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Combining partial liquid ventilation with nitric oxide to improve gas exchange in acute lung injury

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Abstract *Objective:* To assess the effects of increasing concentrations of inhaled nitric oxide (NO) during incremental dosages of partial liquid ventilation (PLV) on gas exchange, hemodynamics, and oxygen transport in pigs with induced acute lung injury (ALI).
Design: Prospective experimental study.
Setting: Experimental intensive care unit of a university.
Subjects: 6 pigs with induced ALI.
Interventions: Animals were surfactant-depleted by lung lavage to a partial pressure of oxygen in arterial blood (PaO_2) < 100 mmHg. They then received four incremental doses of 5 ml/kg perflubron (LiquiVent). Between each dose the animals received 0, 10, 20, 30, 40, and 0 parts per million (ppm) NO. *Measurements and main results:* Blood gases, hemodynamic parameters, and oxygen delivery were measured after each dose of perflubron as well as after each NO concentration. Perflubron resulted in a dose-dependent increase in PaO_2. At each perflubron dose, additional NO inhalation resulted in a further significant (ANOVA, $p < 0.05$) increase in PaO_2, with a maximum effect at 30 ± 10 ppm NO. The 5 ml/kg perflubron dose led to a significant decrease in mean pulmonary artery pressure, which decreased further with higher NO concentrations.
Conclusions: PLV can be combined with NO administration and results in a cumulative effect on arterial oxygenation and to a decrease in pulmonary artery pressure, without having any deleterious effect on measured systemic hemodynamic parameters.

Key words Perflubron · Partial liquid ventilation · Nitric oxide · ARDS

Introduction

The presence of increased surface tension at the alveolar air-liquid interface during acute lung injury (ALI) leads to end-expiratory alveolar collapse, atelectasis, right-to-left shunt, and a decrease in the partial pressure of oxygen in arterial blood (PaO_2), finally resulting in hypoxemia [1]. Rational therapies to treat this condition are: first, counterbalancing the increased tendency for collapse by applying positive end-expiratory airway pressure (PEEP) to prevent end-expiratory collapse and/or decreasing alveolar surface tension by applying exogenous surfactant. Another option would be elimination of the air-liquid inferface by filling the lung with a fluid that is able to maintain gas exchange. Such a fluid could be perfluorocarbon (PFC), which is capable of dissolving large amounts of respiratory gases. Recently, the use of PFC was modified by filling the injured lung to the functional residual capacity level with PFC and ventilating the lung with normal gas ventilation superimposed on the fluid-filled lung. This type of ventilation is called partial liquid ventilation (PLV), or perfluorocarbon associated gas exchange (PAGE). This technique was used in animals suffering from respiratory

failure of different etiologies showing an improvement in gas exchange [2–9]. In some of these studies, there was a clear dose-dependent effect on oxygenation, creating the possibility of titrating the amount of PFC to its effect. The results of a clinical pilot study on the use of PAGE have recently been published [10]. Besides hypoxemia due to atelectatic regions in the lung, other serious problems complicating the treatment of ALI are impaired ventilation/perfusion matching and pulmonary hypertension. Administration of inhaled nitric oxide (NO) in adult patients with the acute respiratory distress syndrome (ARDS) has been shown to cause selective vasodilation of the pulmonary vasculature of ventilated lung regions, leading to an improved oxygenation due to a decrease in pulmonary right-to-left shunt [11–13].

Based on these findings we hypothesized that, after increasing the area of gas exchange at end-expiration by PLV, the administration of NO by inhalation may further enhance oxygenation and result in lower pulmonary artery pressures. To test this hypothesis, we investigated the effects of increasing concentrations of NO during incremental dosages of PFC on gas exchange, hemodynamics, and oxygen transport in pigs with induced ALI.

