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Combined effects of NO inhalation and intravenous $PGF_{2\alpha}$ on pulmonary circulation and gas exchange in an ovine ARDS model

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Abstract *Objectives:* Inhalation of nitric oxide (NO) selectively dilates pulmonary vessels in well-ventilated regions. Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) is a vasoconstrictor and is reported to enhance hypoxic pulmonary vasoconstriction. The objective of this study was to examine whether the combination of intravenous $PGF_{2\alpha}$ and inhaled NO in ARDS lungs has a beneficial effect on oxygenation.
Design: We investigated the effect of intravenous $PGF_{2\alpha}$ infusion (0.05–10.0 μg/kg per min) with and without NO inhalation (60 ppm) on the hemodynamics and gas exchange in an ovine ARDS model, examining the pulmonary artery pressure versus the flow plot by varying cardiac output.
Measurements and results: After lung lavage, NO inhalation reduced the mean pulmonary arterial pressure (MPAP) by decreasing the zero-flow pressure intercept from 10.6±3.8 (mean±SD) to 8.5±3.8 mmHg ($p<0.05$) with no significant change in slope. NO inhalation improved PaO_2 from 56±12 to 84±38 mmHg ($p<0.005$) and reduced pulmonary shunt from 65±5 to 53±8% ($\dot{Q}s/\dot{Q}t$) ($p<0.001$). The dose-dependent effects of $PGF_{2\alpha}$ infusion were: (1) increased MPAP attributed to an increased slope in pulmonary artery pressure-flow plot; (2) decreased cardiac index; (3) decreased $\dot{Q}s/\dot{Q}t$ with unchanged PaO_2. The dose-dependent decrease in $\dot{Q}s/\dot{Q}t$ after $PGF_{2\alpha}$ infusion was attributed to the decreased cardiac output.
Conclusions: It is suggested that inhalation of NO reduced the critical vascular pressure near alveoli without affecting upstream vessels, while infused $PGF_{2\alpha}$ constricted the larger upstream pulmonary artery vessels without appreciably affecting the critical pressure. Inhalation of NO into well-ventilated lung areas shifted perfusion to well-oxygenated areas, and there was no supplemental shift in blood flow by adding an infusion of $PGF_{2\alpha}$.

Key words Adult respiratory distress syndrome · Nitric oxide · Sheep · Lung lavage · Pulmonary circulation · Pressure-flow relationship

Introduction

Inhalation of nitric oxide (NO) selectively dilates pulmonary vessels in well-ventilated regions without causing systemic hemodynamic effects [1] and can redistribute pulmonary blood flow to well-ventilated (i.e., well oxygenated) lung areas [2], resulting in improved systemic arterial oxygenation. NO inhalation has been widely used in patients with severe adult respiratory distress syndrome (ARDS) [2–4] with severe $\dot{V}_A/\dot{Q}$ mismatching.

Prostaglandine $F_{2\alpha}$ ($PGF_{2\alpha}$) has been reported to enhance hypoxic pulmonary vasoconstriction in isolated

perfused cat lung [5], as well as in anesthetized dogs [6], and was reported to improve systemic oxygenation in a patient with hepatogenic pulmonary angiodysplasia [7]. $PGF_{2\alpha}$ infusion augmented systemic oxygenation during ventilation of one lung when $PGF_{2\alpha}$ was selectively delivered to the non-ventilated pulmonary vessels [8]. If $PGF_{2\alpha}$ constriction is more potent at hypoxic vessels than at normoxic vessels in the lungs, then when $PGF_{2\alpha}$ is delivered to the lungs it is expected to improve systemic oxygenation by reducing the perfusion of poorly oxygenated lung areas, particularly in ARDS lung with severe $\dot{V}_A/\dot{Q}$ mismatching.

We thus expected that the combination of intravenous $PGF_{2\alpha}$ and NO inhalation in ARDS lungs might provide a beneficial effect in redistributing pulmonary blood flow from non-ventilated (i.e., poorly oxygenated) to well-ventilated lung regions by constricting the vessels in non-ventilated lung areas with $PGF_{2\alpha}$, thus adding shunt control to NO-enhanced vasodilation in ventilated lung regions.

The vasodilatory effect of inhaled NO is restricted to the pulmonary vessels, since NO is immediately inactivated by rapid combination with hemoglobin in the blood [9]. The constrictor effect of intravenous $PGF_{2\alpha}$ on lung vessels is reported to be more potent than its effect on systemic circulation [10, 11], since $PGF_{2\alpha}$ is metabolically inactivated by conversion to the dehydro-keto-metabolite at up to 68% of the intravenous dose during a single pass through the pulmonary circulation [12]. At low doses, the vasoconstrictor effect of $PGF_{2\alpha}$ might also be limited to the pulmonary circulation. The combined effects of intravenous $PGF_{2\alpha}$ and inhaled NO were thus expected to be limited to the pulmonary circulation and not produce systemic hemodynamic changes.

