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Inhaled Nitric Oxide *versus* Inhaled Prostacyclin and Intravenous *versus* Inhaled Prostacyclin in Acute Respiratory Failure with Pulmonary Hypertension in Piglets

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ABSTRACT

This study was a prospective, randomized design to compare oxygenation and pulmonary hemodynamics between inhaled nitric oxide (NO) and inhaled prostacylcin (PGI_2), and between inhaled and i.v. PGI_2 in acute respiratory failure with pulmonary hypertension. Acute respiratory failure with pulmonary hypertension was induced in 12 piglets weighing 9–12 kg by repeated lung lavages and a continuous infusion of the stable endoperoxane analogue of thromboxane. Thereafter the animals were randomly assigned either for NO or PGI_2 application. All animals were treated with different concentrations of NO or different doses of PGI_2 applied i.v. and inhaled in random order. Continuous monitoring included ECG, central venous pressure (CVP), mean pulmonary artery pressure (MPAP), mean arterial pressure (MAP), artertial oxygen saturation (SaO_2), and mixed venous oxygen saturation (SvO_2) measurements. NO inhalation of 10 ppm resulted in a significant increase in Pao_2/fraction of inspired oxygen (FiO_2) from 7.8 ± 1.34 kPa to 46.1 ± 9.7 kPa. MPAP decreased significantly from 5.1 ± 0.26 kPa to 3.7 ± 0.26 kPa during inhaled NO of 40 ppm; i.v. infusion of PGI_2 slightly increased oxygenation parameters. A significant increase in Pao_2/FiO_2 up to 32.4 ± 3.1kPa was observed during PGI_2 aerosol delivery ($p < 0.01$); i.v. PGI_2 decreased MAP from 11.5 ± 0.39 kPa to 9.8 ± 0.66 kPa ($p < 0.05$) and MPAP from 5.8 ± 0.53 kPa to 4.5 ± 0.66 kPa, respectively ($p < 0.05$). PGI_2 aerosol delivery significantly decreased the MPAP to 3.7 ± 0.53 kPa ($p < 0.05$) without influencing the MAP. It was concluded that inhaled NO and inhaled PGI_2 act as selective pulmonary vasodilators in acute respiratory failure with pulmonary hypertension resulting in improved oxygenation mainly due to improved mismatch of pulmonary perfusion and ventilation. Intravenous PGI_2 improves oxygenation and pulmonary hemodynamics to a lesser extent than aerosolized PGI_2 and has the risk of systemic hypotension at a higher dose. (***Pediatr Res* 38: 198–204, 1995**)

Abbreviations

ARDS, adult respiratory distress syndrome
Cst, static pulmonary compliance
CVP, central venous pressure
FiO_2, fraction of inspired oxygen
MPAP, mean pulmonary artery pressure
MAP, mean arterial pressure
NO, nitric oxide
NO_2, nitrogen dioxide
$Paco_2$, partial pressure of arterial carbon dioxide
Pao_2, partial pressure of arterial oxygen
PEEP, positive end-expiratory pressure
PGI_2, prostacyclin
ppm, parts per million
PVR, pulmonary vascular resistance
Qs/Qt, intrapulmonary shunt fraction
Raw, airway resistance
SaO_2, arterial oxygen saturation
SvO_2, mixed venous oxygen saturation
SVR, systemic vascular resistance
U46619, stable endoperoxide analogue of thromboxane

In 1987 NO was reported to be an important endothelium-derived relaxing factor (1, 2). NO is synthesized in the vascular endothelial cell from L-arginine by NO synthase. It rapidly diffuses into the vascular smooth muscle cell and acts by stimulation of guanylate cyclase producing cGMP which mediates vasodilation (3). In the vascular system NO is rapidly bound to Hb forming nitrosylhemoglobin and methemoglobin (4). Therefore, NO acts locally and produces no effects on the systemic vasculature. NO is an unstable free radical, and in the presence of high oxygen concentrations is oxidized to NO_2 which might cause lung injury (5, 6).

Recently, inhaled NO has been described as an effective selective pulmonary vasodilator in different experimental models of pulmonary hypertension (7–11). It improved oxygenation and reduced elevated pulmonary artery pressure in neo-

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nates, infants, and adults with pulmonary hypertension or acute respiratory failure combined with pulmonary hypertension (12–19). Inhaled NO improves ventilation/perfusion mismatch by selectively vasodilating pulmonary vessels of ventilated areas.