Materials and methods

Animal preparation

The study protocol was approved by the university's animal experimental committee. Anesthesia was induced in six female Yorkshire pigs (weight 7 ± 1 kg) with ketamine (10 mg/kg) and midazolam (0.5 mg/kg) and was maintained with a continuous infusion of ketamine (80 μg/kg per min) and midazolam (9 μg/kg per min). All animals were tracheotomized, intubated with a 6.0-mm endotracheal tube fitted with a Filtraflux heat-moisture exchanger with built-in bacterial filter (ICHOR AB, Bromma, Sweden), and cannulated with a carotid artery catheter, a 5-Fr pulmonary artery catheter (SP51055H Viggo-Spectramed, Wiltshire, UK), a continuous blood gas monitoring sensor (Paratrend 7, Pfizer, Biomedical Sensors, High Wycombe, UK) placed in the left femoral artery, and a central venous catheter. During animal preparation, volume controlled ventilation with a Servo 300 ventilator equipped with a built-in NO administration module (Siemens, Solna, Sweden) (set at frequency 20/min, inspiratory time 25%, pause time 10%, inspiratory rise time 5%, PEEP 5 cm H_2O and 100% oxygen) was used. Muscle relaxation was achieved by a continuous infusion of pancuronium bromide (2.5 μg/kg per min). Minute ventilation was set to deliver tidal volumes of 10 ml/kg body weight. These ventilator setting were maintained during the entire study period.

All animals were surfactant-depleted according to Lachmann et al. [14] by repeated lung lavage with warm saline (38 °C, 30 ml/kg) to reduce PaO_2 below 100 mmHg. Subsequently, all animals were ventilated for 1 h to obtain stable baseline values. Following this baseline period, all animals received four intratracheal doses of 5 ml/kg perflubron (LiquiVent; Alliance Pharmaceutical, San Diego, Calif., USA); in between these doses a sequence of different concentrations of NO (0, 10, 20, 30, 40 and 0 ppm NO) was added to the inspiratory gas. Each concentration of NO was administered for about 10 min.

Measurements

Arterial and mixed venous samples were analyzed for blood gases, pH, and mixed venous oxygen saturation (SvO_2) and hemoglobin concentration by conventional methods (ABL-505 OSM-3 combination, Radiometer, Copenhagen, Denmark). This combination was used to calculate base excess (BE), intrapulmonary shunt, arterial oxygen content (CaO_2), oxygen delivery, and arteriovenous oxygen content difference. Additionally, blood gases were monitored continuously by means of a blood gas monitor.

Using Statham P23XL transducer (Spectramed, Oxnard, Calif., USA), systolic, diastolic and mean arterial pressure, as well as systolic (SysPAP), diastolic (DiaPAP), and mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure, and central venous pressure were recorded in all animals. Cardiac output was measured in triplicate using the thermodilution technique with 5 ml saline, using a Sirecust 1280 monitor (Siemens, Danvers, Mass., USA) that also traced heart rate. This monitor was also used to calculate pulmonary vascular resistance and systemic vascular resistance.

All measurements were recorded just prior to a change in PFC and/or NO concentration. At the end of the study period all animals were sacrificed with an intracardiac overdose of KCl.

Statistical analysis

Statistical analyses were performed using the Instat 2.0 biostatistics package (GraphPad Software, San Diego, Calif., USA). For each PFC dose and subsequent NO concentrations, intragroup comparisons were made with repeated measures ANOVA. If ANOVA resulted in a $p < 0.05$, a Dunnett posttest was performed. This posttest used the data measured after each increment of perflubron, with the first 0 ppm NO setting as control value. A p value of 0.05 was taken as significance level. All data are reported as mean values ± standard error of the mean (SEM).

Results

Before and after lung lavage, in all animals all data for blood gases and hemodynamics were comparable ($p > 0.05$, ANOVA). No improvement in blood gases was observed during the 1-h postlavage period. All animals survived the study period.

Gas exchange parameters (Table 1)

Administration of increments of perflubron of 5 ml/kg resulted in an increase in PaO_2 of 22.0, 55.3, 47.5, and 51.2 mmHg (i.e., 35, 58, 28, and 24%, respectively); supplemental NO inhalation at each dose of perflubron resulted in an additional significant increase in PaO_2 with a maximum effect of NO at 20–30 ppm NO (Fig. 1 a). The incremental increases in the perflubron dose did

