

Effect of Inhaled Prostacyclin in Combination with Almitrine on Ventilation–Perfusion Distributions in Experimental Lung Injury

Rolf Dembinski, M.D., Martin Max, M.D.,† Frank López,‡ Ralf Kuhlen, M.D.,† Roland Kurth,‡ Rolf Rossaint, M.D.§*

Background: **Inhaled prostacyclin and intravenous almitrine have both been shown to improve pulmonary gas exchange in acute lung injury (ALI). This study was performed to investigate a possible additive effect of prostacyclin and almitrine on pulmonary ventilation–perfusion ($\dot{V}_A/\dot{Q}$) ratio in ALI compared with inhaled prostacyclin or intravenous almitrine alone.**

Methods: **Experimental ALI was established in 24 pigs by repeated lung lavage. Animals were randomly assigned to receive either 25 ng · kg^{-1} · min^{-1} inhaled prostacyclin alone, 1 μg · kg^{-1} · min^{-1} almitrine alone, 25 ng · kg^{-1} · min^{-1} inhaled prostacyclin in combination with 1 μg · kg^{-1} · min^{-1} almitrine, or no specific treatment (controls) for 30 min. For each intervention, pulmonary gas exchange and hemodynamics were analyzed and $\dot{V}_A/\dot{Q}$ distributions were calculated using the multiple inert gas elimination technique. The data was analyzed within and between the groups by analysis of variance for repeated measurements, followed by the Student-Newman-Keuls test for multiple comparison when analysis of variance revealed significant differences.**

Results: **All values are expressed as mean ± SD. In controls, pulmonary gas exchange, hemodynamics, and $\dot{V}_A/\dot{Q}$ distribution remained unchanged. With prostacyclin alone and almitrine alone, arterial oxygen partial pressure (Pao_2) increased, whereas intrapulmonary shunt ($\dot{Q}_S/\dot{Q}_T$) decreased ($P < 0.05$). Combined prostacyclin and almitrine also increased Pao_2 and decreased $\dot{Q}_S/\dot{Q}_T$ ($P < 0.05$). When compared with either prostacyclin or almitrine alone, the combined application of both drugs revealed no additional effect in gas exchange or $\dot{V}_A/\dot{Q}$ distribution.**

Conclusions: **The authors conclude that, in this experimental model of ALI, the combination of 25 ng · kg^{-1} · min^{-1} prostacyclin and 1 μg · kg^{-1} · min^{-1} almitrine does not result in an additive improvement of pulmonary gas exchange or $\dot{V}_A/\dot{Q}$ distribution when compared with prostacyclin or almitrine alone.**

IN the acute respiratory distress syndrome (ARDS), ventilation–perfusion ($\dot{V}_A/\dot{Q}$) mismatching is an important reason for arterial hypoxemia .[1,2] Pulmonary blood flow is partly diverted to nonventilated or only poorly ventilated lung areas, and pulmonary ventilation is partly diverted toward lung areas with no or only poor perfusion. Therefore, the fraction of inspired oxygen (F_{IO_2}) has only a limited effect on arterial oxygenation in ARDS, and strategies to reduce $\dot{V}_A/\dot{Q}$ mismatching are important in the therapy of this lung disorder.

Inhalation of short-acting vasodilators such as nitric oxide and prostacyclin and intravenous administration of almitrine are experimental procedures that have been shown to improve $\dot{V}_A/\dot{Q}$ distributions in ARDS by a redistribution of pulmonary blood flow.[3–6] Inhaled nitric oxide and prostacyclin dilate pulmonary vasculature selectively in ventilated lung areas because of their application mode and rapid inactivation. The increase of perfusion in ventilated lung areas improves the $\dot{V}_A/\dot{Q}$ ratio in these areas and reduces the blood flow to hypoventilated areas.[3–5] Intravenous almitrine has been suggested to constrict pulmonary vasculature preferentially in hypoventilated lung areas. In these areas, pulmonary blood flow is decreased for the benefit of ventilated lung areas.[6]

Recent studies revealed an additional effect of combined nitric oxide and almitrine on $\dot{V}_A/\dot{Q}$ distributions and pulmonary gas exchange in experimental acute lung injury (ALI) and clinical ARDS.[7–12] The aim of this study was to determine possible additional effects of combined prostacyclin and almitrine on $\dot{V}_A/\dot{Q}$ distribution in experimental ALI.

Materials and Methods

Animal Preparation

The experimental protocol was approved by the appropriate governmental institution (Bezirksregierung, Koeln, Germany), and the study was performed according to the Helsinki convention for the use and care of animals.

