Inhalation of a nitric oxide synthase inhibitor to a hypoxic or collapsed lung lobe in anaesthetized pigs: effects on pulmonary blood flow distribution

F. Fredén, J. E. Berglund, A. Reber, M. Hogman and G. Hedensstrerna

Summary
I.v. administration of the nitric oxide synthase inhibitor, nitro-L-arginine methyl ester (L-NAME), not only reduces blood flow in a hypoxic lung region but also causes systemic vasoconstriction and a decrease in cardiac output. In this study, we delivered nebulized L-NAME 0.2–1 mg kg⁻¹ to the left lower lobe of 10 anaesthetized pigs. The left lower lobe was made hypoxic by selective inhalation of 5% oxygen or collapsed by interrupted ventilation, or both. Inhalation of L-NAME reduced fractional blood flow to the left lower lobe from 5.3 (SD 3.1)% to 1.7 (1.4)% (P<0.05) in lobar hypoxia and from 6.0 (3.3) to 2.7 (2.7)% (P<0.05) in lobar collapse. These reductions were accompanied by a significant increase in PAo₂. There were no significant changes in arterial pressure, cardiac output or heart rate. We have shown that selective inhalation of L-NAME reduced blood flow to a hypoxic or collapsed lung region without systemic effects. The possible role for nitric oxide synthase inhibition in reducing shunt during one-lung ventilation, however, requires further study. (Br. J. Anaesth. 1996;77:413–418)

Key words

In 1980, Furchgott and Zawadski1 reported that vasodilatation caused by acetylcholine was endothelium-dependent and that endothelial cells, when stimulated, can release substances that cause relaxation of vascular smooth muscle. One substance has been identified as nitric oxide23.

There is now evidence that nitric oxide is produced in the lung and is important in the regulation of the tone of the pulmonary vessels. Endogenous nitric oxide production has been demonstrated by Gustafsson and colleagues4 who measured nitric oxide in the exhaled breath of rabbits and humans. When the rabbit was hypoxaemic, the exhaled nitric oxide concentration decreased. Nitric oxide synthase, constitutive and inducible, has been found in many cell types in human lung tissue5.

Inhaled nitric oxide at concentrations of 5–80 ppm has been shown to diminish or abolish the hypoxic vasoconstrictor response and pulmonary hypertension caused by thromboxane analogues in conscious lambs6,7 and in a porcine model of adult respiratory distress syndrome (ARDS)8. Inhalation of nitric oxide may reduce pulmonary hypertension in healthy volunteers breathing hypoxic gas9 and in patients with ARDS10.

When endogenous nitric oxide production was blocked by administration of L-arginine analogues, anaesthetized rabbits developed hypoxaemia and an increase in respiratory frequency11. There was also an increase in pulmonary vascular resistance, which was more marked during hypoxia than during normoxia. In regional lung hypoxia, blockage of endogenous nitric oxide production caused a shift of blood away from the hypoxic region and improved arterial oxygenation12,13. By inhaling nitric oxide to the non-hypoxic region, this blood shift was more accentuated and blood flow to the hypoxic region was almost abolished13. These findings indicate that administration of nitric oxide inhibits hypoxic pulmonary vasoconstriction and that blockage of endogenous nitric oxide production enhances it. The combination of inhaled nitric oxide and nitric oxide synthase inhibitors provides a method of altering pulmonary blood flow distribution that may be of clinical use in acute lung injury and in one-lung ventilation. However, i.v. administration of nitric oxide synthase inhibitors causes systemic effects with increased systemic arterial pressure and lowered cardiac output14.

In this study, we have examined the hypothesis that inhalation of a nitric oxide synthase inhibitor, nitro-L-arginine methyl ester (L-NAME), to a hypoxic lung region would decrease blood flow to this region without causing systemic effects. The study was performed in an animal model where hypoxia was induced in the left lower lobe. To simulate one-lung ventilation we also studied the effect of inhaled L-NAME to a subsequently collapsed left lower lobe.