Table 1 Data on gas exchange parameters in pigs ($n = 6$) with ALI following a combination of perflubron (LiquiVent) and NO. [a] Values are mean ± SEM

	pCO_2 (mmHg)				pH			
Baseline:[b]	55.2 ± 3.1	60.8 ± 7.5	58.6 ± 6.6	56.1 ± 6.2	7.27 ± 0.031	7.25 ± 0.044	7.23 ± 0.059	7.26 ± 0.054
LiquiVent:	5 ml/kg	10 ml/kg	15 ml/kg	20 ml/kg	5 ml/kg	10 ml/kg	15 ml/kg	20 ml/kg
0 ppm NO	52.8 ± 2.5	53.2 ± 4.5	61.0 ± 8.0	57.3 ± 6.4	7.26 ± 0.028	7.25 ± 0.051	7.22 ± 0.061	7.25 ± 0.052
10 ppm NO	50.2 ± 3.2	53.0 ± 5.7	56.7 ± 6.6	52.5 ± 4.6	7.29 ± 0.036	7.26 ± 0.056	7.26 ± 0.058*	7.27 ± 0.048
20 ppm NO	49.2 ± 2.9	53.1 ± 6.0	55.5 ± 6.6*	51.2 ± 4.9*	7.29 ± 0.040	7.26 ± 0.057	7.27 ± 0.056*	7.28 ± 0.046*
30 ppm NO	49.9 ± 3.5	54.5 ± 5.9	54.5 ± 5.8*	51.5 ± 4.9*	7.28 ± 0.047	7.25 ± 0.058	7.27 ± 0.055*	7.29 ± 0.044*
40 ppm NO	50.4 ± 3.7	55.5 ± 6.4	53.4 ± 6.0*	50.7 ± 4.6*	7.28 ± 0.043	7.25 ± 0.057	7.27 ± 0.055*	7.29 ± 0.040*
0 ppm NO	60.8 ± 7.5	58.6 ± 6.6	56.1 ± 6.2	52.2 ± 4.5	7.25 ± 0.044	7.23 ± 0.059	7.26 ± 0.054	7.28 ± 0.036
	Shunt (%)				Mixed venous O_2 saturation (%)			
Baseline:	43.4 ± 7.1	42.3 ± 7.3*	32.4 ± 5.4*	26.5 ± 3.7*	48.5 ± 5.3*	54.9 ± 9.6	65.7 ± 4.7	71.2 ± 3.9
LiquiVent:	5 ml/kg	10 ml/kg	15 ml/kg	20 ml/kg	5 ml/kg	10 ml/kg	15 ml/kg	20 ml/kg
0 ppm NO	37.2 ± 6.2	32.8 ± 6.0	25.6 ± 3.7	19.2 ± 1.9	60.2 ± 7.5	58.9 ± 7.0	67.5 ± 5.0	73.0 ± 3.3
10 ppm NO	32.7 ± 5.6	25.7 ± 3.9	21.5 ± 2.7	19.5 ± 1.9	63.5 ± 7.5	64.6 ± 6.2	73.1 ± 3.6	77.6 ± 4.3*
20 ppm NO	28.7 ± 4.6	25.7 ± 3.5	20.6 ± 2.1	16.4 ± 1.1	63.9 ± 6.7	64.9 ± 5.2	80.6 ± 5.6*	75.1 ± 3.2
30 ppm NO	27.4 ± 4.1	24.1 ± 3.1	21.4 ± 2.5	16.2 ± 1.1	63.4 ± 7.1	66.8 ± 5.9	76.2 ± 3.3*	76.4 ± 2.9
40 ppm NO	28.4 ± 4.2	24.1 ± 3.1	22.7 ± 2.5	16.2 ± 1.2	62.9 ± 7.0	70.0 ± 4.4	75.7 ± 3.8	76.0 ± 3.7
0 ppm NO	42.3 ± 7.3	32.4 ± 5.4	26.5 ± 3.7	19.4 ± 2.3	54.9 ± 9.6	65.7 ± 4.7	71.2 ± 3.9	72.5 ± 3.8
	Arterial oxygen content (ml/dl)							
Baseline:	12.1 ± 0.9	13.7 ± 1.1	15.7 ± 1.2	16.3 ± 1.2				
LiquiVent:	5 ml/kg	10 ml/kg	15 ml/kg	20 ml/kg				
0 ppm NO	13.3 ± 0.9	15.1 ± 1.0	16.5 ± 1.3	17.3 ± 1.0				
10 ppm NO	15.1 ± 0.9*	16.5 ± 1.1*	16.8 ± 1.1	17.0 ± 1.0				
20 ppm NO	15.4 ± 0.8*	16.2 ± 1.1*	17.1 ± 1.1	17.1 ± 0.9				
30 ppm NO	15.8 ± 0.9*	16.3 ± 0.9*	16.7 ± 1.2	17.2 ± 0.9				
40 ppm NO	16.0 ± 0.9*	16.4 ± 0.9*	16.7 ± 1.0	16.9 ± 1.0				
0 ppm NO	13.7 ± 1.1	15.7 ± 1.2	16.3 ± 1.2	16.8 ± 1.0				