In 24 female pigs weighing 30 ± 3 kg (mean ± SD), anesthesia was induced with 5 mg/kg thiopental and maintained with continuous infusion of 5–10 mg · kg^{-1} · h^{-1} thiopental and 8–12 μg · kg^{-1} · h^{-1} fentanyl. Muscle relaxation was achieved with 0.2–0.4 mg · kg^{-1} · h^{-1} pancuronium. Animals were positioned supine, intubated with a 8.0–9.0-mm ID endotracheal tube (Mallinckroth, Athlone, Ireland), and submitted to volume-controlled mechanical ventilation (Servo 300 A Ventilator; Siemens Elema, Lund, Sweden) with an F_{IO_2} of 1.0, a respiratory rate of 20 breaths/min, a tidal volume of 10 ml/kg, an inspiratory/expiratory time ratio of 1:2, and a positive end-expiratory pressure of 5 cm H_2O. The

* Resident, † Assistant Professor, ‡ Technical Assistant, § Professor and Head.

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Address correspondence to Dr. Dembinski: Klinik fuer Anaesthesiologie, Universitaetsklinikum der RWTH Aachen, Pauwelsstrasse 30, 52074 Aachen, Germany. Address electronic mail to: Rolf.Dembinski@post.rwth-aachen.de.

Table 1. Hemodynamic Parameters

	Control			PGI_2		
	Base	ALI	C	Base	ALI	PGI_2
HR (beats/min)	92 ± 14	99 ± 7	96 ± 8	86 ± 11	97 ± 17	90 ± 14
MAP (mmHg)	109 ± 9	105 ± 8	102 ± 14	103 ± 8	92 ± 10	92 ± 7
MPAP (mmHg)	16 ± 1	35 ± 3	35 ± 3	17 ± 1	36 ± 3	29 ± 4*†
CVP (mmHg)	5 ± 2	7 ± 2	6 ± 3	6 ± 1	8 ± 2	8 ± 2
PCWP (mmHg)	8 ± 3	8 ± 2	8 ± 2	7 ± 1	8 ± 3	8 ± 3
CO (l/min)	5.2 ± 1.0	4.4 ± 0.8	4.1 ± 0.7	4.4 ± 1.0	4.6 ± 1.4	4.0 ± 1.1

Data are mean ± SD. Hemodynamics at baseline (Base), acute lung injury (ALI), and 30 min after no special treatment (C) in the control group (n = 6 pigs), treatment with 25 $ng \cdot kg^{-1} \cdot min^{-1}$ inhaled prostacyclin (PGI_2) in the PGI_2 group (n = 6 pigs), with 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ intravenous almitrine (ALM) in the almitrine group (n = 6 pigs), and with combined prostacyclin and almitrine in the P/A group (n = 6) pigs.

* $P = 0.05$ when compared with ALI within the group. † $P < 0.05$ when compared with the ALM group. ‡ $P < 0.05$ when compared with the PGI_2 group. § $P < 0.05$ when compared with the P/A group.

HR = heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; CVP = central venous pressure; PCWP = pulmonary capillary wedge pressure; CO = cardiac output.

ventilator setting remained unchanged throughout the study protocol.

A 16-gauge arterial catheter (Vygon, Ecouen, France) and a 8.5-French venous sheath (Arrow Deutschland GmbH, Erding, Germany) were inserted percutaneously into femoral vessels. A right heart catheter (model AH-05050-7.5 F, Arrow Deutschland GmbH) was positioned in a pulmonary artery during transduced pressure guidance.

The blood temperature, determined by means of the pulmonary artery catheter, was maintained at 36.7 ± 0.9°C during the experiment using an infrared warming lamp and a warming pad. A continuous infusion of 4–5 $ml \cdot kg^{-1} \cdot h^{-1}$ of a balanced electrolyte solution was administered for adequate hydration.

Data Acquisition

All hemodynamic measurements were taken in the supine position with zero reference level at the mid-chest. Central venous pressure, mean arterial pressure, mean pulmonary artery pressure (MPAP), and pulmonary capillary wedge pressure were transduced (pvb, Medizintechnik, Kirchseeon, Germany) and recorded (AS/3 Compact, Datex-Ohmeda, Achim, Germany). Cardiac output was measured using standard thermodilution techniques and expressed as the mean of three measurements at end expiration of different respiratory cycles. Heart rate was traced by the blood pressure curve.