Materials and methods
The study was approved by the Animal Research Ethics Committee of Uppsala University. Twelve pigs of Swedish country breed, weighing 25–32 kg, were used in the study. The animals were premedicated with pentobarbital 20 mg kg⁻¹ and atropine 0.5 mg i.p. Anaesthesia was induced 30 min later with pentobarbital 180–360 mg i.v. and maintained with a continuous infusion of chlorothiazole 800–1600 mg h⁻¹ and pancuronium 4–8 mg h⁻¹. Repeated
doses of fentanyl 0.2–0.5 mg i.v. were given as necessary. After induction, the animals were placed in the supine position for the remainder of the study. Isotonic saline 10–15 ml kg\(^{-1}\) h\(^{-1}\) was given for hydration.

**VENTILATION**

A tracheotomy was performed after induction of anaesthesia and two cuffed tracheal tubes were inserted. One tube with an internal diameter of 6.0 mm was positioned in the trachea and the second, with an internal diameter of 4.5 mm, was placed in the bronchus of the left lower lobe. In this way, the left lower lobe could be isolated and ventilated independently, a technique described in detail in a previous report\(^1\). Two synchronized, volume-controlled ventilators (Siemens Servo ventilator 900 C, Siemens Elema, Lund, Sweden) were used and 30% of the total minute ventilation was administered to the left lower lobe. This volume corresponded to the weight of the left lower lobe as a percentage of the total weight of both lungs (unpublished data, Fredén and colleagues, 1993). Both ventilators were adjusted to give a positive end-expiratory pressure (PEEP) of +5 cm H\(_2\)O and the inspired oxygen fraction \(F_{\text{IO}_2}\) was set at 0.8. The oxygen cell of the ventilator was used to measure \(P_{\text{IO}_2}\). Ventilatory frequency was maintained at 20 bpm and tidal volume was adjusted to obtain \(P_{\text{ACO}_2}\) of 5.2–6.2 kPa. To prevent atelectasis, the lungs were ventilated three times with a double tidal volume at the beginning of each measurement period (see experimental design).

**PREPARATION**

An ear vein was cannulated for induction and maintenance of anaesthesia. A triple-lumen, balloon-tipped catheter (Swan Ganz No. 7-French gauge) was introduced via the right external jugular vein to the pulmonary artery for blood sampling and pressure recording. A large bore catheter was inserted into the contralateral jugular vein for infusion purposes with its tip in the superior caval vein. The right carotid artery was cannulated to measure arterial pressure and sample blood.

Via a median sternotomy, the artery to the left lower lobe and the pulmonary artery were identified, ultrasonic flow probes were attached and connected to a flowmeter (probes, 6 SB and 12 SB; flowmeter, T208; Transonic, Ithaca, NY, USA).

**MEASUREMENTS**

Arterial, central venous and pulmonary artery catheters were attached to appropriate pressure transducers (Sorenson Transpac transducers, Abbott Critical Care Systems, IL, USA). Mean arterial pressure, mean pulmonary arterial pressure, central venous pressure and pulmonary capillary wedge pressure were recorded on a Marquette 7010 monitor (Marquette Electronics Inc., WI, USA). Pressures were averaged over the whole respiratory cycle and the mid-thorax was used as the zero reference level.

Mixed venous and arterial blood samples were collected for blood-gas analysis (ABL 3, Radiometer, Copenhagen, Denmark), oxygen saturation and haemoglobin concentration (OSM 3, Radiometer, Copenhagen, Denmark). Cardiac output and blood flow to the left lower lobe were measured continuously with the flow probes.

Mean airway pressure and expired minute volume were recorded from both ventilators.