* $p < 0.05$

[a] Intragroup comparisons ANOVA with Dunnett posttest if ANOVA $p < 0.05$, using the data after each increment of LiquiVent as control

[b] Baseline represents the data prior to an increase in LiquiVent dose

not result in a statistically significant improvement in arterial carbon dioxide pressure ($PaCO_2$) and pH values; however, these $PaCO_2$ and pH values showed a dose-dependent significant improvement when combined with additional NO administration at the 15 and 20 ml/kg body weight perflubron dose. There were no significant changes in BE during the study period.

The first dose of 5 ml/kg perflubron resulted in a significant improvement in SvO_2 from 48.5 ± 5.3 % to 54.9 ± 9.6 %. Additional NO inhalation at the 15 and 20 ml/kg perflubron doses significantly improved SvO_2 at 10–30 ppm NO.

Shunt was reduced at each increment of perflubron, reaching statistical significance at 10–20 ml/kg perflubron. At each dose of perflubron, additional NO administration further reduced shunt, although these changes were not significant.

Each increment in perflubron resulted in an increase in mean CaO_2; at the 5 and 10 ml/kg perflubron doses, CaO_2 was significantly increased by additional NO administration. At each dose of perflubron, DO_2 was not significantly changed by NO administration.

Online blood gas recordings showed a time-related effect of NO on blood gases. Figure 2 shows the dose-dependent improvement in gas exchange in one animal at a dose of 10 ml/kg perflubron. Figure 3 shows a rapid (< 3 min) decrease in PaO_2 from 140 to 89 mm Hg, as a result of switching from 40 to 0 ppm NO in another animal at a perflubron dose of 5 ml/kg.

Hemodynamics (Table 2)

Administration of 5 ml/kg perflubron to a total dose of 10 ml/kg resulted in a significant decrease in SysPAP (– 14 %) and MPAP (– 11 %). All other decreases in pulmonary artery pressures were observed during additional NO administration: SysPAP showed a significant decrease with an additional 30 ppm NO (15 and 20 ml/

