Individual lung blood flow during unilateral hypoxia: effects of inhaled nitric oxide

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Individual lung blood flow during unilateral hypoxia: effects of inhaled nitric oxide. K. Hambraeus-Jonzon, L. Bindslev, C. Frostell, G. Hedenstierna. ©ERS Journals Ltd 1998.
ABSTRACT: We hypothesized that the diversion of blood away from a hypoxic lung to the opposite oxygenated lung can be enhanced by inhaling nitric oxide (NO) into the oxygenated lung.

We measured individual lung blood flow when 50 ppm NO was selectively inhaled to: a hyperoxic lung during contralateral hypoxia; a normoxic lung during bilateral normoxia; and a hyperoxic lung during bilateral hyperoxia.

Twenty two patients with healthy lungs were studied during intravenous anaesthesia. The lungs were separately and synchronously ventilated. The relative perfusion of each lung was assessed by the inert gas elimination technique.

Unilateral hypoxic (inspiratory oxygen fraction (FI,O$_2$) 0.05) ventilation during contralateral hyperoxia reduced the perfusion of the hypoxic lung from a mean (SD) of 47 (9)% of cardiac output (Q'), to 30 (7)% (p<0.001) of Q'. NO inhalation to the hyperoxic lung increased its blood flow from 70 (7)% to 75 (6)% (p<0.05) of Q', and reduced the blood flow to the hypoxic lung to 25 (6)% (p<0.05). Unilateral NO inhalation during bilateral normoxia or hyperoxia had no effect on pulmonary blood flow distribution.

Nitric oxide inhalation to a hyperoxic lung increases the perfusion to this lung by redistribution of blood flow if the opposite lung is hypoxic.
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The vascular endothelium produces a powerful vasodilating factor that has been identified as nitric oxide (NO) [1]. NO may have a role in the regulation of regional lung blood flow [2]. Blockade of endogenous NO production by an *i.v.* NO synthase inhibitor increased pulmonary vascular resistance (PVR) in hypoxic rabbits. In other rabbit experiments, one-lung hypoxia caused the blood to be diverted away from the hypoxic lung to the opposite hyperoxic lung, and the redistribution was increased during blockade of NO synthase [3]. STAMLER *et al.* [4] partially blocked the L-arginine/NO pathway in humans by giving an arginine analogue in increasing doses and observed how PVR and systemic vascular resistance rose progressively. Inhalation of NO reduces hypoxic pulmonary vasoconstriction, both in animals and humans with healthy and sick lungs [5–7]. The effect of inhaled NO on PVR and arterial oxygen tension (Pa,O$_2$) has also been tested in humans during anaesthesia and one-lung ventilation [8]. Pulmonary artery pressure (Ppa) and PVR were reduced with no change in Pa,O$_2$ in patients with pulmonary hypertension, but there was no effect in patients with normal Ppa. However, it was not clear whether there was a redistribution of blood flow between or within the lungs since no measurements were made of regional blood flow. Significant intrapulmonary redistribution of blood flow away from hypoxic alveoli can occur with no change in Ppa [3]. Moreover, the calculation of PVR suffers from certain limitations [9], and the recording of Pa,O$_2$ may be troublesome because of difficulties in maintaining a constant inspired oxygen fraction (FI,O$_2$) when NO is added to the inspiratory gas. The purpose of the present study was to investigate the effect of unilateral inhalation of NO on individual lung blood flow in patients with normal PVR. If NO did increase diversion of blood away from a hypoxic lung, it would have obvious clinical consequences. We measured the effect of unilateral NO on a hyperoxic lung when the other lung was either hypoxic or hyperoxic, and to a normoxic lung when the other lung was also normoxic, which required that the lungs were ventilated independently. The main finding was that inhalation of NO to a hyperoxic lung had a significant effect on perfusion distribution provided that the other lung was hypoxic. This may make regional inhalation of NO interesting during one-lung anaesthesia. The findings also call for a further investigation of how inhaled NO exerts its effect.