Blood samples were collected simultaneously in duplicate, and analysis of arterial and mixed venous blood gases (Po_2, Pco_2), hemoglobin, Met-hemoglobin(MetHb), CO-hemoglobin (COHb), and oxygen saturation (Hbo_2) was performed immediately. Blood gases were determined using standard blood gas electrodes (ABL 510, Radiometer, Copenhagen, Denmark). The parameters hemoglobin, MetHb, COHb, $Hbao_2$, and $Hb\bar{v}o_2$ were measured *via* species-specific spectroscopy (OSM 3, Radiometer). Venous admixture ($\dot{Q}_{VA}/\dot{Q}_T$) was calculated using the secondary parameters arterial (Cao_2), mixed venous ($C\bar{v}o_2$), and arterial capillary oxygen content (Cco_2):

$$Cao_2\,[ml \cdot dl^{-1}] = (Hb \cdot 1.36) \cdot \frac{Hbao_2}{100} + (Pao_2 \cdot 0.0031)$$

$$Cvo_2\,[ml \cdot dl^{-1}] = (Hb \cdot 1.36) \cdot \frac{Hbvo_2}{100} + (Pvo_2 \cdot 0.0031)$$

Table 2. Gas Exchange

	Control			PGI_2		
	Base	ALI	C	Base	ALI	PGI_2
Pao_2 (mmHg)	511 ± 9	55 ± 9	57 ± 9	529 ± 15	63 ± 14	103 ± 28*
$Paco_2$ (mmHg)	34 ± 6	54 ± 7	59 ± 6	33 ± 0	57 ± 7	57 ± 6
Pvo_2 (mmHg)	60 ± 4	36 ± 6	37 ± 6	64 ± 12	38 ± 6	51 ± 11
Cao_2 (ml/dl)	13.0 ± 1.0	8.3 ± 1.7	8.6 ± 1.9	12.2 ± 0.9	8.0 ± 1.5	10.0 ± 1.2*
Cvo_2 (ml/dl)	10.1 ± 1.0	4.7 ± 1.5	4.7 ± 1.7	9.2 ± 1.5	4.2 ± 1.3	6.1 ± 1.6*
$\dot{Q}_{VA}/\dot{Q}_T$ (%)	6 ± 3	56 ± 8	54 ± 8	5 ± 2	51 ± 13	35 ± 9*

Data are mean ± SD. Gas exchange at baseline (Base), acute lung injury (ALI), and 30 min after no special treatment (C) in the control group (n = 6 pigs), treatment with 25 $ng \cdot kg^{-1} \cdot min^{-1}$ inhaled prostacyclin (PGI_2) in the PGI_2 group (n = 6 pigs), with 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ intravenous almitrine (ALM) in the almitrine group (n = 6 pigs), and with combined prostacyclin and almitrine in the P/A group (n = 6 pigs).

* $P < 0.05$ when compared with ALI within the group.

Pao_2 = arterial oxygen partial pressure; $Paco_2$ = arterial carbon dioxide partial pressure; Pvo_2 = mixed venous oxygen partial pressure; Cao_2 = arterial capillary oxygen content; Cvo_2 = mixed venous capillary oxygen content; $\dot{Q}_{VA}/\dot{Q}_T$ = venous admixture.

Table 1. Continued

ALM			P/A		
Base	ALI	ALM	Base	ALI	P/A
90 ± 13	86 ± 21	81 ± 22	95 ± 5	92 ± 11	85 ± 7
101 ± 10	90 ± 7	95 ± 15	120 ± 11	105 ± 12	101 ± 15
19 ± 2	30 ± 5	33 ± 4*‡§	16 ± 1	34 ± 2	27 ± 3*†
8 ± 2	9 ± 1	8 ± 1	7 ± 1	8 ± 1	7 ± 1
10 ± 2	9 ± 2	9 ± 4	8 ± 2	9 ± 2	9 ± 1
4.3 ± 0.7	3.8 ± 1.1	3.2 ± 1.0	5.4 ± 0.6	4.4 ± 0.9	3.8 ± 1.0

$$Cc_{O_2}\,[ml \cdot dl^{-1}] = (Hb \cdot 1.36) \cdot \left(1 - \frac{COHb}{100} - \frac{MetHb}{100}\right) + (P_{alv}O_2 \cdot 0.0031)$$

$P_{alv}O_2$ (alveolar oxygen partial pressure, mmHg) = $P_{Baro} - P_{H2O} - P_{alv}CO_2$, assuming $F_{IO_2} = 1.0$, P_{Baro} (barometric pressure) = 760 mmHg, P_{H2O} (water vapor pressure) = 47 mmHg, and $P_{alv}CO_2$ (alveolar carbon dioxide partial pressure, mmHg) = $Pa_{CO_2} : 0.8$.

$$\dot{Q}_{VA}/\dot{Q}_T[\%] = \frac{Cc_{O_2} - Ca_{O_2}}{Cc_{O_2} - Cv_{O_2}}$$

The data are presented as the mean of each measurement taken in duplicate.