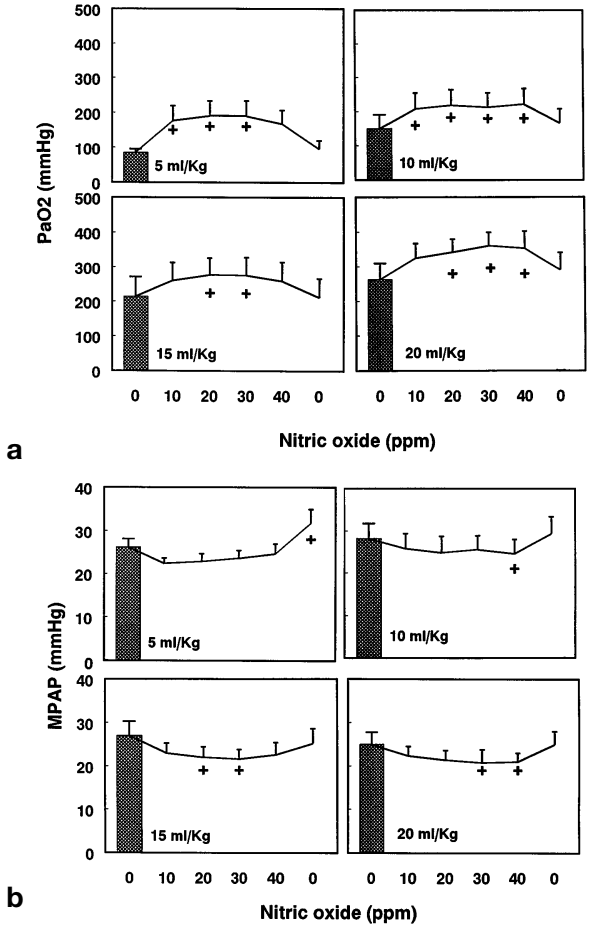

Fig. 1 Arterial oxygen tension PaO_2 **a** and mean pulmonary artery pressure *MPAP* **b** in relation to the amount of LiquiVent followed by different NO concentrations in parts per million *ppm* in pigs ($n = 6$) with acute lung injury. *Bars* represent increments of perflubron. Data are means ± SEM. Intragroup comparisons ANOVA with Dunnet posttest if ANOVA ($p < 0.05$), using the data after each increment of perflubron with the first setting 0 ppm NO as control. $^{+}$ $p < 0.05$

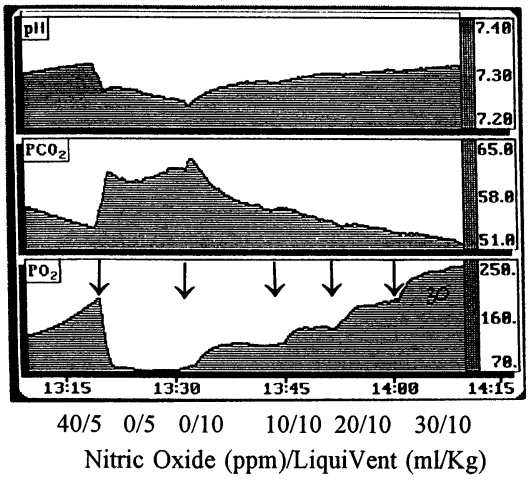

Fig. 2 Print-out from the online blood gas monitor, showing the effect of different doses of inhaled NO *0, 10, 20, 30* ppm on pH, PCO_2, and PO_2 in one pig ventilated with 10 ml/kg LiquiVent

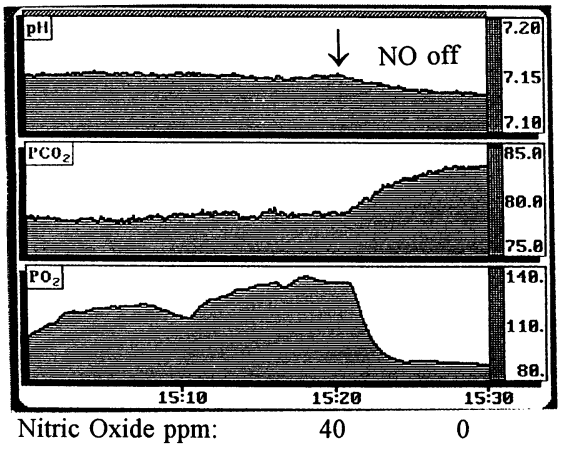

Fig. 3 Print-out from the on-line blood gas monitor, showing the effect on pH, PCO_2, and PO_2 when switching from 40 to 0 ppm NO in one pig ventilated with 5 ml/kg LiquiVent

kg perflubron), DiaPAP showed a significant decrease with an additional 30–40 ppm NO (15 ml/kg perflubron), and MPAP values (Fig. 1 b) showed a significant dose-dependent decrease at the 10, 15, and 20 ml/kg perflubron doses.

Stopping NO administration resulted in a significant rebound hypertension in MPAP at a dose of 5 ml/kg perflubron, with a simultaneous increase in pulmonary vascular resistance. This was reduced significantly at a dose of 10 ml/kg perflubron with 40 ppm NO and at a dose of 15 ml/kg perflubron with 20 ppm NO.

There was a significant decrease in heart rate at the 10 ml/kg perflubron dose with an additional 40 ppm NO. There were no significant changes in any other measured or calculated hemodynamic parameters.

Discussion

The model of induced ALI used in the present study leads to decreased arterial oxygenation as a result of end-expiratory collapse due to surfactant deficiency and is comparable to the changes found in ARDS [14–16].