Patients and methods

Patients

The study was approved by the local ethics committee at the Karolinska Hospital. Patients met the entry criteria

if they were listed for elective major abdominal surgery, were aged 18–60 yrs and gave no history or clinical evidence of cardiopulmonary disease. All patients were given a detailed description of the study, orally as well as in writing, before their consent was obtained. Twenty two patients (13 males and nine females, mean (SD) age 40 (10) yrs, height 173 (10) cm, and weight 67 (12) kg) were studied. There were no complications attributable to the investigation.

Anaesthesia

The experimental design is shown in figure 1. Premedication consisted of morphine (0.15 mg·kg^{-1} *i.m.*) and scopolamine (0.006 mg·kg^{-1} *i.m.*) 1 h before anaesthesia. Before induction of anaesthesia each patient was given midazolam (2–5 mg *i.v.*) and was connected to an electrocardiograph (ECG) and a pulse oximeter. ECG, oxygen saturation, and inspiratory and end-tidal oxygen and carbon dioxide concentrations were monitored continuously (Datex AS/3™ Anaesthesia Monitor; Datex Engström, Helsinki, Finland) during the whole experiment. Anaesthesia was induced by thiopental (5 mg·kg^{-1}). Pancuronium bromide (0.1 mg·kg^{-1}) was given for muscle relaxation, and fentanyl (0.1–0.2 mg) was given for pain relief. Intubation was performed with double-lumen, left-sided endobronchial catheters (Portex Twin Lumen Tube, size 5 or 6;
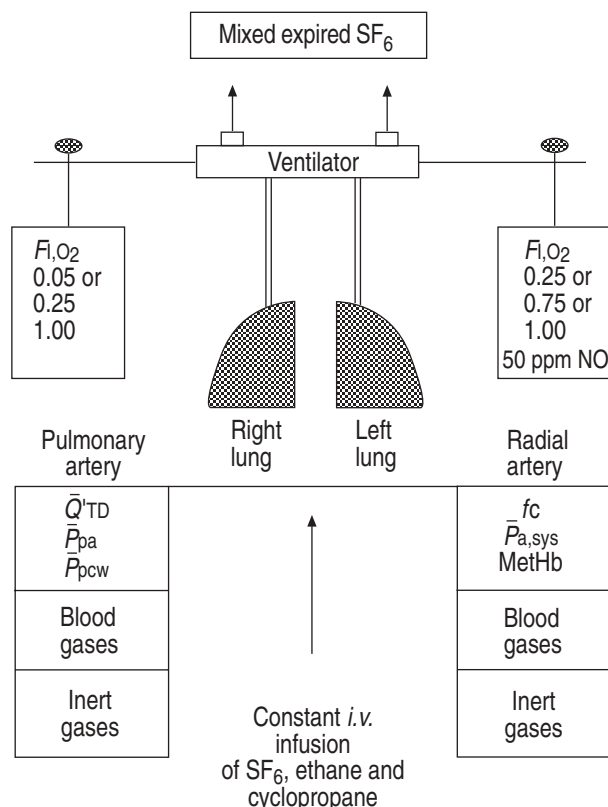

Fig. 1. – The experimental design. F_{I,O_2}: fraction of inspired oxygen; ppm: parts per million; $\bar{Q}'_{TD}$: cardiac output measured by thermodilution; f_C: cardiac frequency; $\bar{P}_{a,sys}$: mean systemic arterial pressure; $\bar{P}_{pa}$: mean pulmonary arterial pressure; $\bar{P}_{pcw}$: pulmonary capillary wedge pressure; MetHb: concentration of methaemoglobin; SF_6: sulphur hexafluoride.

Sims Portex, Keene, NH, USA). The position of the endobronchial tube was checked by fluoroscopy and by inflating each lung separately while auscultating the breath sounds. The lack of leaks from and between the lungs was confirmed by inflating one lung at a time to a constant positive pressure of 10 cmH$_2$O. The different and persistent fractions of expired oxygen during unilateral hypoxia or hyperoxia, as well as the recording of expired NO solely from the lung that received NO during part of the study, were regarded as additional proofs of separation between the lungs. Low and similar peak airway pressures in both lungs were considered signs of unobstructed gas flow thro-ugh the endobronchial tube. Anaesthesia was maintained throughout the experiment with repeated doses of thio-pental (50 mg *i.v.*), midazolam (1–2 mg *i.v.*), and fentanyl (0.05 mg *i.v.*) if systemic artery pressures increased 20% above the initial control value. Pancuronium bromide (1–2 mg) was given if peak airway pressures increased 20% above the initial control value.

