10 in one patient in group NO and in one patient in the control group, requiring manual ventilation of the non-dependent lung. At 1-LV 15, four patients in group NO and five in the control group were re-ventilated (ns). In group NO, nitrogen dioxide concentration remained less than 0.5 ppm throughout the study.

Discussion

We have shown that inhalation of nitric oxide 20 ppm was no more efficacious than placebo in treating hypoxaemia during one-lung ventilation in the lateral decubitus position for open chest surgery. Inhalation of nitric oxide has been reported to alter pulmonary blood flow distribution in both experimental and human studies.10-11 This effect results from the specific endothelium-dependent relaxant action of nitric oxide on arterial vascular smooth muscle cells. When administered by inhalation, this effect is limited to the pulmonary arterial tree, as nitric oxide is inactivated rapidly when it enters the circulation.2 Furthermore, the effect of inhaled nitric oxide is more pronounced in well ventilated zones of the lung and therefore it favours redistribution of pulmonary blood flow to regions with high $\dot{V}/Q$ ratios. Inhaled nitric oxide decreased intrapulmonary shunting in patients with ARDS and therefore improved oxygenation.6 13 14

The effect of prophylactic inhalation of nitric oxide on pulmonary blood flow and oxygenation during one-lung ventilation has been evaluated in non-hypoxaemic patients.7-9 Rich and colleagues studied the effect of inhalation of nitric oxide 20 ppm on pulmonary vascular resistance (PVR) during one-lung ventilation in the supine position in patients undergoing coronary artery bypass grafting.7 In the absence of arterial hypoxaemia and pulmonary hypertension, inhalation of nitric oxide did not significantly change either PVR or $V_a/Q_t$ at an $F_{O_2}$ of 80%. Wilson and colleagues have shown in six non-hypoxaemic patients that prophylactic inhalation of nitric oxide 40 ppm in the lateral decubitus position did not modify significantly $Q_s/Q_t$, mean pulmonary arterial pressure or PVR during
one-lung ventilation.\(^8\) In a recent study by Moutafis and colleagues, prophylactic inhalation of nitric oxide 20 ppm, administered as soon as one-lung ventilation was initiated, did not prevent the decrease in \(P_{A\text{O}_2}\) observed after two-lung ventilation.\(^9\) These studies suggest that, in the absence of hypoxaemia, inhalation of nitric oxide 20 or 40 ppm does not modify oxygenation, probably because nitric oxide does not vasodilate non-ventilated pulmonary vessels.

However, it was not known if nitric oxide would significantly improve oxygenation if hypoxaemia occurred during one-lung ventilation. In these conditions, a severe \(V\dot{A}/Q\) mismatch is present, related mainly to inadequate hypoxic pulmonary vasoconstriction (HPV) and redistribution of pulmonary blood flow.\(^{13}\) We hypothesized that the increase in pulmonary blood flow observed in the ventilated lung could be less than maximal in these hypoxaemic patients, and could be increased further, at least partially, by inhalation of nitric oxide. Several mechanisms could account for submaximal vasodilatation in the ventilated lung during one-lung ventilation. One of the stimuli for pulmonary blood flow regulation is a function of both mixed venous and alveolar oxygen tension.\(^1\) Despite a high alveolar \(P_{O_2}\) in the oxygen-ventilated lung, a decrease in mixed venous oxygen tension during hypoxaemia could have limited pulmonary vasodilatation in that lung. Furthermore, the ventilated lung may have regions of poor ventilation because of the changes induced by general anaesthesia and the lateral decubitus position with the chest open. This may have triggered a certain degree of pulmonary vasoconstriction in this lung. These areas could have been a target for inhaled nitric oxide to produce pulmonary vasodilatation and redistribution of blood flow to the ventilated lung. This hypothesis was supported by a preliminary study of Hambraeus-Jonzon and colleagues who showed in healthy patients that selective inhalation of nitric oxide 50 ppm in the oxygen-ventilated lung increased further blood flow during contralateral ventilation with a low oxygen concentration mixture.\(^{11}\) In our study, comparison of nitric oxide with placebo showed that the level of hypoxaemia may vary widely with time during one-lung ventilation. This phenomenon was observed in the absence of surgical manipulation of pulmonary vessels and may reflect the dynamic state of pulmonary blood flow distribution in these conditions.