$\dot{V}_A/\dot{Q}$ distributions were analyzed using the multiple inert gas elimination technique (MIGET). Briefly, 45 min before the first blood sampling, an isotonic saline solution equilibrated with six inert gases (sulfur hexaflouride, ethane, cyclopropane, halothane, ether, and acetone) was infused into a peripheral vein at a constant rate of 4 ml/min. Samples of arterial and mixed venous blood and mixed expired gas were collected simultaneously at each study point during several respiratory cycles and analyzed immediately by gas chromatography. The expiratory tubing and the mixing box for the expired gas samples were heated above body temperature to avoid a loss of the more soluble gases in condensed vapor. All samples were taken in duplicate. For each inert gas retention (the ratio of the gas concentration in arterial to that in mixed venous blood) and excretion (the ratio of the gas concentration in expired gas to that in mixed venous blood) were calculated. $\dot{V}_A/\dot{Q}$ distributions were estimated as previously described by Wagner *et al.*[13] The duplicate samples were processed separately, resulting in two $\dot{V}_A/\dot{Q}$ distributions for each condition investigated in this study. The presented data are the mean values of $\dot{V}_A/\dot{Q}$ distributions taken in duplicate.

Shunt ($\dot{Q}_S/\dot{Q}_T$) was defined as the fraction of pulmonary blood flow ($\dot{Q}_T$) perfusing unventilated alveoli ($\dot{V}_A/\dot{Q} = 0$). Low $\dot{V}_A/\dot{Q}$ regions were defined as those with $\dot{V}_A/\dot{Q}$ ratios between 0.005 and 0.1, normal $\dot{V}_A/\dot{Q}$ regions as those with $\dot{V}_A/\dot{Q}$ ratios between 0.1 and 10, and high $\dot{V}_A/\dot{Q}$ regions as those with $\dot{V}_A/\dot{Q}$ ratios between 10 and 100. Data for $\dot{V}_A/\dot{Q}$ distributions are presented as the fraction of pulmonary blood flow perfusing each lung region and expressed as $\dot{Q}_{low}$, $\dot{Q}_{normal}$, and $\dot{Q}_{high}$. Dead space ventilation ($\dot{V}_D/\dot{V}_T$) was defined as the fraction of gas entering unperfused lung units ($\dot{V}_A/\dot{Q} > 100$). The position of the distributions was also described by the mean $\dot{V}_A/\dot{Q}$ ratio for perfusion and ventilation (mean$\dot{Q}$, mean$\dot{V}_A$) and their dispersion by the log SD of both perfusion (log SD$\dot{Q}$) and ventilation (log SD$\dot{V}_A$). These parameters of dispersion do not take into account either shunt or dead space.

The residual sum of squares was the result of testing the compatibility of the inert gas data to the derived $\dot{V}_A/\dot{Q}$ distribution by the least squares method. An indication of acceptable quality of the $\dot{V}_A/\dot{Q}$ distributions is

Table 2. Continued

ALM			P/A		
Base	ALI	ALM	Base	ALI	P/A
525 ± 27	60 ± 19	99 ± 42*	521 ± 25	69 ± 16	122 ± 49*
33 ± 3	50 ± 6	52 ± 12	35 ± 3	56 ± 6	59 ± 4
62 ± 7	35 ± 10	41 ± 9	59 ± 6	41 ± 7	51 ± 9
12.2 ± 1.4	8.7 ± 2.0	10.9 ± 1.4*	12.9 ± 0.5	8.7 ± 1.6	10.4 ± 1.2*
10.3 ± 1.4	5.0 ± 1.7	6.8 ± 1.5*	10.3 ± 0.9	5.2 ± 1.9	6.6 ± 1.7*
7 ± 3	51 ± 15	34 ± 12*	5 ± 2	49 ± 11	34 ± 10*