Ventilation

After induction of anaesthesia, paralysis, and tracheal intubation, the double lumen tube was connected to a specially designed Engström ventilator with two separate bag-in-box circuits and pressure-operated nonrebreathing valves. Compressed air was delivered to both bag-in-box chambers by the same piston. The respiratory frequency (12 breaths·min^{-1}) in the two circuits remained equal and synchronous with an inspiration:expiration ratio of 1:2. Each circuit was fed from independent flow meters which enabled individual gas mixtures to be supplied to the two lungs. The expired gas volumes from each lung were measured by a spirometer (Gould, Godart expirograph; Gould, Godart, Bilthoven, the Netherlands) and sampled separately in two bags. The lungs were ventilated with equally large tidal volumes to both lungs to obtain an arterial carbon dioxide tension (P_{a,CO_2}) of 4. 5–6.0 kPa. All gas volumes were converted to the volumes at body temperature and pressure, saturated with water vapour (BTPS).

Delivery of nitric oxide

NO was given from a mixture of 200 ppm NO, balance nitrogen (AGA Specialgas; AGA Gas AB, Sundbyberg, Sweden) by a volumetrically calibrated flowmeter conn-ected by a Y-piece to the low-flow inlet of the ventilator. The inspired gas was passed through a canister containing soda lime to absorb any NO$_2$. The concentrations of inspired NO and NO$_2$ were measured in the inspiratory limb of the ventilator tubing, more than 20 cm from the Y-piece, using chemiluminescence detection (9841 NOx; Measurements Controls Corporation, Englewood, USA). Inspired NO$_2$ was less than 0.5 parts per million (ppm).

Haemodynamics

One peripheral venous catheter was inserted for inert gas infusion and another for infusion of anaesthetic agents. The left radial artery was cannulated for pressure recordings and blood sampling. All pressures were recorded with

pressure transducers (Gould Statham P23; Gould Statham Instruments Inc., Hato Rey, Puerto Rico), the signal being fed into an amplifier (Hellige; Hellige GmbH, Freiburg, Germany). The transducers were calibrated against a saline manometer positioned at the mid-thoracic level and zero-ed against atmospheric pressure.

Regional perfusion and shunt

To assess the relative perfusion to the two lungs, the shunt and the cardiac output ($\overline{Q}$'), three poorly soluble gases, sulphur hexafluoride (SF_6), ethane and cyclopropane in saline were constantly infused (3 mL·min^{-1}). Measurements started 40 min after the beginning of the infusion. Mixed expired gas was collected from each lung under steady state conditions and the tracer gas concentrations were measured by gas chromatography (Hewlett Packard gas chromatograph 5890; Hewlett Packard, Palo Alto, Ca, USA). The coefficient of variation for duplicate samples was 3–4%. The ratio between the amount of exhaled SF_6 from the two lungs was assumed to reflect their perfusion ratio. The overall shunt was calculated by measuring the retention (arterial/mixed venous concentration ratio) of the three gases, and using an extrapolation technique [10] the shunt was calculated for both lungs together as perfusion of lung regions with a ventilation/perfusion ratio of less than 0.005. Separate values for the two lungs would have required sampling from the pulmonary veins which was not possible in this study.

The reliability of the method has been confirmed previously in animal experiments [11].

Oxygen and carbon dioxide in blood

The Pa,O_2, mixed venous oxygen tension ($P\overline{v}$,O_2), Pa,CO_2, pH and arterial oxygen saturation (Sa,O_2) were measured or calculated by standard blood gas analysis (ABL 300, Radiometer A/S, Brønshøj, Denmark).