The specific questions in this study were: (1) Will $PGF_{2\alpha}$ administration result in improved oxygenation by reducing the perfusion of poorly oxygenated lung areas in ARDS lungs? (2) Will $PGF_{2\alpha}$ and NO administration together prove beneficial in redistributing pulmonary blood flow from non-ventilated to well-ventilated lung regions?

To answer these questions, we investigated the dose-dependent effects of a wide dose range of intravenous $PGF_{2\alpha}$ (0.05–10.0 μg/kg per min) on oxygenation as well as hemodynamic parameters in an ARDS model with and without NO inhalation.

Materials and methods

These studies were approved by the Subcomittee on Research Animal Studies of the Massachusetts General Hospital and conform with the *Guide for the care and use of laboratory animals* published by the US National Institutes of Health. Thirteen Suffolk lambs weighing 28–32 kg were anesthetized with intravenous pentobarbital sodium (30 mg/kg), intubated, and mechanically ventilated at 10–20 breaths/min and 15 ml/kg tidal volume with a large animal ventilator (Harvard Apparatus, Natick, Mass.) to produce a $PaCO_2$ of 35–45 mmHg. Positive end-expiratory pressure (PEEP) was maintained at 7.2 mmHg (10 cmH_2O). Fractional inspired oxygen was 0.89 to 1.0 and monitored continuously (Hudson Ventronics Division, Temecula, Calif.). Anesthesia was maintained by a continuous intravenous infusion of 4 mg/kg per h pentobarbital sodium, and muscles were paralyzed by administering pancuronium (0.1 mg/kg) every 2 h. Core body temperature was maintained at 36–39 °C with an external heater.

A 7F thermodilution pulmonary artery (PA) catheter (Edwards Laboratory, Santa Ana, Calif.) was placed via the right external jugular vein through an 8F introducer (Cordis, Miama, Fla.). Mean PA pressure (MPAP) and central venous pressure were measured through the catheter. Blood samples for mixed venous blood gas tensions were obtained through the PA catheter. PO_2, PCO_2, and blood pH were measured using an automated blood gas analyzer (Model 238 pH/Blood gas analyzer, Ciba-Corning) at 37 °C and were corrected for body temperature measured by the PA catheter. Cardiac output was measured by the thermodilution method and indexed to body surface area. The body surface area in m^2 for sheep was calculated as body weight $(kg)^{2/3} \times 0.121$ [13]. A polyvinyl chloride catheter was placed in the femoral artery to measure mean systemic arterial pressure (MSAP) and obtain arterial blood samples for blood gas measurements. A left atrial line was placed by a sterile left thoracotomy via the fifth intercostal space to measure mean left atrial pressure (LAP). After left arterial catheter insertion, an initial intravenous dose of 300 U/kg heparin was administered, and subsequently 100 U/kg was given every 2 h to prevent clotting.

To manipulate cardiac output and obtain pressure-flow (MPAP–CI) plots, a 12F Foley catheter with a 10 ml balloon was placed in the inferior vena cava to regulate venous return, and the left carotid artery was connected to the left jugular vein with a large-bore polyethylene tube (3.5 mm ID at arterial side and 7 mm ID at venous side) with a screw clamp to control the arteriovenous shunt flow. The sequence of the cardiac output manipulations (control, balloon inflation of the inferior vena cava, and a-v shunt open) was randomized. Hemodynamic and gas exchange parameters were measured 5 to 10 min after the manipulation of cardiac output.

A double-lumen endotracheal tube (39Fr, Sheridan Catheter Inc., Argyle, N.Y.) was placed through a tracheostomy for lung lavage. Bilateral lung lavage was performed with 0.5% polyoxyethylene-sorbitan mono-oleate (Tween 80, Sigma Chemical, St. Louis, Mo.) in 37 °C saline according to Rovira et al. [14]. Briefly, each lung was lavaged twice with 250 ml fluid. After each lavage, the fluid in the airway was drained by gravity and vigorously suctioned. To achieve a homogeneous distribution of lavage fluid, the position of the sheep was changed from supine to the lateral position and vice versa during lavage. The residual volume of the lavage solution was about 30%. After lavage the double-lumen tube was exchanged for a tracheostomy tube. For 30 min after lavage, the ventilation rate or tidal volume was modified to attain a $PaCO_2$ of 35–45 mmHg, and pHa was adjusted to between 7.3 and 7.5 by injecting a sodium bicarbonate solution. One hour after lavage, pulmonary and systemic hemodynamic parameters and blood gas tensions were measured. The same measurements were repeated after $PGF_{2\alpha}$ infusion, with or without 60 ppm NO inhalation. The NO concentration of inspired gas was continuously monitored by a chemiluminescence NO-NOx analyzer (Model 14A, Thermo Environmental Instruments, Franklin, Mass.). $PGF_{2\alpha}$ (Sigma Chemical, St. Louis, Mo.), dissolved in a saline solution, was continuously infused through the femoral vein. The dose of $PGF_{2\alpha}$ was randomly chosen from 0.05 to 10 μg/kg per min. Hemodynamic and gas exchange parameters were measured after 15 min of $PGF_{2\alpha}$ infusion and 30 min of NO inhalation, since preliminary studies showed that these parameters stabilized after 5 min of continuous $PGF_{2\alpha}$ infusion and 15 min of NO inhalation.