PGI_2, an arachidonic acid metabolite, is a potent dilator of the arterial and venous vessels by increasing the concentration of cAMP in vascular smooth muscle cells (20). PGI_2 has been applied in a variety of clinical and experimental conditions with pulmonary hypertension (21–25). However, vasodilation occurs in both the pulmonary and systemic vessels which might result in systemic hypotension. In addition, as PGI_2 vasodilates pulmonary vessels in ventilated and nonventilated areas of the lung, increased intrapulmonary shunt with increased venous admixture might occur. Recently, aerosolized PGI_2 has been reported both in clinical and experimental settings to be a selective pulmonary vasodilator without side effects on the systemic vasculature (26, 27).

The aim of this study is to compare the pulmonary and hemodynamic effects of inhaled NO and inhaled PGI_2 in an animal model of acute respiratory failure with pulmonary hypertension. In addition, we evaluated the differences between inhaled and i.v. PGI_2 on the pulmonary and hemodynamic effects.

METHODS

The protocol was approved by the Institutional Animal Research Committee and the care of the animals was in accordance with guidelines for ethical animal research.

In 12 piglets of either sex, weighing 10 ± 0.6 kg, premedicated with azaperone (8 mg/kg) and atropine (0.02 mg/kg), anesthesia was induced with ketamine (10 mg/kg) and thereafter maintained by a continuous infusion of fentanyl (0.15 μg/kg/min), pentobarbital sodium (4 mg/kg/h), and pancuronium (0.3 mg/kg/h). After placing a 5.5-mm inside diameter Hi-Lo cuffed tube (Hi-Lo jet tube, National Catheter Corp., Malinckrodt, Glen Falls, NY) via tracheostomy, controlled mechanical ventilation was established using a volume controlled, time cycled ventilator (Veolar, Hamilton Comp., Rhazüns, Switzerland). Tidal volume was set at 10–12 mL/kg, respiratory rate at 20/min, inspiratory/expiratory ratio at 1:2, PEEP at 4 cmH_2O, and FiO_2 at 0.21. Initially a 4 Fr double-lumen catheter (Duocath, Peter von Berg Medizintechnik, Kirchseeon, FRG) was inserted into the right subclavian vein for nutrition and anesthesia. After induction of anesthesia, a Ringer solution was infused, initially, at a rate of 10 mL/kg in 30 min followed by a continuous infusion of 5 mL/kg/h. A 5.5 Fr thermodilution O_2 saturation fiber-optic pulmonary artery catheter (Edwards Swan-Ganz Oximetry TD catheter, Edwards Critical Care Division, Irvine, CA) was placed into the pulmonary artery by peripheral cutdown of the external jugular vein. A 4 Fr O_2 saturation catheter (Edslab double lumen O_2 Sat II catheter, Edwards Critical Care Division) was inserted via the right common carotid artery and placed into the thoracic aorta for continuous arterial oximetry measurement. A short 16-gauge catheter (Abbocath, Abbott Ireland LTD, Sligo, Republic of Ireland) was placed into the femoral artery for continuous pressure recording. A second 4 Fr double-lumen catheter (Duocath, Peter von Berg Medizintechnik) was placed via the left external jugular vein.

Hemodynamic monitoring. Heart rate and rhythm, right atrial, pulmonary artery, and peripheral artery pressures were recorded continuously on a multichannel recorder (SMU 612 monitor, PPG Hellige Corp., Freiburg, FRG) using 0.9% saline filled transducers (Monitoring Kit NM-081-D, Peter von Berg Medizintechnik). All pressures were referenced to the midthorax. Cardiac output was measured at end-expiration by the thermodilution technique as the mean of three determinations after injection of 5 mL 0°C 0.9% saline. SVR was calculated as MAP divided by cardiac output. PVR was calculated as MPAP divided by cardiac output. Two oxygen saturation monitors (Baxter Sat2 Oximeter; Baxter Healthcare Corporation, Edwards Critical Care Division, Irvine, CA) were used for continuous arterial and mixed venous oximetry measurements.

Respiratory monitoring. Arterial and mixed venous blood samples were taken for measurements of Hb, oxygen saturation, Po_2, Pco_2, and pH using an automatic blood gas system (AVL 995, AVL Corp., Graz, Austria). In addition the SaO_2 and SvO_2 oxygen saturations and arterial methemoglobin fraction (CO-Oxylite AVL 912, AVL Corp.) were analyzed. End-tidal CO_2 concentrations and the fraction of inspired and expired oxygen were measured with a multigas analyzer (PPG Hellige Corp., Freiburg, FRG). Airway pressures, tidal volume, Cst, and Raw were measured with a Bicore CP-100 monitor (Bicore Monitoring Systems, Irvine, CA).