Cardiac output

A triple-lumen, thermistor-tipped, balloon catheter (Swan-Ganz® No. 7F; Baxter Edwards Critical Care, Irvine, CA, USA) was introduced percutaneously by a sleeve technique into the right subclavian vein and the tip of the catheter was advanced to the right middle pulmonary artery during the monitoring of ECG and pressures. The position of the catheter was confirmed by fluoroscopy. $\overline{Q}$' was measured both by thermodilution ($\overline{Q}$'TD) and calculated from the elimination of SF_6 ($\overline{Q}$'SF_6). The results from the two methods were compared using the Bland Altman plot [12]. The mean (SD) difference was -0.3 (1.0) L·min^{-1}. For measurements of $\overline{Q}$' by thermodilution the thermal indicator was 10 mL of 5% glucose at 0–2°C injected into the right atrium. The first measurement was ignored and cardiac output was derived from the mean of the three consecutive measurements (CO, venous oxygen saturation ($S\overline{v}$,O_2) computer, Abbot Laboratories, North Chicago, IL, USA). Since the relative perfusion of each lung was assessed by the elimination of SF_6, we have used $\overline{Q}$'SF_6 for all presentations of data and calculations including $\overline{Q}$'.

Experimental protocol

The patient was supine throughout the study. Three different protocols were used. In all three the left lung was ventilated with hyperoxic (FI,O_2 0.75–1.0) or normoxic (FI,O_2 0.25, balance nitrogen) gas. During part of the experiments the left lung received NO at a concentration of 50 (4) ppm. The right lung was ventilated with either hypoxic (FI,O_2 0.05, balance nitrogen), hyperoxic or normoxic gas. The protocols are detailed below. All references to time, include 10 min of measurements at the end of each ventilator setting before any change of inhaled gas composition.

Protocol I: NO to the hyperoxic lung during contralateral hypoxia. Both lungs were initially ventilated with hyperoxic gas for 25 min. The right lung was then made hypoxic while the left lung was still hyperoxic. After 25 min of unilateral hypoxia, NO was added to the hyperoxic gas to the left lung for 20 min. The NO was then turned off while unilateral hypoxia was continued for a further 25 min. Finally, both lungs received hyperoxic gas for 25 min. Twelve patients (cases 1–12) were studied according to this protocol. For safety reasons, the left lung was ventilated with pure oxygen (FI,O_2 1.0) during contralateral hypoxia. However, when NO was added to the inspired gas the FI,O_2 decreased to 0.75, as an effect of admixing the NO/N_2 gas. When we saw that the arterial oxygenation could be kept at a safe level with one lung hypoxic and the other lung ventilated with an FI,O_2 of 0.75, we added four more patients (cases 13–16), in whom FI,O_2 and $P\overline{v}$,O_2 were kept constant when NO was inhaled. During right lung hypoxia, the left lung was first ventilated with an FI,O_2 of 1.0 for 25 min, followed by a further 25 min on FI,O_2 0.75, before NO was given at a maintained FI,O_2 of 0.75. This also enabled analysis of any time dependence of the response to unilateral hypoxia.

Protocol II: NO to one lung during bilateral normoxia. Both lungs were ventilated with normoxic gas throughout the protocol. After 25 min, NO was added to the normoxic gas ventilating the left lung. After 20 min the NO was turned off while bilateral normoxia was continued for a further 25 min. Six patients participated in this protocol (cases 17–22).

Protocol III. NO to one lung during bilateral hyperoxia. Both lungs were ventilated with hyperoxic gas throughout the protocol. After 25 min, NO was added to the hyperoxic gas ventilating the left lung. After 20 min the NO was turned off, while bilateral hyperoxia was continued for a further 25 min. Six patients participated in this protocol (cases 7–12). They were then included in protocol I to increase the number of patients in that group without exceeding the number of patients that we were allowed to study.

Statistical analysis

Data in the text, tables and figures are presented as mean (SD). A two-way analysis of variance was applied to each continuous variable to find out if there were any differences between various measurement periods within each set of experiments. The patients (random) and the measurement periods (fixed) made up the two block factors.