Data analysis

Pulmonary and systemic vascular resistance [mmHg/(l/min)] were indexed to the body surface area (m^2) as PVRI and SVRI and calculated as the pressure differences divided by the cardiac index [mmHg/(l/min per m^2)]. Hemoglobin concentration was measured spectrophotometrically (model 300-N, Gilford Instruments, Oberlin, Ohio) using the cyanohemoglobin method. Pulmonary shunt ratio, $\dot{Q}s/\dot{Q}t$, was calculated as $(Cc'O_2 - CaO_2)/(Cc'O_2 - CvO_2)$, where CaO_2 is the oxygen content in arterial blood, CvO_2 the oxygen content in mixed venous blood, $Cc'O_2$ the oxygen content equilibrated with PAO_2 (torr), which was calculated as $PIO_2 - PaCO_2$ at FIO_2 near 1 [15]. After temperature correction for PO_2, PCO_2, and pH, the oxygen content in the blood was calculated using a standard formula [16]. $\dot{D}O_2$ [ml(STPD)/min] was calculated as CaO_2 [ml(STPD)/dl] $\times \dot{Q}$[l/min] $\times 10$[dl/l], and was indexed to the body surface area as $\dot{D}O_2$ [ml(STPD)/min per m^2].

We calculated the ratio (R) for each parameter obtained after $PGF_{2\alpha}$ infusion (with or without NO inhalation) by dividing by the control value of the parameter before the infusion (no $PGF_{2\alpha}$ with or without NO inhalation). The dose-dependent effect of $PGF_{2\alpha}$ infusion ranging from 0.05 to 10.0 μg/kg per min on the R value of each parameter was obtained with 15 measurements using 13 sheep without NO inhalation (one to two measurements/one sheep), as well as with 18 measurements with NO inhalation using the 13 sheep (one to two measurements/one sheep). In some sheep, before, between, and after the different $PGF_{2\alpha}$ doses, the baseline values were confirmed as stable.

Assuming no difference in the R values (similar response to $PGF_{2\alpha}$) between with and without NO inhalation, a sigmoid dose-response curve fitting was employed using a least squares method based upon all measurements (with and without NO inhalation), as

$$R = 1 - (1 - E_{max}) \times [PGF_{2\alpha}]/(ED_{50} + [PGF_{2\alpha}]) \quad (1)$$

where ED_{50} is the dose of 50% response, E_{max} is the amount of 100% response, and $[PGF_{2\alpha}]$ is the amount of $PGF_{2\alpha}$ (μg/kg per min) infused.

To examine the change of the pressure-intercept as well as the slope of MPAP–CI plots based upon all the measurements (with and without NO inhalation), sigmoid curve fitting was employed as

$$\Delta\text{pressure-intercept or } \Delta\text{slope} = E_{max} \times [PGF_{2\alpha}]/(ED_{50} + [PGF_{2\alpha}]) \quad (2)$$

where Δpressure-intercept is the increase in the pressure-intercept after $PGF_{2\alpha}$ infusion; Δslope is the increase in slope after $PGF_{2\alpha}$ infusion.

MPAP–CI plots and $\dot{Q}s/\dot{Q}t$–CI plots were obtained by interpolating MPAP–CI and $\dot{Q}s/\dot{Q}t$–CI values from the regression equation, where an r value > 0.75 was chosen to express linear relationships, and the pressure-intercept (MPAP extrapolated to CI = 0) and slope of each plot were obtained for all sheep ($n = 13$) before lavage, after lavage, after NO inhalation, and for 8 sheep during $PGF_{2\alpha}$ infusions ranging from 0.05 to 5.0 μg/kg per min without NO inhalation (one dose/sheep), and for 12 sheep during $PGF_{2\alpha}$ infusion with NO inhalation (one dose/sheep).

The $\dot{Q}s/\dot{Q}t$–CI plot was obtained during $PGF_{2\alpha}$ infusion, and $\dot{Q}s/\dot{Q}t$ measured during $PGF_{2\alpha}$ infusion was corrected to a $\dot{Q}s/\dot{Q}t$ value corresponding to the CI without $PGF_{2\alpha}$, since $PGF_{2\alpha}$ infusion decreased CI and $\dot{Q}s/\dot{Q}t$ was decreased dependent upon CI, as reported in other studies [17–19].