Administration of PGI_2. PGI_2 was supplied as the sodium salt of epoprostenol (Flolan, Wellcome, London, UK) dissolved in glycine buffer and diluted with 0.9% saline at a concentration of 10 μg/ml. It was applied as an aerosol or as continuous infusion at the same concentration. For inhalation of PGI_2 as aerosol a nebulizer chamber (Intersurgical Ltd., Twickenham, UK) and an oxygen flowmeter (Dräger Austria GesmbH., Vienna, Austria) with flow rates of 3–6 L/min was used. The aerosol was delivered at the connection of the ventilatory circuit with the flow sensor of the ventilatory circuit (MR 390 15 mm tubings, Fisher & Paykel Healthcare, Panmure, Auckland, NZ) near the endotracheal tube. Primarily, the nebulizer chamber was filled with 1 mL of the above described PGI_2 solution followed by a continuous infusion of 30–60 ng/kg/min into the nebulizer chamber via a 20-gauge catheter (Venflon, Viggo-Spectramed, Helsinborg, Sweden) inserted into a small bored side hole of the nebulizer chamber. During aerosol delivery of PGI_2 the tidal volume of the ventilator was reduced to obtain comparable mean airway pressures. Intravenous infusion of PGI_2 was started at 5 ng/kg/min and was subsequently increased up to 40 ng/kg/min.

Administration of NO. NO was obtained as 900 ppm in nitrogen (Pulmomix forte, Messer-Griesheim, Austria) and applied using the Pulmonox system. The Pulmonox is a microprocessor controlled system which allows NO delivery at concentrations from 1 to 40 ppm and continuous inspiratory measurement of NO/NO_2 using the chemiluminescence method. A flow-box incorporated into the inspiratory limb of the ventilatory circuit transfers the inspiratory flow rate of the ventilator to the Pulmonox system which adapts the NO dosage

on a continuous basis. NO was administered into the inspiratory limb of the ventilatory circuit close to the endotracheal tube using an airway sampling adapter (Engström Sampling adapter, Gambro Engström, Bromma, Sweden). The system was calibrated before each treatment/measurement with special calibration gases.

Protocol. After this instrumentation the animals were allowed to rest for 30 min before control measurements were performed. Before starting the lung lavage procedure the FiO_2 of the ventilator was increased to 1.0 and the PEEP levels to 1 kPa. In addition, a Tris infusion was started to obtain a stable pH throughout the study period. Acute respiratory failure ($SaO_2 < 85\%$) was induced by repeated lung lavages using 0.9% saline (20–30 mL/kg/lavage). After the last lung lavage the stable endoperoxide analog of thromboxane (U46619, Cascade Biochem Ltd., Bershire, UK) was infused at a rate of 0.4–0.8 μg/kg/min to increase the mean PAP above 4.6 kPa. Thereafter the animals were randomly assigned either for NO or PGI_2 application. To obtain a pulmonary vasodilator dose-response curve during U46619 infusion all animals were treated with different concentrations of NO (1, 2, 5, 10, 20, and 40 ppm) or different doses of PGI_2 (5, 10, 20, and 40 ng/kg/min as continuous i.v. infusion and 30 and 60 ng/kg/min as an aerosol). Intravenous and inhaled PGI_2 were applied in random order. Measurements were taken after 10–15 min of each NO concentration or PGI_2 dosis or after a stable period of 5 min. Five minutes after termination of NO or PGI_2 application a last measurement was taken under hypoxic conditions.

All animals tolerated the experimental protocol. After the end of the trial the animals were killed with an overdose of potassium chloride.

Data analysis. Values are given as mean ± SEM. Initially a multifactorial analysis of variance for repeated measures was applied using the Statview 4.0 software for Macintosh. If a significant difference was determined, the intragroup differences were determined using the paired *t* test and the intergroup differences by unpaired *t* test with a *p* value of <0.05 being considered significant.

RESULTS

Three to six lung lavages significantly decreased Cst from 1.7 ± 0.04 to 0.84 ± 0.02 mL/kPa/kg ($p < 0.01$) and Pao_2/FiO_2 from 65.2 ± 1.5 to 8.2 ± 0.5 kPa ($p < 0.01$). Simultaneously Raw increased from 4.6 ± 0.13 to 7.4 ± 0.3 kPa/L/s ($p < 0.01$). The infusion of U46619 significantly increased MPAP and PVR by 141 and 321%, respectively ($p < 0.01$).

NO. Blood gas parameters, arterial and mixed venous oxygen saturations, mean airway pressure, and intrapulmonary shunt fraction are summarized in Table 1. NO inhalation resulted in a significant increase in oxygenation parameters. The highest Pao_2/FiO_2 values of 46.1 ± 9.7 kPa were observed during inhalation of 10 ppm NO. A further increase in the NO concentration resulted in a slight decrease in Pao_2/FiO_2 values. When NO concentration was stepwise increased from 1 to 40 ppm, FiO_2 decreased from 1.0 to 0.9 ± 0.05 ($p < 0.01$). Qs/Qt improved significantly during NO inhalation of 10–40 ppm. No significant differences were observed in pulmonary mechanics during NO inhalation.