The results of our study show that PLV is an effective therapy, leading to a dose-dependent improvement in gas exchange in surfactant-depleted pigs. These findings confirm the results from previous reports on PLV [5, 8]. The beneficial effect of PLV on gas exchange is mediated through the physical presence of PFC in the alveoli preventing them from expiratory collapse. This collapse usually accounts for two-thirds the time of the respira-

Table 2 Data on hemodynamic parameters in pigs ($n = 6$) with ALI following the combination of perflubron (LiquiVent) and NO. [a] Values are mean ± SEM

	Mean arterial pressure (mmHg)				Systolic pulmonary pressure (mmHg)			
Baseline[b]:	96.2 ± 5.4	91.0 ± 6.8	95.5 ± 5.1	91.7 ± 3.8	37.8 ± 3.4	39.4 ± 3.6*	37.6 ± 4.8	33.4 ± 4.1
LiquiVent:	5 ml/kg	10 ml/kg	15 ml/kg	20 ml/kg	5 ml/kg	10 ml/kg	15 ml/kg	20 ml/kg
0 ppm NO	94.0 ± 5.0	97.8 ± 4.7	95.7 ± 6.7	93.5 ± 4.4	32.0 ± 1.7	33.8 ± 4.2	33.4 ± 3.6	31.8 ± 3.1
10 ppm NO	96.8 ± 5.5	98.0 ± 6.6	93.0 ± 6.3	89.3 ± 3.8	27.0 ± 0.8	32.2 ± 3.6	28.0 ± 2.5	28.4 ± 2.5
20 ppm NO	95.8 ± 6.0	92.5 ± 5.0	93.3 ± 5.4	90.7 ± 3.9	28.0 ± 1.9	31.0 ± 4.0	27.4 ± 2.1	28.2 ± 2.5
30 ppm NO	91.3 ± 7.7	93.2 ± 7.3	93.8 ± 5.1	87.7 ± 5.9	28.2 ± 2.5	32.2 ± 3.7	26.8 ± 3.0*	27.0 ± 3.4*
40 ppm NO	93.8 ± 5.2	94.7 ± 6.2	90.5 ± 3.1	89.0 ± 7.3	30.4 ± 2.9	31.4 ± 4.1	30.0 ± 3.0	27.8 ± 2.6
0 ppm NO	91.0 ± 6.8	95.5 ± 5.1	91.7 ± 3.8	90.0 ± 6.4	39.4 ± 3.6	37.6 ± 4.8	33.4 ± 4.1	30.6 ± 3.7
	Diastolic pulmonary pressure (mmHg)				Central venous pressure (mmHg)			
Baseline:	24.0 ± 1.6	24.4 ± 3.4	22.8 ± 4.1	17.6 ± 3.0	4.5 ± 1.1	4.8 ± 1.0	4.5 ± 1.4	5.3 ± 1.2
LiquiVent:	5 ml/kg	10 ml/kg	15 ml/kg	20 ml/kg	5 ml/kg	10 ml/kg	15 ml/kg	20 ml/kg
0 ppm NO	20.6 ± 2.0	22.0 ± 3.3	20.8 ± 3.2	17.6 ± 3.0	4.2 ± 1.1	4.3 ± 1.1	5.0 ± 1.4	5.2 ± 1.2
10 ppm NO	18.0 ± 1.8	17.0 ± 5.4	17.0 ± 2.5	15.8 ± 1.8	4.0 ± 1.4	5.8 ± 1.0	4.7 ± 1.3	3.7 ± 1.0
20 ppm NO	18.6 ± 2.0	19.4 ± 3.9	16.6 ± 2.7	14.6 ± 1.9	3.3 ± 1.0	5.2 ± 1.1	5.2 ± 1.3	6.3 ± 0.9