Statistical analysis

Values are expressed as means ± SD unless noted. A paired t-test was used to compare hemodynamic and gas exchange parameters as well as slopes and intercepts. After fitting the $PGF_{2\alpha}$ dose-response curve, the statistical significance compared with a null hypothesis, i.e., no response after intravenous $PGF_{2\alpha}$ infusion, was evaluated applying the chi-square likelihood ratio test with 2 degrees of freedom (i.e., ED_{50} and E_{max}).

Results

Changes in hemodynamic and gas exchange parameters after lung lavage and NO inhalation

After lung lavage the MPAP significantly increased ($p < 0.005$ differs versus baseline), PaO_2 significantly decreased ($p < 0.005$), and $\dot{Q}s/\dot{Q}t$ was significantly increased ($p < 0.005$), while MSAP, LAP, CI, PVRI, SVRI, and $\dot{D}O_2$ did not change significantly (Table 1). When NO inhalation followed lavage, MPAP and $\dot{Q}s/\dot{Q}t$ decreased ($p < 0.001$), while PaO_2 increased ($p < 0.005$). However, MSAP, LAP, CI, PVRI, SVRI, and $\dot{D}O_2$ did not change significantly.

Table 1 Hemodynamic and gas exchange parameters before and after lung lavage with and without NO inhalation and/or $PFG_{2\alpha}$ infusion. Values are mean ± SD (*LL* after lung lavage, *NO* NO 60 ppm inhalation, *PG 0.5* $PGF_{2\alpha}$ 0.5 μg/kg per min infusion, *PG 5* $PGF_{2\alpha}$ 5 μg/kg per min infusion)

	n	MSAP (mmHg)	MPAP (mmHg)	LAP (mmHg)	CI ($l \cdot min^{-1} \cdot m^{-2}$)	PVRI ($mmHg \cdot l^{-1} \cdot min \cdot m^2$)	SVRI	PaO_2 (torr)	$\dot{Q}s/\dot{Q}t$ (%)	$\dot{D}O_2$ [mlO_2 (STPD) $\cdot min^{-1} \cdot m^{-2}$]
Baseline (before lung lavage)	13	103 ± 16	14.8 ± 3.6	5.3 ± 2.6	4.2 ± 2.1	2.9 ± 1.3	27.7 ± 9.9	424 ± 109	22 ± 10	549 ± 329
Lung lavage	13	102 ± 16	19.9 ± 3.7***	5.5 ± 4.6	4.7 ± 1.4	3.5 ± 2.0	22.6 ± 8.2	56 ± 12****	65 ± 5****	501 ± 223
LL + NO	13	99 ± 20	16.5 ± 3.1****	5.4 ± 3.7	4.2 ± 1.4	2.9 ± 1.2	24.3 ± 8.7	84 ± 38***	53 ± 8****	478 ± 211
LL + PG 0.5	6	103 ± 13*	22.9 ± 3.7	3.3 ± 3.5	5.1 ± 1.4	3.9 ± 2.2	18.9 ± 3.6	40 ± 7*	70 ± 6	480 ± 158
LL + NO + PG 0.5	7	97 ± 15	17.3 ± 1.6*	4.4 ± 3.9	4.4 ± 0.7	3.1 ± 1.5	21.8 ± 4.9	60 ± 12	58 ± 8	466 ± 107
LL + NO + PG 5	5	102 ± 36*	20.6 ± 5.2	4.8 ± 6.0	3.1 ± 0.8	5.1 ± 3.1	33.1 ± 16.6	71 ± 34	50 ± 13*	329 ± 50

Paired t-test for baseline vs LL, LL vs LL + NO, LL + NO vs LL + NO + PG, LL vs LL + PG: *$p < 0.05$; **$p < 0.01$; ***$p < 0.005$; ****$p < 0.001$

Changes in hemodynamic and gas exchange parameters with $PGF_{2\alpha}$ infusion

$PGF_{2\alpha}$ infusion produced a significant dose-dependent increase in MPAP (Fig. 1a), PVRI (Table 2), MSAP (Fig. 1b), and SVRI (Table 2), while the CI was low during $PGF_{2\alpha}$ infusion at higher doses (Fig. 1c).

Intravenous $PGF_{2\alpha}$ infusion at doses ranging from 0.05 to 10 μg/kg per min did not significantly change the