**EXPERIMENTAL DESIGN**

After preparation, a rest period of 30 min was allowed before baseline measurements were obtained. Each set of measurements comprised mean arterial pressure, mean pulmonary artery pressure, heart rate, central venous pressure, pulmonary capillary wedge pressure, cardiac output, blood flow to the left lower lobe, arterial and mixed venous blood-gas tensions, saturations and airway pressures. \(F_{\text{IO}_2}\) was maintained at 0.8 in the right lung and the upper and middle lobes of the left lung. Three different settings were used for the left lower lobe: baseline and control (\(F_{\text{IO}_2}\) 0.8), lobar hypoxia (5% oxygen, 5% carbon dioxide and 90% nitrogen (AGA, Lidingo, Sweden)) and lobar collapse (with the ventilator to the left lower lobe disconnected). Thirty minutes were allowed at each setting before measurements were made.

\(\text{L-NAME} \) (Sigma Chemical Co, St Louis, MO, USA) was dissolved in isotonic saline 20 ml and delivered to the left lower lobe with an ultrasonic nebulizer (De Vilbiss, Ultraneb 99, PA, USA). Inhalation of \(\text{L-NAME} \) was always performed during lobar hypoxia as preliminary experiments had shown that inhalation during normoxia caused systemic effects, presumably because of increased absorption of \(\text{L-NAME} \) caused by larger lobar blood flow.

The different experiments used in the study are outlined in table 1. In four animals, the effect of inhaled \(\text{L-NAME} \) was tested during both lobar hypoxia and lobar collapse. To ensure that a preceding period of lobar hypoxia did not interfere with any effects of lobar collapse on blood flow or vice versa, three animals were investigated with lobar collapse only and three with lobar hypoxia only. Evaluation of these different designs showed no differences in the response to lobar hypoxia or collapse and therefore the results are given for the two groups: lobar hypoxia \((n=7)\) and lobar collapse \((n=7)\).

Re-opening of the left lower lobe after lobar collapse was controlled in two ways. Via the thoracotomy, the lobe was examined visually to ensure that no parts of the lobe were atelectatic and, before inhalation of \(\text{L-NAME} \), fractional blood flow to the left lower in the control situation was compared with the baseline recording.

In three of the animals with lobar collapse, a third period of lobar collapse was induced, measurements were performed and followed by i.v. injection of \(\text{L-arginine} 1 \text{ g kg}\(^{-1}\) (Sigma Chemical Co, St Louis, MO, USA) to reverse the effect of \(\text{L-NAME} \), and new recordings were performed.

In two additional animals, \(\text{L-NAME} 0.2 \text{ mg kg}\(^{-1}\) was delivered to both lungs and systemic and pulmonary haemodynamic measurements, and arterial and mixed venous blood-gas tensions were measured during normoxia and hypoxia \((F_{\text{IO}_2} 0.12)\) before and after inhalation. Cardiac output was measured with thermodilution as no thoracotomy was performed, 10 ml of isotonic saline at room temperature were injected as a bolus and cardiac output was computed.
Inhalation of nitric oxide synthase inhibitors in regional hypoxia

Table 1  A survey of the three different experimental designs used in the study showing $F_{0}$ to the right lung and upper and middle lobes of the left lung ($F_{0}$ LL), and $F_{0}$ to the left lower lobe ($F_{0}$ LLL). "X" marks the different steps in each experiment. Experiment I included four animals and experiments II and III three each. Experiments I and II were used for the “lobar hypoxia” group ($n=7$) and experiments II and III for the “lobar collapse” group ($n=7$) (see tables 2 and 3).

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Lobar collapse</th>
<th>Control</th>
<th>Lobar hypoxia</th>
<th>Inhalation L-NAME</th>
<th>Lobar hypoxia</th>
<th>Control</th>
<th>Lobar collapse</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F_{0}$ RL</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>$F_{0}$ LLL</td>
<td>0.8</td>
<td>Non-vent.</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.8</td>
<td>Non-vent.</td>
<td>0.8</td>
</tr>
<tr>
<td>Experiment I (n=4)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Experiment II (n=3)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Experiment III (n=3)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Table 2  Lobar perfusion and arterial oxygenation in the two groups given lobar inhalation of L-NAME (mean (sd)). Fractional blood flow to the left lower lobe ($Q_{LLL}/Q_{T}$) and arterial oxygenation at baseline ($F_{O_{2}}$, 0.8), during lobar hypoxia-collapse before and after L-NAME, and in the control situation ($F_{O_{2}}$, 0.8). Ten animals were used for these two groups; of these, four were studied during both lobar hypoxia and lobar collapse, hence $n=7$ in both groups (also see table 1). Wilcoxon signed rank test was performed to compare baseline with control (*$P<0.05$) and to compare conditions during lobar hypoxia-collapse before and after L-NAME ($\ddagger P<0.05$).