Table 3. MIGET Data

	Control			PGI_2		
	Base	ALI	C	Base	ALI	PGI_2
$\dot{Q}_S/\dot{Q}_T$ (%)	3 ± 1	56 ± 10	56 ± 10	3 ± 3	48 ± 14	38 ± 11*
$\dot{Q}_{low}$ (%)	9 ± 3	7 ± 7	8 ± 10	7 ± 11	6 ± 5	11 ± 9
$\dot{Q}_{normal}$ (%)	88 ± 4	37 ± 8	36 ± 7	90 ± 11	46 ± 15	52 ± 18*
Mean $\dot{Q}$ (l/min)	0.56 ± 0.11	0.90 ± 0.49	1.11 ± 0.82	0.61 ± 0.18	0.80 ± 0.31	0.54 ± 0.26
Log SD$\dot{Q}$	1.30 ± 0.23	1.68 ± 0.90	1.53 ± 1.00	0.83 ± 0.59	1.59 ± 0.71	1.63 ± 0.84
$\dot{V}_D/\dot{V}_T$ (%)	56 ± 4	66 ± 2	66 ± 3	58 ± 5	66 ± 7	70 ± 2
Mean $\dot{V}_A$ (l/min)	0.99 ± 0.01	2.20 ± 0.74	2.56 ± 0.97	0.93 ± 0.25	2.02 ± 0.66	1.61 ± 0.51
Log SD$\dot{V}_A$	0.44 ± 0.08	0.43 ± 0.08	0.45 ± 0.11	0.46 ± 0.16	0.57 ± 0.21	0.54 ± 0.25

Data are mean ± SD. Multiple inert gas elimination technique (MIGET) data at baseline (Base), acute lung injury (ALI), and 30 min after no special treatment (C) in the control group (n = 6 pigs), treatment with 25 $ng \cdot kg^{-1} \cdot min^{-1}$ inhaled prostacyclin (PGI_2) in the PGI_2 group (n = 6 pigs), with 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ intravenous almitrine (ALM) in the almitrine group (n = 6 pigs), and with combined prostacyclin and almitrine in the P/A group (n = 6 pigs).

* $P < 0.05$ when compared with ALI within the group.

$\dot{Q}_S/\dot{Q}_T$ = pulmonary shunt; $\dot{Q}_{low}$ = fraction of pulmonary blood flow perfusing low $\dot{V}_A/\dot{Q}$ regions; $\dot{Q}_{normal}$ = fraction of pulmonary blood flow perfusing normal $\dot{V}_A/\dot{Q}$ regions; mean $\dot{Q}$ = mean blood flow ($\dot{Q}_S/\dot{Q}_T$ excluded); log SD$\dot{Q}$ = log standard deviation of pulmonary blood flow ($\dot{Q}_S/\dot{Q}_T$ excluded); $\dot{V}_D/\dot{V}_T$ = dead space ventilation; mean $\dot{V}_A$ = mean ventilation ($\dot{V}_D/\dot{V}_T$ excluded); log SD$\dot{V}_A$ = log standard deviation of ventilation ($\dot{V}_D/\dot{V}_T$ excluded).

a residual sum of squares of 5.348 or less in half of the experimental runs (50th percentile).[14] In the present study, 57% of residual sum of squares was less than 5.348.

Experimental Protocol

After animal preparation, a baseline measurement of all values was performed. ALI was induced by surfactant depletion caused by repeated lung lavage with saline, as previously described and evaluated by Lachmann *et al*.[15] Each lavage was performed with 40 ml/kg saline prewarmed to a temperature of 37.0°C. During the lavages the animals were disconnected from the respirator (Servo 300 A Ventilator, Siemens Elema) for less than 1 min. Values for ALI were collected after the Pa_{O_2} remained persistently below 100 mmHg for 1 h without any additional lavage. Subsequently, animals were randomized to investigate four different conditions for 30 min: (1) 25 $ng \cdot kg^{-1} \cdot min^{-1}$ aerosolized prostacyclin alone (n = 6); (2) 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ almitrine alone (n = 6); (3) combination of 25 $ng \cdot kg^{-1} \cdot min^{-1}$ aerosolized prostacyclin and 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ almitrine (n = 6); or (4) controls with no specific treatment (n = 6).

As previously described, prostacyclin (Wellcome, London, United Kingdom) was administered *via* continuous ultrasonic nebulization of a prostacyclin solution into the inspiratory limb of the respiratory circuit.[16] The rate of the nebulized solution was calculated before the study by measuring the consumption of the fluid in the nebulizer chamber (Model 6302 595 E 400 E, Siemens Elema) over the time. The prostacyclin solution was prepared by dissolving 500 μg prostacyclin in 50 ml glycine diluent. Before the administration, the solution was individually diluted according to the nebulization rate and the weight of each animal.