Table 1. – Effects of nitric oxide (NO) to the hyperoxic lung during contralateral hypoxia

	p-values	Control 1	Unilateral hypoxia 1	NO to left lung	Unilateral hypoxia 2	Control 2
F_{I,O_2}						
Right lung		1.00	0.05	0.05	0.05	1.00
Left lung		1.00	1.00	0.75	1.00	1.00
NO_{LL} ppm		-	-	50	-	-
$Q'_{LL}/\overline{Q}'$ %	<0.0001	53 (9)	70 (7)*	75 (6)*	74 (7)	59 (7)*†
$\overline{Q}'_{SF_6}$ L·min^{-1}	0.9094	4.6 (1.2)	4.6 (0.8)	4.4 (0.8)	4.6 (1.2)	4.4 (1.7)
$\overline{P}_{a,sys}$ mmHg	0.0333	68 (6)	68 (6)	66 (9)	67 (7)	71 (7)*†
$\overline{P}_{pa}$ mmHg	0.0301	11 (3)	12 (2)*	12 (3)	13 (3)	12 (2)*
$\overline{P}_{pcw}$ mmHg	0.6103	7 (2)	7 (1)	7 (2)	7 (2)	7 (2)
S_{a,O_2} %	<0.0001	99.9 (0.0)	98.8 (0.9)*	97.7 (1.7)*	99.1 (0.8)*	99.9 (0.0)*
P_{a,O_2} kPa	<0.0001	63.0 (11.8)	21.0 (9.0)*	15.7 (6.0)	23.9 (8.6)*	65.5 (6.5)*
$P_{\overline{v},O_2}$ kPa	<0.0001	7.7 (1.3)	6.0 (0.6)*	5.7 (0.6)	6.1 (0.8)	7.2 (0.8)*†
P_{a,CO_2} kPa	0.1036	5.4 (0.7)	5.5 (0.5)	5.5 (0.5)	5.5 (0.5)	5.3 (0.6)

Values are presented as mean, and SD in parenthesis, for 12 subjects. Note the reduced inspiratory oxygen fraction (F_{I,O_2}) during the admixing of NO. The p-values are for data collection periods from two-way analysis of variance. *: p<0.05 *versus* preceding value; †: p<0.05 *versus* initial control value. NO_{LL}: NO supplied to left lung; Q'_{LL}: perfusion of the left lung; $\overline{Q}'$: cardiac output; $\overline{Q}'_{SF_6}$: $\overline{Q}'$ measured by sulphur hexafluoride (SF_6) elimination; $\overline{P}_{a,sys}$: mean systemic artery pressure; $\overline{P}_{pa}$: mean pulmonary artery pressure; $\overline{P}_{pcw}$: mean capillary wedge pressure; S_{a,O_2}: arterial oxygen saturation; P_{a,O_2}: arterial oxygen tension; $P_{\overline{v},O_2}$: mixed venous oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension.

The residual variance was used as the test factor and Fisher's test of least significance was used as the *post hoc* test. A probability of less than 0.05 was accepted as significant. The p-values were corrected for multiple comparisons in the least significance difference test. All analyses were made with the SOLO Statistical System (version 4.0, BMDP Statistical Software Inc., Los Angeles, CA, USA).

Results

General findings

During hyperoxic ventilation of both lungs, cardiac output, inert gas shunt and vascular pressures were similar to those in previous studies with global hyperoxia [13–15]. No, or only minor, changes were seen in cardiac output and in systemic artery pressures ($P_{a,sys}$) during unilateral hypoxia or addition of NO to the inhaled gas (tables 1, 2 and 3). The shunts during the initial control periods in set 1, 2 and 3 were 7 (7)%, 3 (2)%, and 10 (10)%, respectively. Since there were no significant changes in shunt between the different data collecting periods within each set of experiments we have assumed a maintained and even distribution of the inert gas shunt within and between the lungs during each set of experiments. These results will not be dealt with further.

Effects of unilateral NO inhalation to the hyperoxic lung during contralateral hypoxia

During the initial control period of bilateral hyperoxia, the right lung blood flow was 47 (9)% and left 53 (9)%. Hypoxic ventilation of the right lung caused a small but significant increase in mean pulmonary artery pressure ($\overline{P}_{pa}$) from 11 to 12 mmHg (p<0.05). The perfusion of the hypoxic right lung decreased to 30 (7)% and the perfusion of the hyperoxic left lung increased to 70 (7)% (p<0.001) (table 1, figure 2). The addition of NO to the inhaled gas to the left lung during ongoing hypoxic ventilation of the right lung, resulted in a further significant increase in the left lung blood flow to 75 (6)% (p<0.05) and a corresponding reduction in the right lung blood flow to 25 (6)%