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Before L-NAME</th>
<th>After L-NAME</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobar hypoxia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Q_{LLL}/Q_{T}$ (%)</td>
<td>23.2 (5.5)</td>
<td>5.3 (3.1)</td>
<td>1.7 (1.4)†</td>
<td>18.8 (4.5)*</td>
</tr>
<tr>
<td>$P_{O_{2}}$ (kpa)</td>
<td>39.8 (8.5)</td>
<td>23.3 (6.7)</td>
<td>28.8 (9.2)†</td>
<td>36 (4.6)</td>
</tr>
<tr>
<td>Lobar collapse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P_{O_{2}}$ (kpa)</td>
<td>21.2 (6.5)</td>
<td>6.0 (3.3)</td>
<td>2.7 (2.7)†</td>
<td>19.2 (4.0)</td>
</tr>
</tbody>
</table>

Table 3  Inhalation of L-NAME during lobar hypoxia and lobar collapse (mean (sd)). Data shown are baseline ($F_{O_{2}}$, 0.8) before lobar hypoxia-collapse, during lobar hypoxia-collapse before and after inhalation of L-NAME, and in the control situation ($F_{O_{2}}$, 0.8) after inhalation of L-NAME. Ten animals were used for these two groups; of these, four were studied during both lobar hypoxia and lobar collapse, hence $n=7$ in both groups (also see table 1). Cardiac output ($Q_{T}$), arterial carbon dioxide tension ($P_{aCO_{2}}$), mean arterial pressure (MAP), heart rate (HR), mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), mixed venous oxygen tension ($F_{O_{2}}$) and pulmonary vascular resistance (PVR) are shown. Wilcoxon signed rank test was performed to compare baseline with control in the two groups ($*P<0.5$) and to compare conditions during lobar hypoxia-collapse before and after L-NAME ($\ddagger P<0.05$).