Almitrine (Euthérapie, Neuilly-sur-Seine, France) was infused continuously as a solution of 15 mg almitrine bismesylate dissolved in 5 ml malonic acid and diluted in 45 ml saline solution immediately before use.

To exclude a possible effect of the diluent, during the experimental conditions a corresponding amount of glycine buffer alone was nebulized in controls and animals receiving almitrine alone, and a corresponding dose of malonic acid was administered in controls and animals receiving prostacyclin alone.

After 30 min, all hemodynamic and gas exchange parameters as well as MIGET data were determined. At the end of the study, all animals were killed with an intravenous application of potassium chloride.

Statistical Analyses

All values are expressed as mean ± SD. Statistical analyses were performed using the SigmaStat for Windows 5.0 software package (Jandel, San Rafael, CA). Each parameter was analyzed by two-way analysis of variance for repeated measures to compare ALI values with those after the intervention within each group and to compare ALI values and intervention values between the intervention groups. These statistical analyses were followed by the Student-Newman-Keuls test for all pairwise comparison when analysis of variance revealed significant results. P values < 0.05 were considered significant.

Results

All animals survived the entire study period. Examination of all animals by a veterinary surgeon before the study confirmed the absence of any sign of infection or pulmonary disease. No differences in baseline parameters were observed between the animals. Total hemoglobin, Met-hemoglobin, and CO-hemoglobin remained unchanged throughout the study. A mean of 10 ±

Table 3. Continued

ALM			P/A		
Base	ALI	ALM	Base	ALI	P/A
3 ± 2	52 ± 17	34 ± 14*	3 ± 2	51 ± 10	37 ± 10*
2 ± 4	2 ± 4	7 ± 11	8 ± 5	10 ± 5	17 ± 9
95 ± 5	46 ± 19	59 ± 23*	89 ± 6	39 ± 10	46 ± 11*
0.55 ± 0.05	1.55 ± 0.62	1.01 ± 0.48	0.57 ± 0.11	0.53 ± 0.33	0.36 ± 0.15
0.56 ± 0.43	0.90 ± 0.59	1.11 ± 0.90	1.20 ± 0.48	1.98 ± 0.32	2.05 ± 0.27
63 ± 6	64 ± 8	65 ± 9	54 ± 5	68 ± 8	69 ± 2
0.72 ± 0.17	2.32 ± 0.58	2.17 ± 0.81	0.93 ± 0.14	1.44 ± 0.32	1.39 ± 0.48
0.38 ± 0.12	0.44 ± 0.12	0.52 ± 0.15	0.38 ± 0.05	0.38 ± 0.07	0.44 ± 0.07

2 lavages had to be performed to obtain a stable ALI with a decrease of Pa_{O_2} from 522 ± 20 to 62 ± 15 mmHg. In controls, no differences in hemodynamics, gas exchange, and MIGET parameters were determined within 30 min after initiation of ALI (tables 1–3).

Hemodynamic parameters are summarized in table 1. Systemic hemodynamics (heart rate, mean arterial pressure, central venous pressure, pulmonary capillary wedge pressure, cardiac output) remained unchanged throughout the entire study period, whereas MPAP revealed significant changes as a result of experimental procedures: inhaled prostacyclin and combined prostacyclin–almitrine induced a decrease in MPAP when compared with ALI and almitrine ($P < 0.05$). In contrast, almitrine increased MPAP when compared with ALI, prostacyclin, and combined prostacyclin–almitrine ($P < 0.05$).

Gas exchange parameters are summarized in table 2. None of the experimental interventions had any influence on Pa_{CO_2}. Inhalation of prostacyclin, infusion of almitrine, as well as the combination of prostacyclin and almitrine caused an increase in Pa_{O_2} and a decrease in $\dot{Q}_{VA}/\dot{Q}_T$ when compared with ALI ($P < 0.05$). No differences in Pa_{O_2} and $\dot{Q}_{VA}/\dot{Q}_T$ were revealed between combined prostacyclin–almitrine and prostacyclin or almitrine alone.