The hemodynamic parameters during NO inhalation are summarized in Table 2. There was no change in heart rate, CVP, MAP, and PVR during inhaling different doses of NO. MPAP decreased significantly from 5.1 ± 0.02 kPa to 3.7 ± 0.02 kPa ($p < 0.05$) during inhalation of 40 ppm NO. Although cardiac output decreased slightly by 19%, SVR increased significantly by 35% ($p < 0.05$) during NO inhalation with simultaneous infusion of U46619. Methemoglobin levels were 1.2 ± 0.1% during inhalation of 1 ppm of NO and increased to 2.1 ± 0.25% ($p < 0.01$) when NO concentration was increased to 40 ppm. NO_2 levels were below 0.5 ppm during inhalation of 1 to 40 ppm NO.

PGI_2. Blood gas parameters, arterial and mixed venous oxygen saturations, mean airway pressure, and intrapulmonary shunt fraction are given in Table 3. Intravenous infusion of PGI_2 slightly increased oxygenation parameters. The highest Pao_2/FiO_2 values of 14.1 ± 4.1 kPa were observed during infusion of 40 ng/kg/min of PGI_2. A significant increase in Pao_2/FiO_2 up to 32.4 ± 3.1 kPa was observed during PGI_2 inhalation ($p < 0.01$). During inhaled PGI_2 the Qs/Qt values were significantly lower than during i.v. PGI_2 application ($p < 0.05$). Pulmonary mechanics (Cst, Raw) did not change significantly during inhaled and i.v. PGI_2 application. During i.v. PGI_2 application, MAP and MPAP decreased by 15 and 23%, respectively ($p < 0.05$), and heart rate increased by 18% ($p < 0.05$). There was no change in PVR and SVR. PGI_2 aerosol application did not change heart rate, MAP, and CVP. However, a significant decrease in MPAP and PVR by 22 and 36%, respectively ($p < 0.05$) was observed.

Table 1. *Blood gases, oxygenation variables, mean airway pressure and intrapulmonary shunt fraction in six piglets with acute respiratory failure and pulmonary hypertension pre, during, and post NO inhalation (mean ± SEM)*

Parameters	Baseline	Lavage + U46619	NO-1ppm	NO-5ppm	NO-10ppm	NO-40ppm	Post-NO
pH	7.35 ± 0.01	7.37 ± 0.02	7.39 ± 0.02	7.42 ± 0.01	7.42 ± 0.02	7.41 ± 0.02	7.37 ± 0.02†
Pao_2/FiO_2 (kPa)	63 ± 0.8	7.8 ± 1.3**	14.3 ± 0.1**†	36.1 ± 6.9**†	46.1 ± 9.7†	43.4 ± 9.4	10.1 ± 1.8**†
SaO_2 (%)	97 ± 0.9	79 ± 4.1**	90 ± 5.1*†	99 ± 0.4†	99 ± 0.4	99 ± 0.3	82 ± 3.3**†
SvO_2 (%)	71 ± 1.8	45 ± 3.7**	60 ± 3.7**†	66 ± 5.1	66 ± 4.7	65 ± 5.2	40 ± 5.4**†
Paw (kPa)	0.91 ± 0.06	1.58 ± 0.03**	1.56 ± 0.04**	1.63 ± 0.03**	1.61 ± 0.03**	1.63 ± 0.04**	1.66 ± 0.04**
Qs/Qt (%)	16 ± 1.2	53 ± 6.2**	43 ± 5.1**†	22 ± 3.3†	17 ± 3.2	17 ± 3.4	43 ± 6.1**†

* $p < 0.05$.

** $p < 0.01$ denotes significant differences to the baseline levels.

† $p < 0.05$ denotes a significant difference to the former measured value.

Table 2. *Hemodynamic data in six piglets with acute respiratory failure and pulmonary hypertension pre, during and post NO inhalation (mean ± SEM)*