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Before L-NAME</th>
<th>After L-NAME</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobar hypoxia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Q_{T}$ (litre min$^{-1}$)</td>
<td>2.9 (0.6)</td>
<td>3.1 (0.7)</td>
<td>2.8 (0.5)</td>
<td>2.7 (0.6)</td>
</tr>
<tr>
<td>$P_{aCO_{2}}$ (kpa)</td>
<td>5.44 (0.9)</td>
<td>6.07 (0.8)</td>
<td>6.21 (0.5)</td>
<td>5.27 (0.6)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>84 (11)</td>
<td>87 (14)</td>
<td>87 (17)</td>
<td>90 (12)</td>
</tr>
<tr>
<td>HR (beat min$^{-1}$)</td>
<td>118 (18)</td>
<td>130 (21)</td>
<td>139 (26)</td>
<td>132 (30)</td>
</tr>
<tr>
<td>MPAP (mm Hg)</td>
<td>18 (3)</td>
<td>23 (4)</td>
<td>25 (4)†</td>
<td>22 (3)*</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>7 (1.4)</td>
<td>8 (1.6)</td>
<td>9 (1.6)</td>
<td>9 (2.2)*</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>6 (2.7)</td>
<td>7 (2.5)</td>
<td>7 (2.4)</td>
<td>8 (3.1)</td>
</tr>
<tr>
<td>$P_{O_{2}}$ (kpa)</td>
<td>5.9 (0.5)</td>
<td>5.9 (0.4)</td>
<td>6.1 (0.8)</td>
<td>5.8 (0.5)</td>
</tr>
<tr>
<td>PVR (dyne s cm$^{-5}$)</td>
<td>303 (47)</td>
<td>383 (104)</td>
<td>449 (136)‡</td>
<td>425 (118)</td>
</tr>
<tr>
<td>Lobar collapse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Q_{T}$ (litre min$^{-1}$)</td>
<td>3.1 (0.7)</td>
<td>3.2 (0.7)</td>
<td>3.0 (0.5)</td>
<td>2.8 (0.4)</td>
</tr>
<tr>
<td>$P_{aCO_{2}}$ (kpa)</td>
<td>5.6 (0.6)</td>
<td>6.0 (0.3)</td>
<td>6.2 (0.4)</td>
<td>5.8 (0.5)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>80 (7)</td>
<td>83 (10)</td>
<td>88 (9)</td>
<td>85 (6)</td>
</tr>
<tr>
<td>HR (beat min$^{-1}$)</td>
<td>116 (16)</td>
<td>121 (16)</td>
<td>136 (20)</td>
<td>130 (7)</td>
</tr>
<tr>
<td>MPAP (mm Hg)</td>
<td>17 (2)</td>
<td>20 (5)</td>
<td>23 (2)</td>
<td>21 (3)*</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>7 (0.9)</td>
<td>8 (2.8)</td>
<td>8 (1.9)</td>
<td>8 (1.1)</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>6 (2.7)</td>
<td>7 (3.1)</td>
<td>6 (1.8)</td>
<td>6 (1.7)</td>
</tr>
<tr>
<td>$P_{O_{2}}$ (kpa)</td>
<td>5.9 (0.4)</td>
<td>5.8 (0.3)</td>
<td>5.8 (0.5)</td>
<td>6.0 (0.4)</td>
</tr>
<tr>
<td>PVR (dyne s cm$^{-5}$)</td>
<td>276 (57)</td>
<td>309 (101)</td>
<td>401 (85)‡</td>
<td>389 (83)*</td>
</tr>
</tbody>
</table>

Statistics

All data are given as mean (sd). Two paired comparisons were performed: between baseline data before inhalation and control data after inhalation of L-NAME; and between lobar hypoxia–collapse data before and after inhalation of L-NAME. Wilcoxon’s signed rank test was used and $P<0.05$ was considered significant.

Results

Table 2 shows fractional blood flow to the left lower lobe and arterial oxygenation for the two groups with lobar hypoxia and lobar collapse, and table 3 shows other essential data for the two groups. The following recordings are presented: baseline, hypoxia–collapse preceding administration of L-NAME, hypoxia–collapse during lobar hypoxia–collapse before and after inhalation of L-NAME (mean (sd)).
pcollapse subsequent to l-NAME and the last control recording.

BASELINE
At baseline, cardiac output, mean arterial pressure, mean pulmonary arterial pressure, central venous pressure and pulmonary capillary wedge pressure values were similar to those reported previously for pigs undergoing mechanical ventilation with healthy lungs. Fractional blood flow to the left lower lobe was 23.2 (5.5)% in the hypoxic group and 21.1 (6.5)% in the lobar collapse group, which is in accordance with previous reports. Arterial oxygenation was good with $\text{PaO}_2$ values of 38.9 (8.5) kPa and 37.5 (9.9) kPa, respectively. Both groups were normocapnic. During the course of the experiment, mean airway pressure in the left lower lobe varied from 8.7 (0.5) to 9.9 (0.2) cm H$_2$O and, in the right lung and upper and middle lobes of the left lung, 9.9 (0.4) to 10.4 (0.2) cm H$_2$O; these changes were not significant (data not shown in tables).