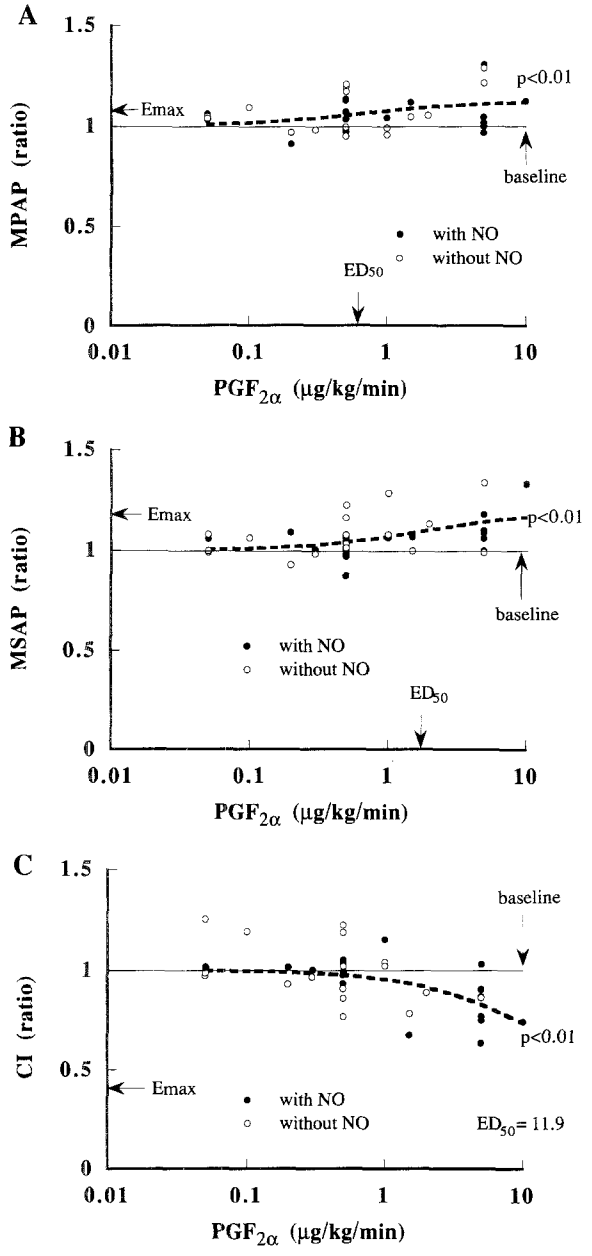

Fig. 1 Hemodynamic parameters during $PGF_{2\alpha}$ infusion with or without 60 ppm NO inhalation. Each parameter is expressed as a relative ratio to the baseline level (before $PGF_{2\alpha}$ infusion). **A** Mean pulmonary arterial pressure (*MPAP*); **B** mean systemic arterial pressure (*MSAP*); **C** cardiac index (*CI*)

Table 2 ED_{50} and E_{max} of the dose-response curves of intravenous $PGF_{2\alpha}$ infusion (*Unit for* ED_{50} μg/kg per min, E_{max} no unit (expressed as a ratio to the baseline value before $PGF_{2\alpha}$ infusion) except for pressure-intercept, mmHg, and slope, mmHg/(l/min per m^2) for MPAP – CI plot, *Qs/Qt corrected* Qs/Qt value corrected for the reduced cardiac output during $PGF_{2\alpha}$ infusion based upon the Qs/Qt – CI plot)

Parameter	*n*	ED_{50}	E_{max}	
MPAP	37	0.64	1.12	**
PVRI	33	2.97	1.70	**
MSAP	37	1.75	1.20	**
SVRI	37	14.6	2.65	**
CI	37	11.9	0.42	*
PaO_2	33	–	1.00	NS
Qs/Qt	33	4.79	0.82	**
DO_2	33	3.58	0.68	**
Qs/Qt corrected	20	–	1.00	NS
Pressure-intercept	21	0.68	1.77	NS
Slope	21	20.0	6.13	**

*$p<0.05$, **$p<0.01$ differs versus no response to intravenous $PGF_{2\alpha}$ infusion

PaO_2 (Table 2), while Qs/Qt (Fig. 2a), and DO_2 (Table 2) were decreased at higher doses of $PGF_{2\alpha}$ infusion.

Changes in Qs/Qt with $PGF_{2\alpha}$ infusion obtained on the Qs/Qt – CI plots at corrected CI values

When Qs/Qt values during $PGF_{2\alpha}$ infusion with or without NO inhalation were recorded on the Qs/Qt – CI plots at a CI value equal to the control value (before the $PGF_{2\alpha}$ infusion with or without NO inhalation), the Qs/Qt values were unchanged at all levels of $PGF_{2\alpha}$ infusion (see Fig. 2b).

Hemodynamic and gas exchange parameters at 0.5 and 5.0 μg/kg per min $PGF_{2\alpha}$ compared with baseline

MPAP was significantly increased ($p<0.05$ differs versus the value before $PGF_{2\alpha}$ infusion) at 0.5 μg/kg per min $PGF_{2\alpha}$ infusion during NO inhalation (see Table 1). At 5.0 μg/kg per min $PGF_{2\alpha}$ infusion, MSAP was significantly increased ($p<0.05$) during NO inhalation, while Qs/Qt was significantly decreased and MPAP did not change. Without NO inhalation, 0.5 μg/kg per min $PGF_{2\alpha}$ infusion significantly increased MSAP ($p<0.05$), and significantly decreased PaO_2.