Parameters	Baseline	Lavage + U46619	NO-1ppm	NO-5ppm	NO-10ppm	NO-40ppm	Post-NO
Heart rate/min	135 ± 11	137 ± 9	127 ± 6	127 ± 3	123 ± 3	122 ± 10	164 ± 17
Cardiac output (L/min)	2.8 ± 0.3	1.6 ± 0.1**	1.6 ± 0.2**	1.5 ± 0.2**	1.4 ± 0.2**	1.3 ± 0.1**	1.1 ± 0.1**
MAP (kPa)	9.1 ± 0.5	13.3 ± 0.6**	13.3 ± 0.4**	13.6 ± 0.5**	13.9 ± 0.5*	13.9 ± 70.9**	12.3 ± 1.4**†
PAP (kPa)	1.9 ± 0.2	5.1 ± 0.2**	4.3 ± 0.2**†	3.9 ± 0.4**	3.9 ± 0.4**	3.7 ± 0.3**	6.3 ± 4**†
PVR (kPa/L/min)	0.73 ± 0.70.1	3.2 ± 0.47**	3.1 ± 0.7**	3.2 ± 0.7**	3.3 ± 0.78**	3.2 ± 0.67**	5.7 ± 0.78**†
SVR (kPa/L/min)	3.4 ± 0.43	8.2 ± 0.62**	9.0 ± 1.0**	9.5 ± 1.1**	10.9 ± 1.2**†	11.1 ± 0.77**	10.9 ± 1.26**
PVR/SVR	0.22 ± 0.02	0.39 ± 0.04**	0.32 ± 0.03**†	0.29 ± 0.03*	0.26 ± 0.03*	0.28 ± 0.04*	0.53 ± 0.06**†

* $p < 0.05$.
** $p < 0.01$ denotes significant differences to the baseline levels.
† $p < 0.05$ denotes a significant difference to the former measured value.

Table 3. *Blood gases, oxygenation variables, mean airway pressure, and intrapulmonary shunt fraction in six piglets with acute respiratory failure and pulmonary hypertension pre, during, and post PGI_2 application (mean ± SEM)*

Parameters	Baseline	Lavage + U46619	PGE_2-5 (ng/kg/min)	PGI_2-10 (ng/kg/min)	PGI_2-40 (ng/kg/min)	PGI_2-Aerosol (ng/kg/min)	Post-PGI_2
pH	7.39 ± 0.02	7.35 ± 0.03	7.36 ± 0.03	7.37 ± 0.03	7.37 ± 0.02	7.42 ± 0.02†	7.36 ± 0.02†
Pao_2/FiO_2 (kPa)	65 ± 1.5	6.9 ± 0.4**	8.3 ± 0.8**	10.7 ± 2.7**	14.1 ± 4.1**†	32.4 ± 3.1*†	8.6 ± 1.3**†
SaO_2 (%)	97 ± 0.9	73 ± 6.1**	82 ± 5.9*†	79 ± 7.6*	85 ± 5.2*†	97 ± 0.8†	82 ± 4.9*†
SvO_2 (%)	71 ± 4.1	42 ± 2.6**	41 ± 3.8**	42 ± 7.4**	48 ± 7.5*†	57 ± 6.3*†	34 ± 5.6**†
Paw (kPa)	1.02 ± 0.07	1.73 ± 0.13*	1.71 ± 0.13*	1.71 ± 0.14*	1.72 ± 0.09*	1.78 ± 0.13*	1.78 ± 0.12*
Qs/Qt (%)	16 ± 1.1	59 ± 8.2**	43 ± 6.2**†	42 ± 5.3**	39 ± 5.1*	23 ± 1.6†	40 ± 4.6**†

* $p < 0.05$.
** $p < 0.01$ denotes significant differences to the baseline levels.
† $p < 0.05$ denotes a significant difference to the former measured value.

Table 4. *Hemodynamic data in six piglets with acute respiratory failure and pulmonary hypertension pre, during and post PGI_2 application (mean ± SEM)*

Parameters	Baseline	Lavage + U46619	PGI_2-5 (ng/kg/min)	PGI_2-10 (ng/kg/min)	PGI_2-40 (ng/kg/min)	PGI_2-Inhal. (ng/kg/min)	Post-PGI_2
Heart rate/min	161 ± 8	163 ± 12	167 ± 12	185 ± 10*†	192 ± 5*	168 ± 6†	200 ± 5**†
Cardiac output (L/min)	2.4 ± 0.2	1.5 ± 0.2**	1.4 ± 0.2**	1.4 ± 0.2**	1.33 ± 0.2**	1.3 ± 0.2**	0.70 ± 0.1**†
MAP (kPa)	9.7 ± 0.52	11.5 ± 0.39*	11.3 ± 0.93*	11.4 ± 0.79*	9.8 ± 0.66†	11.8 ± 0.39**†	8.6 ± 1.2**†
MPAP (kPa)	2.5 ± 0.26	5.8 ± 0.53**	5.0 ± 0.53**†	5.0 ± 0.53**	4.5 ± 0.66*	3.72 ± 0.53†	5.9 ± 0.39**†
PVR (kPa/L/min)	1.1 ± 0.29	4.34 ± 0.67**	4.0 ± 0.74**	3.9 ± 0.67**	4.2 ± 0.78**	3.4 ± 0.41**	8.4 ± 0.94**†
SVR (kPa/L/min)	4.1 ± 0.35	8.3 ± 0.86**	8.7 ± 0.94**	8.6 ± 0.86**	8.5 ± 0.86**	9.9 ± 0.95**†	11.5 ± 1.05**†
PVR/SVR	0.25 ± 0.03	0.51 ± 0.06**	0.45 ± 0.05**	0.45 ± 0.05**	0.47 ± 0.06**	0.32 ± 0.05*†	0.75 ± 0.1**†

* $p < 0.05$.
** $p < 0.01$ denotes significant differences to the baseline levels.
† $p < 0.05$ denotes a significant difference to the former measured value.