Table 2. – Effects of unilateral inhalation of NO during bilateral normoxia

	p-values	Control 1	NO to left lung	Control 2
F_{I,O_2}				
Right lung		0.25	0.25	0.25
Left lung		0.25	0.25	0.25
NO_{LL} ppm		-	50	-
$Q'_{LL}/\overline{Q}'$ %	0.1185	49 (3)	51 (2)	48 (5)
$\overline{Q}'_{SF_6}$ L·min^{-1}	0.3164	4.9 (1.0)	4.9 (1.3)	5.1 (1.2)
$\overline{P}_{a,sys}$ mmHg	0.3880	67 (6)	66 (5)	68 (6)
$\overline{P}_{pa}$ mmHg	0.8083	11 (2)	10 (11)	11 (1)
$\overline{P}_{pcw}$ mmHg	0.8083	8 (2)	8 (1)	8 (1)
S_{a,O_2} %	0.9961	98.4 (0.4)	98.4 (0.5)	98.4 (0.3)
P_{a,O_2} kPa	0.7877	15.9 (1.9)	15.4 (1.9)	15.2 (1.1)
$P_{\overline{v},O_2}$ kPa	0.0276	5.5 (0.3)	5.2 (0.3)*	5.3 (0.3)
P_{a,CO_2} kPa	0.2139	5.0 (0.5)	5.1 (0.5)	5.0 (0.5)

Values are presented as mean, and SD in parenthesis, for 6 subjects. The p-values are for data collection periods from two-way analysis of variance. *: p<0.05 *versus* preceding value. For definitions, see legend to table 1.

of $\overline{Q}'$. Pulmonary vascular pressures were unaffected. On discontinuation of NO during ongoing unilateral hypoxia, distribution of blood flow between the lungs did not change significantly compared with the preceding period of breathing NO. The response varied between subjects (fig. 2). Finally, when both lungs were again ventilated with hyperoxic gas, the perfusion of the right lung increased, but was still significantly lower (p<0.01) than during the initial period of bilateral hyperoxia.

The further reduction in blood flow through the hypoxic lung during the NO breathing may raise the question whether the redistribution during NO inhalation was an effect of hypoxia and time rather than NO alone. This was tested with a protocol in which unilateral hypoxia was maintained for 50 min before NO was given (Protocol I, Cases 13–16). No further change in the distribution of lung blood flow was noted during the additional 25 min of unilateral hypoxia without NO (hypoxic lung blood flow 33 (7)% of $\overline{Q}'$ at 25 min and 32 (7)% at 50 min). The response to NO was similar to that seen in the previous group (hypoxic lung blood flow 28 (5)%).

Table 3. – Effects of unilateral inhalation of NO during bilateral hyperoxia

	p-values	Control 1	NO to left lung	Control 2
F_{I,O_2}				
Right lung		1.00	1.00	1.00
Left lung		1.00	0.75	1.00
NO_{LL} ppm		-	50	-
$Q'_{LL}/\overline{Q}'$ %	0.7500	51 (5)	53 (4)	52 (2)
$\overline{Q}'_{SF_6}$ L·min^{-1}	0.3128	4.8 (1.1)	4.8 (2.1)	4.3 (1.4)
$\overline{P}_{a,sys}$ mmHg	0.4400	68 (8)	68 (7)	66 (7)
$\overline{P}_{pa}$ mmHg	0.0563	10 (2)	9 (2)	10 (2)
$\overline{P}_{pcw}$ mmHg	0.0584	6 (1)	6 (1)	6 (1)
S_{a,O_2} %	0.2649	99.9 (0.1)	99.8 (0.1)	99.9 (0.0)
P_{a,O_2} kPa	0.0073	54.9 (9.5)	48.8 (7.7)	60.2 (9.3)*
$P_{\overline{v},O_2}$ kPa	0.2560	8.1 (1.6)	7.5 (0.9)	7.6 (1.8)
P_{a,CO_2} kPa	0.5156	5.6 (0.5)	5.4 (0.6)	5.5 (0.7)