30 ppm NO	18.8 ± 1.8	19.8 ± 3.6	15.2 ± 1.7*	14.2 ± 2.6	3.5 ± 1.1	4.8 ± 1.0	5.5 ± 1.5	4.8 ± 0.6
40 ppm NO	19.4 ± 2.2	17.8 ± 3.3	15.2 ± 2.5*	14.2 ± 1.6	4.0 ± 1.2	4.3 ± 1.1	4.7 ± 1.3	6.3 ± 0.5
0 ppm NO	24.4 ± 3.4	22.8 ± 4.1	17.6 ± 3.0	19.4 ± 2.7	4.8 ± 1.0	4.5 ± 1.4	5.3 ± 1.2	6.2 ± 0.4
	Heart rate (beats/min)				CO (l/min)			
Baseline:	152.5 ± 10.2	156.7 ± 10.0	143.7 ± 8.1	148.7 ± 8.6	1.1 ± 0.1	0.9 ± 0.1	1.0 ± 0.2	1.1 ± 0.1
LiquiVent:	5 ml/kg	10 ml/kg	15 ml/kg	20 ml/kg	5 ml/kg	10 ml/kg	15 ml/kg	20 ml/kg
0 ppm NO	152.0 ± 10.4	153.7 ± 9.7	144.7 ± 10.2	152.8 ± 10.4	1.0 ± 0.1	0.9 ± 0.2	1.0 ± 0.1	1.1 ± 0.1
10 ppm NO	150.7 ± 8.5	149.8 ± 9.2	144.8 ± 8.7	152.2 ± 9.8	1.0 ± 0.2	1.0 ± 0.2	1.1 ± 0.1	1.1 ± 0.2
20 ppm NO	155.5 ± 11.3	148.8 ± 8.1	145.7 ± 8.0	149.2 ± 10.0	1.0 ± 0.1	1.1 ± 0.2	1.1 ± 0.1	1.0 ± 0.2
30 ppm NO	155.8 ± 11.4	144.2 ± 10.3	146.2 ± 8.1	149.2 ± 9.6	0.9 ± 0.2	1.0 ± 0.2	1.0 ± 0.1	1.0 ± 0.1
40 ppm NO	152.3 ± 10.4	139.2 ± 8.4*	149.2 ± 8.3	152.8 ± 11.7	0.9 ± 0.2	1.0 ± 0.1	1.1 ± 0.1	1.1 ± 0.1
0 ppm NO	156.7 ± 10.0	143.7 ± 8.1	148.7 ± 8.6	140.8 ± 6.7	0.9 ± 0.1	1.0 ± 0.2	1.1 ± 0.1	1.1 ± 0.2
	Pulmonary wedge pressure (mmHg)				PVR (dynes.s/cm^5)			
Baseline:	6.2 ± 0.5	6.6 ± 1.3	5.4 ± 1.0	5.2 ± 1.0	1828 ± 249	2452 ± 418	2092 ± 414	1603 ± 315
LiquiVent:	5 ml/kg	10 ml/kg	15 ml/kg	20 ml/kg	5 ml/kg	10 ml/kg	15 ml/kg	20 ml/kg
0 ppm NO	5.2 ± 0.2	6.0 ± 1.0	5.6 ± 0.7	4.8 ± 0.9	1743 ± 223	2407 ± 586	1871 ± 408	1649 ± 339
10 ppm NO	4.0 ± 0.6	5.6 ± 0.9	5.2 ± 1.1	4.8 ± 1.0	1754 ± 428	1999 ± 505	1401 ± 234	1461 ± 270
20 ppm NO	6.0 ± 0.9	5.0 ± 0.8	5.2 ± 1.2	5.0 ± 0.8	1546 ± 272	1859 ± 557	1353 ± 225*	1456 ± 294
30 ppm NO	6.0 ± 0.9	5.0 ± 1.0	4.6 ± 1.0	4.6 ± 1.0	1742 ± 324	1913 ± 435	1414 ± 232	1356 ± 284
40 ppm NO	5.6 ± 1.0	5.4 ± 1.0	4.4 ± 1.1	5.4 ± 0.7	1946 ± 433	1732 ± 369*	1388 ± 260	1299 ± 225
0 ppm NO	6.6 ± 1.3	5.4 ± 1.0	5.2 ± 1.0	4.6 ± 0.9	2452 ± 418*	2092 ± 414*	1603 ± 315	1755 ± 364