Although the highest Pao_2/FiO_2 values were obtained with inhaled NO of 10–20 ppm, there was no significant difference in oxygenation parameters (Figs. 1 and 2) and pulmonary hemodynamics (Figs. 3 and 4) between NO inhalation and PGI_2 aerosol application. However, there was a significant difference in these parameters between NO inhalation and i.v. PGI_2 application. After termination of both treatments, oxygenation and hemodynamic deteriorated within 2–5 min in all animals.

DISCUSSION

Acute respiratory failure in neonates, infants, and adults is often associated with pulmonary hypertension. In an early stage of acute lung injury, pulmonary hypertension is mediated by vasoactive substances (28), whereas in the late phase structural remodeling of the pulmonary vasculature with medial hypertrophy and reduction in luminal diameter may cause pulmonary hypertension (29). Clinical studies have shown

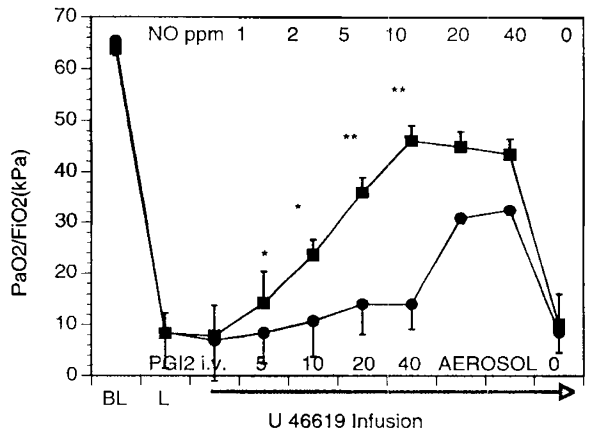

Figure 1. Pao_2/Fio_2 ratio (mean ± SEM) during inhaled NO or inhaled and intravenous PGI_2 in acute respiratory failure with pulmonary hypertension. *BL*, baseline. Asterisks indicate differences between both groups (NO, ■, *vs* PGI_2, ●); *$p < 0.05$; **$p < 0.01$.

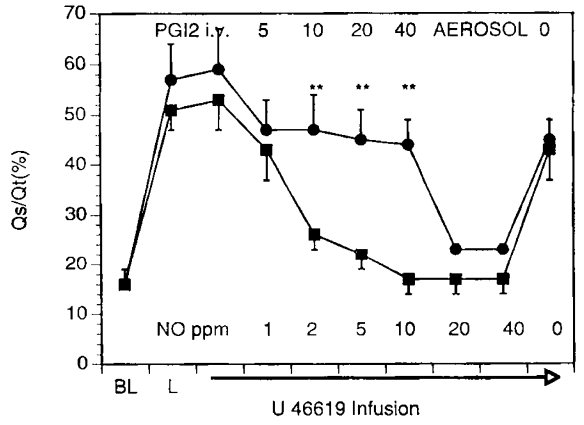

Figure 2. QsQt (mean ± SEM) during inhaled NO or inhaled and intravenous PGI_2 in acute respiratory failure with pulmonary hypertension. *BL*, baseline. Asterisks indicate differences between both groups (NO, ■, *vs* PGI_2, ●); $^{**}p < 0.01$.

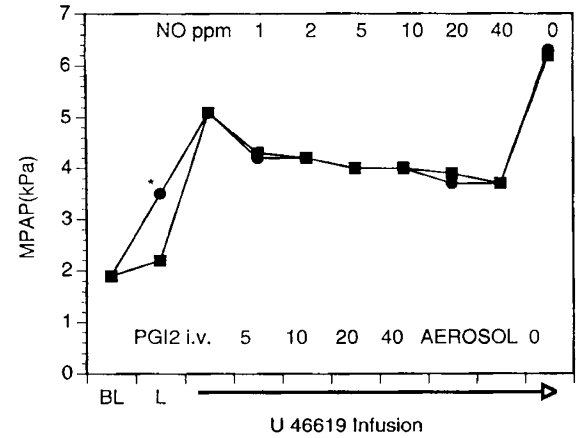

Figure 3. MPAP (mean ± SEM) during inhaled NO or inhaled and intravenous PGI_2 in acute respiratory failure with pulmonary hypetension. *BL*, baseline. Asterisks indicate differences between both groups (NO, ■, *vs* PGI_2, ●); $^{*}p < 0.05$.