Values are presented as mean, and SD in parenthesis, for 6 subjects. The p-values are for data collection periods from two-way analysis of variance. *: p<0.05 *versus* preceding value. For definitions, see legend to table 1.
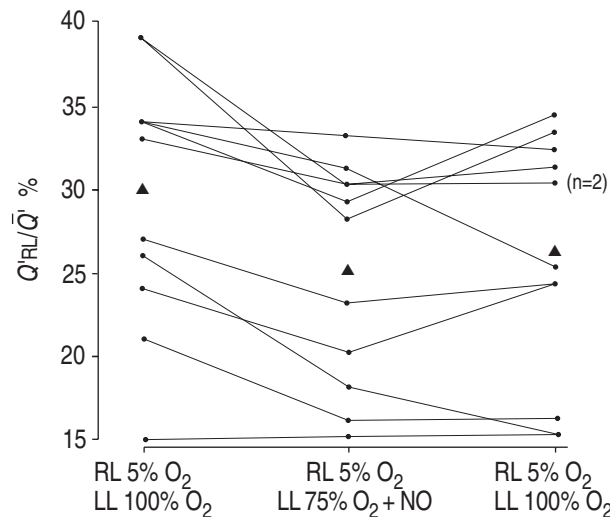

Fig. 2. – Percentage blood flow to the hypoxic (F_{I,O_2} = 0.05) lung during contralateral nitric oxide (NO) inhalation and hyperoxia (n=12). Note the further decrease in relative blood flow to the hypoxic lung in 11 out of 12 cases when NO is given to the other, hyperoxic lung, and the varying effect 25 min after the discontinuation of NO. The solid triangles indicate mean values. Q'_{RL}: perfusion of right lung; $\overline{Q}'$: cardiac output; RL: right lung; LL: left lung.

The S_{a,O_2} was high or normal in all experiments. The single lowest P_{a,O_2} (8.5 kPa) and S_{a,O_2} (90.6%) was observed in case 13 during unilateral hypoxia and contralateral ventilation with F_{I,O_2} 0.75 without NO. In cases 13–16, who were ventilated at a constant F_{I,O_2} of 0.75 before and during NO-inhalation, P_{a,O_2} increased from 12.7 (6.5) to 13.8 (5.5) kPa. In cases 1–12, the expected increase in P_{a,O_2} due to the increase from 70 to 75% of $\overline{Q}'$ to the hyperoxic lung, was obscured by the decrease in F_{I,O_2} from 1.0 to 0.75 due to the addition of NO to the inspired oxygen. $P_{\overline{v},O_2}$ fell during one-lung hypoxia, but was not affected when NO was given.

Effects of unilateral NO inhalation during bilateral normoxia

Neither the addition nor the withdrawal of NO inhalation to the left lung during bilateral normoxia caused any effects on individual lung blood flow or pulmonary vascular pressures (table 2).

Effects of unilateral NO inhalation during bilateral hyperoxia

Neither the addition nor the withdrawal of NO inhalation to the left lung during bilateral hyperoxia caused any effects on individual lung blood flow or pulmonary vascular pressures (table 3).

Methaemoglobin

The mean methaemoglobin concentration was 0.8 (0.2) % at the beginning of the study and was unaffected at the end of the experiment after 20 min of NO breathing (0.8 (0.2)%), with no differences among the protocols.