A relatively small percentage of patients experienced hypoxaemia during one-lung ventilation. This may be a result in part of inclusion of patients with a very similar initial lung perfusion ratio between the operated and contralateral ventilated lung. In fact, it has been shown that the incidence of hypoxaemia increased proportionally with inadequate hypoxic alveolar \(Q/s\) variables.\(^{17,18}\) Furthermore, Barberà and colleagues have shown recently that inhalation of nitric oxide during two-lung ventilation may further impair oxygenation in COPD patients.\(^{19}\) This effect was related to pulmonary vasodilatation induced by nitric oxide in poorly ventilated lung areas and to an increase in \(V\dot{A}/Q\) abnormalities. However, patients with moderate COPD were not excluded from our study, as we wanted to assess the effect of nitric oxide in conditions relevant to clinical practice in thoracic surgery. Because of the relatively small number of patients included, the power of the study \((1-\beta)=0.80\) for an \(\alpha=0.05\) could be considered insufficient. However, although a larger study would provide more power, it seems unlikely that a clinical effect of nitric oxide compared with placebo would be demonstrated.

Anaesthesia was maintained in all patients with isoflurane and fentanyl. Isoflurane produces a decrease in PVR that may be mediated in part by endogenous nitric oxide, and inhibits single-lung HPV in a dose-dependent manner.\(^{20,21}\) However, compared with i.v. agents, the increase in intrapulmonary shunting related to isoflurane inhalation at \(\leq1\) MAC was shown to be moderate in humans.\(^{22}\) Therefore, as we were not studying the effect of isoflurane per se, the usual anaesthetic procedure at our institution was carried out. HPV has been reported to be reduced by arterial vasodilators and enhanced by \(\beta\)-blockers.\(^1\) These agents may have altered the response observed during one-lung ventilation and therefore patients receiving these agents were excluded.

As it was impossible to perform a dose–response curve, the widely used concentration of nitric oxide 20 ppm was chosen. In patients with ARDS, oxygenation was improved with low doses of inhaled nitric oxide (\(\leq10\) ppm).\(^{14}\) In contrast, potential toxic effects may limit the concentration of nitric oxide that can be administered safely to a patient. In our study, nitrogen dioxide concentration remained less than 0.5 ppm in the NO group. We did not measure methaemoglobin-bin blood concentrations because of the short period of nitric oxide inhalation and because methaemoglobin concentrations have been shown to remain less than 2\% when a concentration of nitric oxide \(\leq80\) ppm is used.\(^{2,6,14,17}\) A nitric oxide leak to the non-ventilated lung could have inhibited HPV and counteracted the beneficial effect of nitric oxide in the ventilated lung.\(^7\) This hypothesis was raised in the study by Rich and colleagues, who performed one-lung ventilation using a Univent tracheal tube (Fuji Systems, Tokyo, Japan). Although this is unlikely with a double-lumen tube, in preliminary studies we assessed the absence of a nitric oxide leak into the non-ventilated lung by measuring nitric oxide concentration in the main bronchus of the lung.

Because of the study design, invasive monitoring of pulmonary blood flow was not possible, as consecutive patients undergoing thoracic surgery were selected. Therefore, we have not proved an effect of nitric oxide on \(Q/s\) variables. However, in our study, the results suggest that the increase in vasodilatation induced by nitric oxide in the ventilated lung, if present, was minimal and not sufficient to decrease intrapulmonary shunting. Prophylactic
reinforcement of HPV in the non-ventilated lung by the use of a peripheral chemoreceptor agonist such as almitrine, together with nitric oxide inhalation, has been proposed by Moutafis and colleagues to prevent the decrease in \( \text{PaO}_2 \) during one-lung ventilation for thoracoscopic procedures. Whether or not such combinations are helpful in treating severe hypoxaemia during one-lung ventilation needs further investigation.

Acknowledgements

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References

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