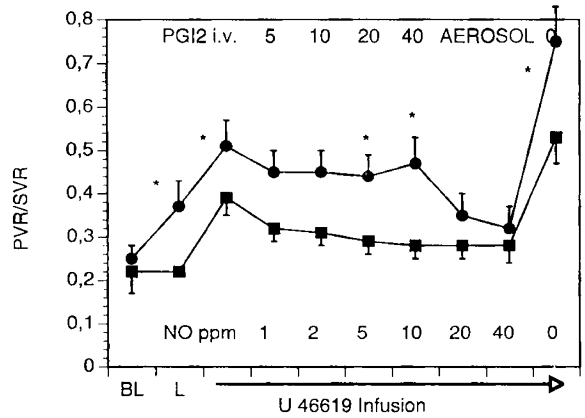

Figure 4. The ratio of PVR to SVR (mean ± SEM) during inhaled NO or inhaled and intravenous PGI_2 in acute respiratory failure with pulmonary hypertension. *BL*, baseline. Asterisks indicate differences between both groups (NO, ■, *vs* PGI_2, ●); $^{*}p < 0.05$.

increased levels of prostanoids in bronchoalveolar lavage of patients with ARDS (30). In addition, increased levels of circulatory thromboxane A_2, a potent vasoconstrictor, may be responsible for pulmonary hypertension in ARDS (31). In our animal model severe acute respiratory failure with pulmonary hypertension was simulated by repeated lung lavages and continuous infusion of U46619.

The main finding of our study was that both inhaled PGI_2 and inhaled NO act as selective pulmonary vasodilators with improvement in oxygenation and pulmonary hemodynamics without causing systemic vasodilation.

PGI_2 is the main metabolite of arachidonic acid produced in endothelial cells with potent vasodilating properties of both the arterial and venous vasculature. It has been successfully used in a variety of experimental conditions and patients with pulmonary hypertension (21–25). The dosis of i.v. PGI_2 application ranges from 5–35 ng/kg/min. The limitations of i.v. applied PGI_2 as a nonselective vasodilator are its risk to systemic hypotension and its possible risk to increased intrapulmonary shunting by vasodilating pulmonary vessels of ventilated and nonventilated areas. Recently, PGI_2 was applied as aerosol in three patients with ARDS (26). The authors observed a decrease of PVR by 30% and a significant increase of Pao_2/FiO_2 from 15.9 ± 2.4 kPa to 22.8 ± 1.6 kPa. The authors concluded that redistribution of blood flow from nonventilated to aerosol-accessible areas resulted in improved matching of ventilation and perfusion and improved oxygenation. In addition, they speculated that an increase in the dose of aerosolized PGI_2 might cause "spillover" of the prostanoid into the systemic circulation.

In 1993 Welte *et al.* (27) reported their investigation on the effects of PGI_2 aerosol on pulmonary and systemic circulation compared with NO inhalation in 6 dogs with hypoxic pulmonary hypertension. A PGI_2 aerosol delivered at a rate of 0.87 ± 0.26 ng/kg/min reduced hypoxia-induced increase of PAP by 48% and PVR by 52% within 6–10 min without systemic vasodilation. NO inhalation of 50 ppm decreased PAP and PVR by 76% and 73%, respectively. The authors concluded that aerosolized PGI_2 is a selective pulmonary vasodilator, but less potent than inhaled NO, in hypoxia induced pulmonary hypertension. In our study inhaled PGI_2 significantly improved oxygenation, reduced Qs/Qt, PAP, and PVR with no influence on the systemic vasculature. Intravenous PGI_2 slowly improved oxygenation. In contrast to other findings doses up to 40 ng/kg/min did not increase Qs/Qt. Whereas PAP decreased significantly during i.v. PGI_2 infusion MAP remained stable up to a PGI_2 infusion rate of 10 ng/kg/min. However, a significant decrease in MAP was noticed during infusion of 40 ng/kg/min of PGI_2. The PVR/SVR ratio was significantly lower during inhaled PGI_2 than during i.v. PGI_2 indicating the local vasodilating effect of inhaled PGI_2. In our study the inhaled PGI_2 dose of 30–60 ng/kg/min was significantly higher than the dose applied by Welte *et al.* (27) in dogs and slightly higher than the dose applied to humans with ARDS (26). The real aerosol deposit in the lungs is rather small (<5%) (31, 32) and cannot be easily determined. In our animal trial we did not measure PGI_2 aerosol particles in the airways and did not measure PGI_2 metabolites in the circulation. However, from the clinical point of view the inhaled PGI_2 aerosol was effective in terms of improved oxygenation and pulmonary circulation without negative systemic vascular effects. However, the exact dose and the optimal form of PGI_2 aerosol delivery has to be

shown in further studies. Inhaled PGI_2 was reported to have bronchodilatory effects in asthma (33). However, our results did not show any effect on Raw either during PGI_2 infusion or aerosol therapy.