The PA pressure-intercept and slope of MPAP – CI plots

The zero-flow PA pressure-intercept of MPAP – CI plots significantly increased after lung lavage, but returned to

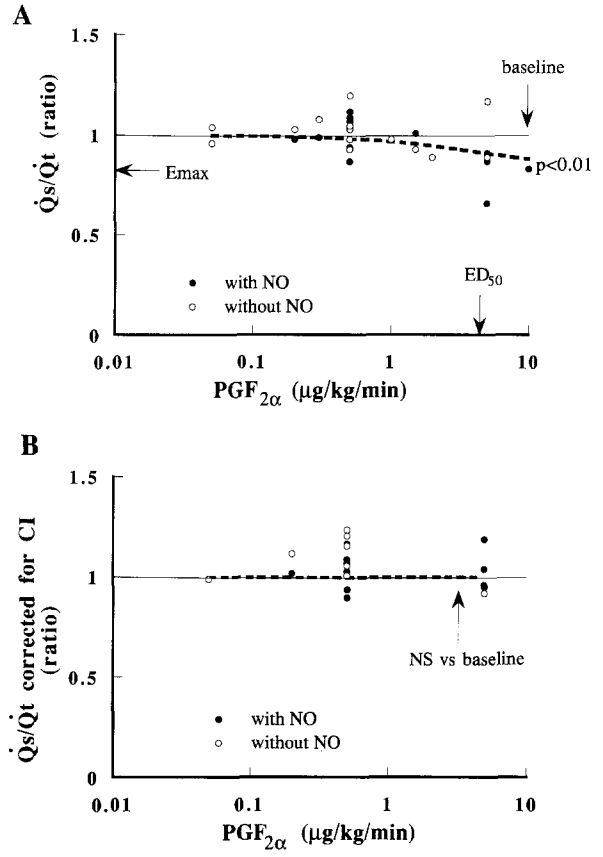

Fig. 2 $\dot{Q}s/\dot{Q}t$ during $PGF_{2\alpha}$ infusion ranging from 0.05 to 10.0 μg/kg per min with or without 60 ppm NO inhalation, **A**, and $\dot{Q}s/\dot{Q}t$ corrected to the cardiac output without $PGF_{2\alpha}$ infusion based upon $\dot{Q}s/\dot{Q}t$–CI plots **B**

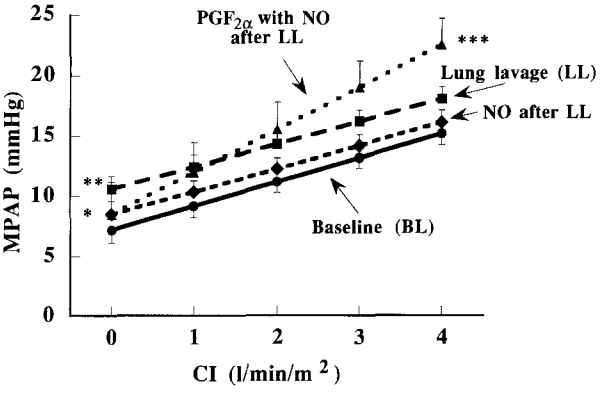

Fig. 3 MPAP–CI graph. *Baseline* before lung lavage; *lung lavage* after lung lavage; *NO* 60 ppm NO inhalation after lung lavage. $n = 13$, mean ± SE (error bar); $PGF_{2\alpha}$, 5.0 μg/kg per min intravenous infusion with NO inhalation after lung lavage, $n = 4$. Zero-flow PA pressure intercept: $^{*}p < 0.05$ for LL versus BL; $^{**}p < 0.01$ for NO versus LL. The slope of MPAP–CI graphs: $^{***}p < 0.05$ for $PGF_{2\alpha}$ with NO after LL versus NO

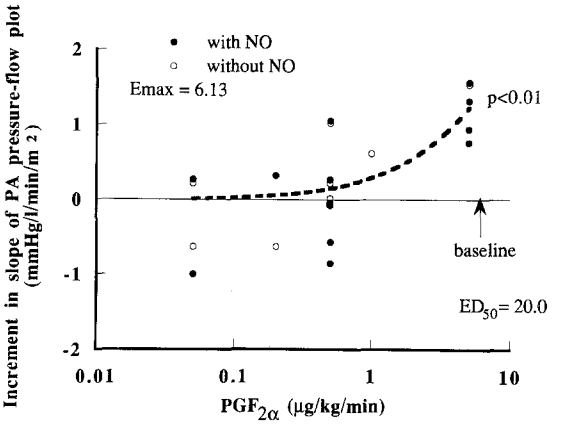

Fig. 4 $PGF_{2\alpha}$ dose-response of the slope of the PA pressure-flow plot. A dose-dependent increase of the slope was noted

the baseline level after 60 ppm NO inhalation without any significant change in the slope, while 5.0 μg/kg per min $PGF_{2\alpha}$ infusion with NO inhalation significantly increased the slope without any significant change in the zero-flow PA pressure-intercept compared with NO inhalation without $PGF_{2\alpha}$ infusion (Fig. 3).