LOBAR HYPOXIA AND L-NAME
Hypoxia of the left lower lobe caused a marked reduction in fractional blood flow to the left lower lobe to 5.3 (3.1)% and a decrease in $\text{PaO}_2$. Mean pulmonary arterial pressure increased by a mean of 5 mm Hg. Delivery of l-NAME to the hypoxic left lower lobe caused a further reduction in fractional blood flow to the left lower lobe to 1.7 (1.4)% ($P<0.05$) (see fig. 1) and a significant increase in $\text{PaO}_2$. There were no changes in mean cardiac output, heart rate or mean arterial pressure. When the left lower lobe was collapsed a second time, after inhalation of l-NAME, fractional blood flow to the left lower lobe decreased to 2.7 (2.7)% ($P<0.05$) (fig. 2) and $\text{PaO}_2$ increased significantly. There was a small, non-significant increase in mean pulmonary arterial pressure. There were no significant changes in cardiac output, heart rate or mean arterial pressure. When the left lower lobe at the end of the experiment was ventilated with 80% oxygen, fractional blood flow to the left lower lobe and $\text{PaO}_2$ did not differ significantly from baseline (data not shown in tables).

LOBAR COLLAPSE AND L-NAME
Collapse of the left lower lobe caused a reduction in fractional blood flow to the left lower lobe to 6.0 (3.3)% and a decrease in $\text{PaO}_2$. There was also an increase in mean pulmonary arterial pressure by a mean of 3 mm Hg. Re-opening of the lobe ($\text{FiO}_2.0.8$) before l-NAME increased fractional blood flow to the left lower lobe to 19.4 (4.0)% and $\text{PaO}_2$ to 35.8 (6.3) kPa. These values did not differ significantly from baseline (data not shown in tables).

L-ARGININE
I.v. injection of l-arginine 1 mg kg$^{-1}$ to three animals reversed the reduction in fractional blood flow to the left lower lobe caused by inhaled l-NAME. In these pigs with lobar collapse, mean fractional blood flow to the left lower lobe was 9.1% before l-NAME and 3.9% after, while injection of l-arginine increased it to 8.7% (fig. 3).

L-NAME TO BOTH LUNGS
After delivery of l-NAME to both lungs in two animals, there was an increase in mean arterial pressure of approximately 20 mm Hg both during normoxia and hypoxia. There was also an increase in mean pulmonary arterial pressure (3 mm Hg during normoxia and 4–5 mm Hg during hypoxia), but there was no change in cardiac output or arterial oxygenation.

Discussion
The major finding of this study was that selective inhalation of a nitric oxide synthase inhibitor to an hypoxic or subsequently collapsed lobe reduced...
Inhalation of nitric oxide synthase inhibitors in regional hypoxia

When mean pulmonary arterial pressure increased by inhalation of L-NAME caused only a small increase in mean arterial pressure and cardiac output, except when L-NAME and nor L-arginine (L-NAME) and after infusion of L-arginine (L-NAME + L-Arginine). L-Arginine reversed the effect of L-NAME in all three animals.

In regional hypoxia, i.v. administration of nitric oxide synthase inhibitors constricts pulmonary vessels and that this effect is more pronounced during hypoxic conditions. In regional hypoxia, i.v. administration of nitric oxide synthase inhibitors enhances hypoxic pulmonary vasoconstriction and thus diverts blood flow away from the hypoxic region and improves arterial oxygenation. However, i.v. administration of L-NAME causes an increase in mean arterial pressure and decrease in cardiac output, except when used in very small doses.

Administration of L-NAME via the airways to the target organ, that is the hypoxic lobe, caused a reduction in lobar blood flow similar to that seen during i.v. infusion. A much lower dose was delivered by nebulization than by infusion (0.2–1 mg kg⁻¹ vs 30 mg kg⁻¹); however, no dose–response experiments were performed in either study. In this way, systemic effects could also be avoided and neither cardiac output nor mean arterial pressure changed. In addition, inhalation of L-NAME caused a small increase in mean pulmonary arterial pressure by approximately 2–3 mm Hg, which can be compared with the pronounced increase seen after i.v. administration, when mean pulmonary arterial pressure increased by more than 15 mm Hg. Delivery of L-NAME to both lungs in two animals, caused systemic effects with a pronounced increase in mean arterial pressure, presumably because of higher uptake of L-NAME to the systemic circulation.