During the entire study period, the MIGET analysis showed no lung regions with a high $\dot{V}_A/\dot{Q}$ ratio. A summary of the other MIGET data is presented in table 3. Analysis of $\dot{V}_A/\dot{Q}$ distributions revealed no changes in $\dot{Q}_{low}$ and $\dot{V}_D/\dot{V}_T$ as a result of either intervention. A decrease in $\dot{Q}_S/\dot{Q}_T$ and an increase in $\dot{Q}_{normal}$ were observed with prostacyclin alone, almitrine alone, and combined prostacyclin–almitrine ($P < 0.05$). No differences in $\dot{Q}_S/\dot{Q}_T$ and $\dot{Q}_{low}$ were revealed between combined prostacyclin–almitrine and prostacyclin or almitrine alone. For all conditions, mean $\dot{Q}$ and mean $\dot{V}_A$ as well as log SD$\dot{Q}$ and log SD$\dot{V}_A$ remained unchanged.

The distribution of ventilation and perfusion after 30 min without treatment, inhalation of prostacyclin alone, administration of almitrine alone, and combined application of prostacyclin–almitrine is demonstrated for one animal from each group in figure 1.

Discussion

The aim of this study was to determine the effects of the combined application of inhaled prostacyclin and intravenous almitrine on the $\dot{V}_A/\dot{Q}$ distributions in experimental lung injury. Our major finding was that, although combined prostacyclin–almitrine improved gas exchange as a result of redistribution of pulmonary blood flow from nonventilated regions toward ventilated lung areas when compared with ALI, no additional improvement of the $\dot{V}_A/\dot{Q}$ distributions was revealed when compared with inhaled prostacyclin or intravenous almitrine alone.

In ARDS, pulmonary gas exchange is impaired because of a mismatching of ventilation and perfusion in the lung.[2] Experimental ALI in this study was also characterized by disturbed $\dot{V}_A/\dot{Q}$ distributions and revealed no differences in hemodynamics, gas exchange, and MIGET data when compared between the groups. Furthermore, control animals remained stable with regard to all measured parameters during the study period of 30 min (fig. 1). These findings indicate a stable and reproducible model of lung injury with a decreased gas exchange caused by impaired $\dot{V}_A/\dot{Q}$ distributions similar to those in ARDS. Nevertheless, this experimental model may reflect clinical situations in which the disturbances in gas exchange are mainly caused by atelectasis. However, although the model reflects primarily atelectasis, the histologic findings correspond to clinical ARDS.[15]

Aerosolized prostacyclin has been shown to improve pulmonary gas exchange in experimental ALI and ARDS.[4,5,17] Accordingly, inhaled prostacyclin alone improved gas exchange because of a decrease of $\dot{Q}_S/\dot{Q}_T$ and an increase of $\dot{Q}_{normal}$ in this study (fig. 1). The simultaneous decrease of MPAP is in accordance with the suggested mechanism of a selective pulmonary vasodilation.

Almitrine bismesylate is a peripheral chemoreceptor stimulant[18] that has been reported to improve oxygenation in ALI.[6] In contrast to prostacyclin, the mechanism by which almitrine acts is not well understood, but it is suggested that almitrine may cause a pulmonary vasoconstriction preferentially in unventilated lung areas by affecting pulmonary vessels directly.[19,20] This mechanism of almitrine may divert blood flow from nonventilated to ventilated lung regions and therefore reduce