A dose-dependent increase in the slope of the MPAP–CI plot during $PGF_{2\alpha}$ infusion ranging from 0.05 to 5.0 μg/kg per min was noted (see Fig. 4), while there was no change of the PA pressure-intercept with $PGF_{2\alpha}$ infusion ranging from 0.05 to 5.0 μg/kg per min (Table 2).

Discussion

ARDS model

One cause of the microatelectasis that occurs in ARDS patients is believed to be an acute lung surfactant disorder due to altered surfactant composition and pool size, abnormal surfactant metabolism, and inactivation of alveolar surfactant by serum proteins present within the airspace [20]. The ARDS model we used was reported by Lachmann et al. [21] and results in the collapse and flooding of alveoli, producing major inhomogeneities of ventilation and perfusion distribution. In this model the lung's vascular system should not be damaged, and it therefore differs from many other ARDS models (e.g., oleic acid). Using this lavage model, Rovira et al. [14] reported stable hemodynamic and gas exchange measurements after lavage for up to 4 h. Therefore, we chose to study this ARDS model.

Hemodynamics and gas exchange after NO inhalation

NO is a potent vasodilator that is normally produced in vascular endothelial cells and activates soluble guanylate cyclase in vascular smooth muscle cells [22], resulting in an increased level of guanosine 3′, 5′-cyclic monophosphate. NO inhalation produces dilatation of pulmonary resistance vessels by this mechanism, but is rapidly inactivated by combination with hemoglobin molecules in the blood [9]. The effect of inhaled NO was limited to the pulmonary circulation and it produced no changes in the systemic circulation, as previously reported [1, 23].

The concentration of inhaled NO we selected was 60 ppm, since at this concentration PaO_2 improved maximally in the lavaged lung in a dose-response study by Rovira et al. [14]. Inhaled NO increases PaO_2 and decreases $\dot{Q}s/\dot{Q}t$ in lavaged lungs. Since inhaled NO would be delivered to alveoli along with oxygen, vessels in well-ventilated regions would be dilated, and perfusion would be shifted from poorly ventilated to well-ventilated lung areas with a lower regional vascular resistance, resulting in improved matching of ventilation and perfusion. It is also possible that inhaled NO, delivered to peripheral airways, dilated the bronchioles of well-ventilated lung areas, resulting in a further improvement of the matching of ventilation and perfusion in the lungs. The bronchodilatory effect of inhaled NO has been reported in guinea pigs [24] and humans [25]. The presence of nitric oxide synthase in airway nerves [26] suggests a regulatory role of NO in controlling airway resistance.

One of the aims of ARDS therapy is to avoid barotrauma due to increased airway pressure by decreasing PEEP and mean airway pressure while maintaining adequate PaO_2 and $\dot{D}O_2$. The improvement in PaO_2 after NO inhalation will contribute to the reduction in PEEP levels in clinical situations.

Another aim of ARDS therapy is to improve oxygenation of vital tissues. The level of tissue oxygenation is indirectly evaluated by PaO_2, SaO_2, $P\bar{v}O_2$, $\dot{D}O_2$, etc. In our studies, the mean value of $\dot{D}O_2$ was decreased after lavage and was improved after NO inhalation, but due to the wide variation in $\dot{D}O_2$, no significant difference was detected. Since NO therapy for ARDS patients is nearly always combined with ventilation at a high FIO_2, $\dot{D}O_2$ will not necessarily be greatly improved. However, although individual therapies cannot significantly improve the survival rate, the survival rate of ARDS patients has been improved by combining different therapies (such as pressure-limited mechanical ventilation with PEEP and permissive hypoventilation, selective ventilation of the lungs, placing patients in the prone or lateral positions, dehydration, and extracorporeal membrane oxygenation). Inhaled NO therapy will complement these therapies.

Hemodynamic and gas exchange after $PGF_{2\alpha}$ infusion with and without NO inhalation

Assuming no difference in R values (similar response to $PGF_{2\alpha}$) between with and without NO inhalation, $PGF_{2\alpha}$ dose-response curves indicated that $PGF_{2\alpha}$ infusion increased the PVRI at a low infusion dose (ED_{50} is 2.97 μg/kg per min, see Table 2), while SVRI increased at a higher dose of $PGF_{2\alpha}$ (ED_{50} is 14.6 μg/kg per min, see Table 2), and CI decreased, most likely due to the increase in SVRI.

The assumption of a similar response to $PGF_{2\alpha}$ between with and without NO inhalation was considered to be valid at the lower dose of $PGF_{2\alpha}$ (about 0.5 mg/kg per min) but could not be evaluated at the higher dose of $PGF_{2\alpha}$ (about 5 μg/kg per min) due to the small number of measurements we obtained without NO inhalation.

$PGF_{2\alpha}$ is reported to be metabolized during a single pass through the pulmonary circulation [12]. The vasoconstrictor activity of $PGF_{2\alpha}$ is believed to be limited to the pulmonary circulation at low intravenous doses [10, 11], while pulmonary metabolism of $PGF_{2\alpha}$ can be saturated at higher doses, and vasoconstriction of the systemic circulation becomes prominent, as indicated by the increased SVRI.