Inhalation of nitric oxide synthase inhibitors, L-NAME and N⁵-monomethyl-L-arginine (N⁵-NMMA), has been shown previously to cause an increase in tracheal tone and also to induce airway hyper-responsiveness to histamine, carbacol and methacholine. In this study, mean airway pressure did not change during or after inhalation of L-NAME but this does not preclude smaller alterations in airway tone.

In regional hypoxia, the hypoxic vasoconstrictor response has been reported to be complete after 15 min of hypoxia; prolonged hypoxia does not appear to potentiate or decrease this response although one study reported differently. Our measurements were performed after 30 min of hypoxia, at a time when the vasoconstrictor response was assumed to be stable. In atelectasis, the vascular response is of similar magnitude, but Glasser and colleagues reported it to be slower, with a maximal response after 60 min. Our recordings were made after 30 min of lobar collapse, which according to Glasser and colleagues is too early, however, we found that lobar blood flow was always stable after 15–20 min of lobar collapse.

Repeated hypoxic challenges have been reported to potentiate the hypoxic vasoconstrictor response in lobar hypoxia in the dog which, in our study, could be a cause of error. However, there are also reports showing no potentiation of hypoxic pulmonary vasoconstriction in dogs with unilateral hypoxia or in humans. To our knowledge, there are no reports of repeated regional hypoxia induced in pigs but unpublished data from our laboratory showed no enhancement of the hypoxic response after three periods of lobar hypoxia, each lasting for 30 min (Fredén and colleagues, 1995).

In the ventilated lung, alveolar oxygen is the most important determinant of hypoxic pulmonary vasoconstriction but, in atelectasis, P⁰V₂O becomes more important. A reduction in P⁰V₂O could therefore decrease fractional blood flow to the left lower lobe and be a source of error; however P⁰V₂O did not alter in any of the groups in our study (see table 3).

The clinical implication of this study is one-lung ventilation in thoracic surgery. Inhalation of L-NAME to the lung that is not to be ventilated would, according to our results, decrease shunting and improve arterial oxygenation. Improvement in P⁰V₂O in this study was not impressive but it is important to keep in mind that the pig is known to develop a very strong vascular response to hypoxia, and blood flow to the left lower lobe was reduced markedly during hypoxia or the collapse per se (see table 2). Furthermore, the effect of L-NAME may have been more marked if one entire lung had been rendered hypoxic rather than just one lobe. The use of one lobe instead of one lung in this study was because of the bronchial anatomy of the pig, which makes separation of the two lungs difficult. However, increased absorption of L-NAME to the circulation and ensuing systemic effects cannot be excluded if L-NAME is delivered to a whole lung.

In ARDS, inhalation of nitric oxide has been shown to improve oxygenation and lower pulmonary artery pressures. A combination of inhaled nitric oxide and i.v. administration of nitric oxide synthase inhibitor has been tested in animal models of ARDS. Although the results have varied, it appears to be an interesting approach to constrict vessels in shunt areas. Obviously our model based on inhalation of L-NAME would not be feasible in ARDS; it might even be harmful, as L-NAME would only reach the ventilated areas and probably increase the degree of shunting.

In conclusion, the present study has shown that the selective delivery of nebulized L-NAME reduces blood flow to a hypoxic or collapsed lung lobe without causing any systemic effects. It may, in the future, be a way of reducing shunting during one lung ventilation; this, however, requires further study.
Acknowledgements
The study was supported by grants from the Swedish Medical Research Council No. 5315, Marquette Electronics Inc., WI, USA, the Laerdal Foundation for Acute Medicine, Stavanger, Norway and the AGA Medical Foundation, Lidingo, Sweden. We thank Monika Hall for technical assistance.

References

British Journal of Anaesthesia