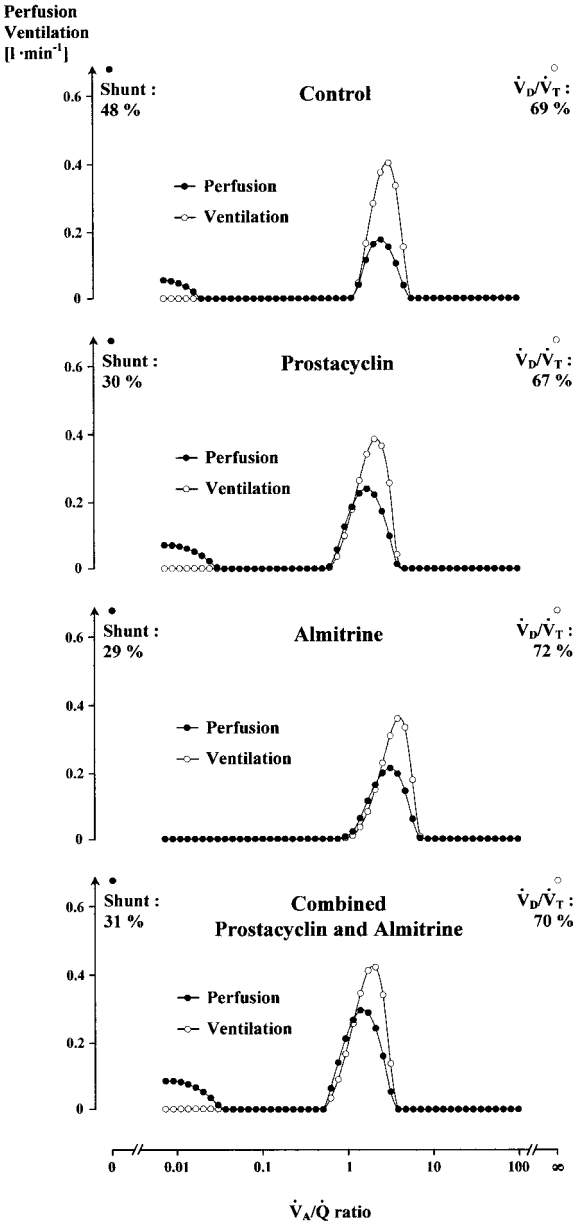

Fig. 1. Pulmonary ventilation and perfusion plotted against 50 lung compartments with different ventilation perfusion ($\dot{V}_A/\dot{Q}$) ratios in one representative animal from each group 30 min after untreated acute lung injury (Control), administration of 25 ng · kg^{-1} · min^{-1} inhaled prostacyclin (Prostacyclin), administration of 1 μg · kg^{-1} · min^{-1} intravenous almitrine (Almitrine), and administration of 25 ng · kg^{-1} · min^{-1} inhaled prostacyclin in combination with 1 μg · kg^{-1} · min^{-1} intravenous almitrine (Combined Prostacyclin and Almitrine). Shunt = blood flow to lung regions with $\dot{V}_A/\dot{Q}$ = 0; Dead space ventilation ($\dot{V}_D/\dot{V}_T$) = ventilation to lung regions with $\dot{V}_A/\dot{Q}$ greater than 100.

$\dot{Q}_S/\dot{Q}_T$, as was shown in the report by Reyes *et al.*[6] in patients with ARDS receiving almitrine. In the present study, almitrine also reduced $\dot{Q}_S/\dot{Q}_T$ for the benefit of perfusion of better-ventilated lung regions (fig. 1). The fact that almitrine produced an increase in MPAP is consistent with the hypothesis of pulmonary vasoconstriction caused by almitrine.

Our group has shown that the combination of inhaled nitric oxide with almitrine has an additional effect on the improvement of $\dot{V}_A/\dot{Q}$ distribution in the surfactant washout model of experimental ALI.[12] In contrast, combined prostacyclin–almitrine in this study failed to reveal additional effects (fig. 1).

Usually, the administration of aerosolized prostacyclin is associated with the problem that alveolar concentrations cannot be measured. Therefore, doses of inhaled prostacyclin demonstrating selective vasodilation in the literature may not reflect the effective portion of the drug in the lung. However, in nonclinical and clinical trials, doses used for selective vasodilation ranges from 1 to 50 ng · kg^{-1} · min^{-1} prostacyclin.[4,5,15,21,22] In this study, with 25 ng · kg^{-1} · min^{-1} prostacyclin, the mean of those doses was chosen to avoid vasodilation in lung areas with decreased ventilation but to provide the proposed effect of selective vasodilation. MIGET data suggested the administered dose to be effective in this ways and stable mean arterial pressure values exclude a possible spillover effect on systemic circulation.

In recent trials reporting an effect of almitrine in experimental and clinical lung injury, almitrine was administered in different doses ranging from 2 to 16 μg · kg^{-1} · min^{-1} demonstrating an improvement of pulmonary gas exchange with high-dose as well as low-dose almitrine infusion.[6,9,23–25] To minimize the expected increase in MPAP, we previously performed a dose–response trial that revealed a dosage of 1 μg · kg^{-1} · min^{-1} almitrine to be effective with regard to an improvement of gas exchange.[26] Furthermore, 1 μg · kg^{-1} · min^{-1} almitrine has been shown to be effective alone and in combination with inhaled nitric oxide in the same setting of experimental ALI.[12] According to these data, we used this dosage in the present study. Consequently, the effects of almitrine alone on $\dot{V}_A/\dot{Q}$ distribution were comparable to those observed previously.

The combination of both drugs did not reveal any improvement of the effects observed with each drug alone. Therefore, we conclude that combined inhaled prostacyclin and intravenous almitrine are not suitable for the treatment of $\dot{V}_A/\dot{Q}$ mismatching in this model of experimental ALI.

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