The apparent improvement in $\dot{Q}s/\dot{Q}t$ at the higher $PGF_{2\alpha}$ doses was primarily due to the decreased CI. This apparent improvement in $\dot{Q}s/\dot{Q}t$ at reduced CI has also been reported in other studies in dogs with oleic acid lung injury [17, 18] and in ARDS patients [19]. The reduced $\dot{Q}s/\dot{Q}t$ is not a sign of enhanced hypoxic vasoconstriction, which would improve the matching of ventilation and perfusion in the lungs, but rather is due to the reduced shunt flow caused by the decreased total pulmonary perfusion.

Pressure-flow plots

MPAP–CI graphs (Fig. 3) showed a significant increase in the zero-flow PA pressure-intercept without any change in slope after lung lavage. Since lung lavage should create considerable inhomogeneity in the distribution of perfusion in the lungs, the pressure-intercept of the MPAP–CI graph would only indicate the composite sum of the individual critical pressures of perfused vessels, each weighted by the fractional conductance [27–29] of vessels in zone 2 conditions, or left atrial pressure with zone 3 conditions. Even with PEEP set at 10 cm H_2O, which was higher than left atrial pressure, zone 2 conditions would not be homogeneously created within the lungs, since the high $\dot{Q}s/\dot{Q}t$ level suggest that many open vascular channels were isolated from alveolar pressure, and these vessels should not develop zone 2 conditions [30]. Lung lavage is, however, believed primarily to increase the critical pressures of vessels near alveoli (zone 2), since an

increase of the number of zone 3 shunting vessels would tend to reduce the pressure-intercept towards left atrial pressure [29, 31]. The upstream resistance, expressed as the slope of the MPAP–CI plot, was not influenced by lavage. These observations are similar to the results reported in a canine ARDS model induced by oleic acid infusion [32].

After NO inhalation, MPAP–CI graphs showed a significant decrease in the pressure-intercept without any significant change in the slope (Fig. 3). Since the lungs were primarily in zone 2 conditions and left atrial pressure remained constant in zone 3 conditions, the decrease in the pressure-intercept suggested that inhaled NO dilated vessels near alveoli (alveolar or extra-alveolar vessels, possibly pulmonary venules [33]), while inhaled NO did not influence the upstream resistance.

After $PGF_{2\alpha}$ infusion MPAP–CI graphs showed a significant increase in the slope without any significant change in the pressure-intercept (Fig. 3), and the slope of MPAP–CI plots showed a dose-dependent increase, while the pressure-intercept did not change with $PGF_{2\alpha}$ infusion. Sada et al. [34], analyzing enlarged radiographic images of pulmonary vessels, reported that the site of vasoconstriction with a low-dose $PGF_{2\alpha}$ injection was mainly in pulmonary arteries in cats and that pulmonary veins constricted at higher doses of $PGF_{2\alpha}$. $PGF_{2\alpha}$ is reported to constrict the large and small pulmonary arteries of rats [35] and cats [5]. Hyman [36] reported the site of $PGF_{2\alpha}$ vasoconstriction to be pulmonary veins and upstream vessels (possibly arteries) in dogs. Thus it is suggested that $PGF_{2\alpha}$ constricts the relatively large lung vessels that may have little or no role in pulmonary vascular closure with zone 2 conditions.

The reported PO_2 dependence of $PGF_{2\alpha}$ vasoconstriction of the pulmonary artery [5, 6] may only occur in large pulmonary vessels. In that case, $PGF_{2\alpha}$ vasoconstriction would depend upon the PO_2 of mixed venous blood and would not be influenced by alveolar oxygenation. Studying unilateral alveolar hypoxia in dogs, Sprague et al. [37] reported that $PGF_{2\alpha}$ doses ranging from 0.01 to 0.1 μg/kg per min did not redistribute pulmonary perfusion toward the well-oxygenated lung.

Almitrine has been reported to enhance hypoxic pulmonary vasoconstriction [38], and in sharp contrast to $PGF_{2\alpha}$ the combination of NO inhalation and almitrine improves the efficiency of arterial oxygenation in ARDS patients [4, 39]. It is possible that a low dose of almitrine increases the tone of closing vessels, and thus the combination of almitrine and NO inhalation enhances the redistribution of perfusion toward well-ventilated lung regions.

In conclusion, with the sheep lavage model of ARDS, intravenous $PGF_{2\alpha}$ administration alone improved oxygenation due to a concomitant decrease in cardiac output. The combination of intravenous $PGF_{2\alpha}$ administration and NO inhalation did not improve arterial oxygenation. From a functional study of pressure-flow plots, it is suggested that the site of action of NO is near alveoli, while the site of action of $PGF_{2\alpha}$ is in upstream resistance vessels in this ARDS model.

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