* $p < 0.05$

[a] Intragroup comparisons ANOVA with Dunnett post-test if ANOVA ($p < 0.05$), using the data after each increment of LiquiVent as control

[b] Baseline represents the data prior to an increase in LiquiVent dose

tory cycle. The high dissolved volume of oxygen (perflubron; 55 ml/100 ml at 37 °C and at 1 atmosphere of pressure) continues to oxygenate the blood during the expiratory period, resulting in improved arterial oxygenation. Furthermore, PFC enhances alveolar recruitment in the surfactant-deficient, atelectatic lung [17].

Pulmonary hypertension due to pulmonary vasoconstriction and/or widespread vascular obstruction is a common finding in severe ALI or ARDS [18]. Due to an increased microvascular filtration pressure, pulmonary hypertension can increase the accumulation of extravascular lung water [19]. This extravascular lung water may lead to worsening oxygenation, resulting in further increase in hypoxic vasoconstriction. Furthermore, pulmonary hypertension can cause right ventricular dysfunction [20]. Because of its selective pulmonary vasodilating properties, inhaled NO was suggested as a therapy for pulmonary hypertension [13]. NO therapy is feasible because NO is short-acting, is easily titrated to its effect, and can readily be removed from the lungs [21].

Our study also shows that administration of NO, after pretreatment with PFC, results in a further improvement in gas exchange, with a simultaneous decrease in pulmonary artery pressures. The successful combination of NO and PFC was first reported in a hypoplastic congenital diaphragmatic hernia lamb model [9]. However, this lamb model is a neonatal model in which the pathophysiology of respiratory failure is different from that of ALI in adults.

Figure 1 a shows that the maximal effect of additional NO inhalation resulted in a more than 100 % increase in PaO_2 values (48.9 ± 10.6 to 177.1 ± 42.1 mmHg) at the 5 ml/kg perflubron dose. A similar increase in PaO_2 was obtained with the next increment of 5 ml/kg perflubron alone. At the higher doses of perflubron, additional NO inhalation resulted in a smaller increase (30–50 %) in PaO_2 values, whereas each subsequent increment in perflubron showed an equal increase in PaO_2 as obtained with NO administration at the previous perflubron dose. These effects indicate that, after an initial improvement in PaO_2 by administration of perflubron, a further increase in oxygenation can be obtained by either a low dose of perflubron in combination with NO or a higher dose of perflubron without NO.

The well-known finding that high NO concentrations decrease PaO_2 by diffusing to nonventilated lung regions, dilation of the vessels in these areas, resulting in an increase in right-to-left shunt [22], was observed in our experiments only at the 5 ml/kg perflubron dose. This effect, however, was not significant.

The improvement in CO_2 elimination by administration of perflubron was enhanced by additional NO inhalation resulting in an improvement in pH. The findings proved to be statistically significant; however, we cannot attribute this effect to additional NO inhalation alone. Because of the fact that during the study period minute ventilation was not changed, baseline $PaCO_2$ values varied widely. Therefore we question the significance of these findings.

Perflubron has high solubility for respiratory gases. To date there is no information available on the solubility of NO in PFC, nor were we able to measure the amount of NO dissolved. However, online blood gas monitoring showed that changes in NO concentration resulted in rapid changes in PaO_2 (Figs. 2, 3). This rapid response to NO was similar to the time-response curves reported by Gerlach et al. (1–2 min) [21]. The rapid response to changes in NO concentration in our study shows that there is no clinically important effect of PFC on the time-response effect of NO, indicating that the total amount of NO dissolved in perflubron must be low. When applying partial liquid ventilation with perflubron, higher concentrations of inspired oxygen are needed to maintain a high oxygen diffusion gradient, in order to oxygenate the blood adequately. Higher inspired concentrations of oxygen are known to react rapidly with NO to form toxic redox forms of NO [23]. In the present study, no measurements were made to quantify the transformation of NO in the PFC. However, the methemoglobin concentration as well as the mixed expired NO_2 concentration both remained low (< 5 % and < 5 ppm, respectively). Further discussion on the safety of inhaled NO alone or in combination with PFC is beyond the scope of this paper. The toxicity of nitrogen oxides has recently been reviewed [23].

In conclusion, this study showed that the combination of perflubron and NO has a cumulative effect in increasing gas exchange and lowering pulmonary artery pressures. Due to its additive effect it may even be possible to reduce the amount of PFCs by adding NO to get a certain oxygenation which normally results after higher doses of PFC. However, before this combination may be used routinely to treat patients, more basic information is required about, for example, what is happening with NO in the PFC, is there any accumulation of possible radicals in the PFC, and what is the solubility of NO in PFC.

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