Inhaled NO has been demonstrated to be beneficial in adults with pulmonary hypertension (19) and ARDS (18), infants and children with ARDS (17) and pulmonary hypertension associated with congenital heart disease (33), and neonates with pulmonary hypertension (13). Inhaled NO has been shown to reverse acute pulmonary vasoconstriction induced by hypoxia, by a thromboxane analog, or by the heparin-protamin reaction (7, 8). The vasodilator effect of inhaled NO occurred selectively in the pulmonary vessels without causing systemic vasodilation. Recently, Etches *et al.* (12) reported that NO reverses acute hypoxic pulmonary hypertension in the newborn piglet. The animals were given varying concentrations of inhaled NO between 5 and 80 ppm. All doses of NO significantly reduced PAP and PVR with no significant differences between the various doses of NO (12). In our present study a significant increase in oxygenation and a significant decrease in PAP occurred at an inhaled NO concentration of 1 ppm. Furthermore, oxygenation improved constantly with increasing NO concentrations up to 10 ppm. However, further increases in inhaled NO concentration resulted in a slight decrease in oxygenation. This might be due to a lower FiO_2 (FiO_2 0.9 at 40 ppm NO *versus* 1.0–0.98 at 1–10 ppm NO). The lowest PAP levels were seen during 40 ppm of NO. Although PAP decreased significantly in our study, there was no change in PVR. The continuous infusion of U46619 constantly increased systemic vasoconstriction resulting in a gradual decline in cardiac output. The PVR/SVR ratio decreased significantly during NO inhalation, indicating the local vasorelaxing effect of inhaled NO. Recently, Gerlach *et al.* (35) observed improved oxygenation in adults with ARDS with unchanged PAP at very low concentrations of inhaled NO (<1 ppm). They concluded that improved oxygenation results from redistribution of blood flow from nonventilated to ventilated areas of the lungs and not from enhanced pulmonary perfusion.

In our study the Pao_2/FiO_2 ratio was higher and Qs/Qt was lower during inhaled NO of 10 ppm than during inhaled PGI_2. Both inhalational therapies decreased significantly the PAP without any influence on MAP. These findings indicate that both inhaled substances decrease PAP sufficiently and that inhaled NO better improves ventilation-perfusion imbalance than inhaled PGI_2. Dupuy *et al.* (36) demonstrated in guinea pigs that inhaled NO reduced the increased pulmonary resistance induced by an i.v. methacholine infusion by 50%. In contrast Zayek *et al.* (11) could not find any effect of inhaled NO on Raw and tidal volume in newborn lambs with pulmonary hypertension. Our results confirm this finding.

NO is rapidly converted to NO_2 and other toxic oxides of nitrogen by oxidation that can be toxic to the lungs. Greenbaum *et al.* (6) published that inhalation of 2% NO or NO_2 resulted in death due to methemoglobinemia, hypoxemia, and pulmonary edema. The conversion of NO to NO_2 depends on the NO concentration, the FiO_2, and the contact time of both gases. As in our trial, NO was inhaled into the inspiratory limb of the ventilatory circuit near the endotracheal tube and the inspired concentrations of NO_2 were measured to be less than 0.5 ppm even at NO concentrations of 40 ppm. NO is rapidly bound to Hb in the vascular system producing methemoglobin. NO concentrations up to 80 ppm did not increase methemoglobin concentrations in animal trials (7). We measured methemoglobin concentrations up to 2% during NO inhalation of 40 ppm. However, critical levels of methemoglobinemia with reduced oxygen transport might follow prolonged inhalation of high doses of NO. Because of the possible toxicities, as methemoglobinemia due to NO and direct pulmonary injury due to NO_2, NO should be applied cautiously with continuous monitoring of inspiratory NO and NO_2 concentrations.

In conclusion, both inhaled NO and PGI_2 act as a selective pulmonary vasodilators in acute respiratory failure with pulmonary hypertension resulting in improved oxygenation mainly due to improved mismatch of pulmonary perfusion and ventilation. Both inhaled substances have no effects on Raw and Cst. The application of inhaled NO is rather simple. Because of its possible toxicity, inhaled NO requires measurement of NO and NO_2 on a continuous basis. As aerosolized PGI_2 has no known toxic side effects, measurement of the inspired concentration is not necessary. However, the exact dose and aerosol application form has to be investigated in further studies. Intravenous PGI_2 improves oxygenation and pulmonary hemodynamics to a less extent than aerosolized PGI_2 and has the risk of systemic hypotension at a higher dose.

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