Discussion

The main finding of the present study was that unilateral inhalation of NO to a hyperoxic lung increased the relative blood flow to that lung by redistribution of perfusion away from the opposite, hypoxic lung. No such redistribution of blood flow by regional NO inhalation was seen when both lungs were either normoxic or hyperoxic. Various attempts have been made to redistribute blood flow away from the nonventilated lung during one-lung anaesthesia. Some effect is obtained by placing the patient in the lateral position with the nonventilated lung uppermost so that it is less perfused than the dependent lung [16]. However, blood flow through the nonventilated lung can still exceed 30% of $\overline{Q}'$ and create a shunt. External compression of a pulmonary artery by a snare or internal occlusion by inflation of a balloon at the tip of a catheter have been tried in animal experiments, but are considered hazardous and seldom used clinically. Pharmacological means of reducing blood flow to the nonventilated lung by regional infusion of a vasoconstrictor such as prostaglandin $F_{2\alpha}$ [17] or vasodilatation of the ventilated lung by regional infusion of a dilator, such as prostaglandin E_1 [18], have also been tested in animal experiments. This requires catheterization of the pulmonary artery and careful control of the position of the catheter. The vasoactive drug exerts its effects solely in the pulmonary circulation, which presupposes rapid breakdown of the drug and an adequate dose. Inhaled NO gas offers advantages in being easy to administer and by exerting its effect locally in the lung [5, 7]. Inhalation of NO during one-lung anaesthesia decreased pulmonary vascular resistance without impeding arterial oxygenation, although the effect was seen only in patients with pulmonary hypertension [8]. The authors did not test whether and to what extent blood flow had been redistributed between the lungs. In the present study we showed that unilateral inhalation of NO to a hyperoxic lung increased the blood flow to this lung by redistribution of perfusion away from the opposite, hypoxic lung. This occurred in patients with normal P_{pa} values.

The mechanism behind the redistribution of lung blood flow when NO is inhaled into a hyperoxic lung during contralateral hypoxia is not clear. A slow vasoconstrictor response to hypoxia that continues to increase during the period of breathing NO can be ruled out, because no increase in the redistribution of blood flow was seen during prolonged hypoxia. The $P_{\overline{v},O_2}$ was unaltered when NO was added to the hyperoxic lung during contralateral hypoxia. This implies that the increased vasoconstriction in the hypoxic lung cannot be explained by any oxygen-dependent stimulus.

A calculation of the vascular resistance of each lung shows that the addition of NO increased the resistance of the hypoxic lung from 333 (162) to 464 (231) dyn·s·cm^{-5} (p<0.01), whereas the change in PVR in the hyperoxic lung was small and insignificant (from 134 (58) to 144 (53) dyn·s·cm^{-5} during NO inhalation). The difference between the two lungs was significant (p<0.001). It must be borne in mind that these calculations reflect merely the blood flow distribution between the lungs as the driving pressure (Ppa - pulmonary capillary wedge pressure ($\overline{P}$pcw)) is assumed to be similar for the two lungs. However, it may be that the action of inhaled NO is more complex than initially thought, with a possible interplay between regions that directly receive NO and other regions. When inhalation of NO is withdrawn there may be a rebound effect with an increase in Ppa [19]. This may be explained by a down-regulation of endogenous NO production during NO inhalation, as NO inhibits NO synthase activity *in vitro* [20]. Whether regional NO inhalation can reduce the production of NO in other lung regions remains to be seen. Recently, J$_{IA}$ *et al.* [21] found that haemoglobin is S-nitrosylated in the lung when red blood cells are oxygenated, and that the protein might act as an NO group donor during arterial-venous transit. A negative feedback mechanism by circulating nitrate has been suggested as the cause of tolerance to nitroglycerine injections that developed after prolonged infusion of nitroglycerine [22].

An alternative explanation is that the vasoconstriction of the hypoxic lung causes an increased vascular tone in the hyperoxic lung as well, which may then be subject to vasodilation by inhaled NO (although we did not see any effect on Ppa). Inhaled NO had no effect on blood flow distribution if both lungs were normoxic or hyperoxic.

An important observation in the present study was that NO had an effect only if the other lung was hypoxic. It raises the question: by what means does inhaled NO dilate vessels in acute respiratory failure? NO is distributed to the aerated and presumably well-oxygenated lung regions, but it still has an effect, as in the present study.

Another observation in the present study was that when the inhalation of NO was discontinued, its effect remained during ongoing unilateral hypoxia. This is similar to the persisting, or slowly disappearing effect of NO during global hypoxia in healthy volunteers [6], but different from the rapid return to baseline, or even rebound effect, that has been reported on the discontinuation of NO in patients with acute respiratory failure [19]. The cause of these different responses remains to be shown.

Although the addition of inhaled nitric oxide to one lung during independent lung ventilation is an interesting concept, the observed salutary effect on blood flow was moderate. This must be taken into consideration together with the unknown total toxicity profile of nitric oxide and risks connected to the delivery equipment. However, it remains an interesting approach to the management of pulmonary perfusion during one-lung anaesthesia.

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