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EXPERIMENTAL

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Effect of inhaled nitric oxide in combination with almitrine on ventilation-perfusion distributions in experimental lung injury

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Abstract *Objective*: To investigate a possible additive effect of combined nitric oxide (NO) and almitrine bismesylate (ALM) on pulmonary ventilation-perfusion ($\dot{V}_A/\dot{Q}$) ratio.
Design: Prospective, controlled animal study.
Setting: Animal research facility of a university hospital.
Interventions: Three conditions were studied in ten female pigs with experimental acute lung injury (ALI) induced by repeated lung lavage: 1) 10 ppm NO, 2) 10 ppm NO with 1 μg/kg per min ALM, 3) 1 μg/kg per min ALM. For each condition, gas exchange, hemodynamics and $\dot{V}_A/\dot{Q}$ distributions were analyzed using the multiple inert gas elimination technique (MIGET).
Measurement and results: With NO + ALM, arterial oxygen partial pressure (PaO_2) increased from 63 ± 18 mmHg to 202 ± 97 mmHg while intrapulmonary shunt decreased from 50 ± 15 % to 26 ± 12 % and blood flow to regions with a normal $\dot{V}_A/\dot{Q}$ ratio increased from 49 ± 16 % to 72 ± 15 %. These changes were significant when compared to untreated ALI ($p < 0.05$) and NO or ALM alone ($p < 0.05$), although improvements due to NO or ALM also reached statistical significance compared to ALI values ($p < 0.05$).
Conclusions: We conclude that NO + ALM results in an additive improvement of pulmonary gas exchange in an experimental model of ALI by diverting additional blood flow from non-ventilated lung regions towards those with normal $\dot{V}_A/\dot{Q}$ relationships.

Key words Acute respiratory distress syndrome · Nitric oxide · Almitrine bismesylate · Multiple inert gas elimination technique

Introduction

The acute respiratory distress syndrome (ARDS) is characterized by pulmonary ventilation-perfusion ($\dot{V}_A/\dot{Q}$) mismatching resulting in severe hypoxemia [1, 2]. Inflammatory alterations cause alveolar and interstitial edema, occlusion of pulmonary microvasculature and pulmonary arterial hypertension resulting in the simultaneous presence of perfused lung areas with decreased ventilation and ventilated lung regions with decreased perfusion [2, 3, 4, 5]. Therefore, hypoxemia is often refractory to an increased inspiratory oxygen fraction (FIO_2) and the improvement of $\dot{V}_A/\dot{Q}$ distributions is an important goal in the treatment of ARDS.

Recent studies have demonstrated the possibility of optimizing gas exchange and $\dot{V}_A/\dot{Q}$ distributions in ARDS patients with inhaled nitric oxide (NO) as well as with intravenous almitrine bismesylate (ALM) [6, 7]. Inhaled NO has been shown to reduce intrapulmonary right-to-left shunt and to increase arterial oxygenation in ARDS patients by selective pulmonary vasodilation in ventilated lung areas [6]. Intravenous ALM seems to produce pulmonary vasoconstriction preferentially in non-ventilated lung areas [8]. ALM may therefore also

improve pulmonary gas exchange by reducing intra-pulmonary right-to-left shunt in ARDS patients [7].

Acute respiratory distress syndrome combines well ventilated and non-ventilated lung areas. Since the disturbed gas exchange in ARDS is caused mainly by intrapulmonary shunt, an additive effect of NO, which dilates the vasculature of well ventilated lung areas, and ALM, which seems to reinforce hypoxic pulmonary vasoconstriction (HPV) in non-ventilated lung areas, on pulmonary gas exchange has been suggested and several studies have demonstrated a further improvement in pulmonary oxygenation when NO was combined with intravenous ALM [9, 10, 11, 12, 13, 14, 15]. However, these studies provide only limited information concerning $\dot{V}_A/\dot{Q}$ distributions in the lung, and the mechanisms by which a combination of both drugs may improve arterial oxygenation remain unknown.

The multiple inert gas elimination technique (MIGET) was therefore used in this prospective study to investigate $\dot{V}_A/\dot{Q}$ distributions in addition to gas exchange and hemodynamics in ten pigs with experimental lung injury during administration of NO, ALM and combined NO and ALM.

Material and methods

Animal preparation

The experimental protocol was approved by the appropriate governmental institution and the study was performed according to the Helsinki convention for the use and care of animals.

In ten female pigs weighing 29 ± 3 kg (mean ± SD) anesthesia was induced with thiopental (5 mg/kg) and maintained with continuous infusion of thiopental (5–10 mg/kg per h) and fentanyl (8–12 μg/kg per h). Muscle relaxation was achieved with pancuronium (0.2–0.4 mg/kg per h). Animals were positioned supine, intubated with a 8.0–9.0 mm ID endotracheal tube and submitted to volume-controlled mechanical ventilation (Servo 300 A Ventilator, Siemens Elema, Lund, Sweden) with a FIO_2 of 1.0, a respiratory rate of 20/min, a tidal volume of 10 ml/kg, an inspiratory/expiratory time ratio of 1:2 and a positive end-expiratory pressure of 5 cmH_2O. The ventilator setting remained unchanged throughout the entire study protocol. A 16 G arterial line (Vygon, Ecouen, France) and a 8.5 Fr venous sheath (Arrow Deutschland, Erding, Germany) were inserted percutaneously into femoral vessels. A right heart catheter (model AH-05050–7.5 F, Arrow Deutschland, Erding, Germany) was positioned in a pulmonary artery under 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/kg per h of a balanced electrolyte solution was administered for adequate hydration.

Data acquisition

Hemodynamic measurements

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

Gas exchange measurements

Blood samples were collected simultaneously in duplicate and analyses of arterial and mixed venous blood gases (PO_2, PCO_2) were determined using standard blood gas electrodes (ABL 510, Radiometer Copenhagen, Denmark). Hemoglobin (Hb), Met-hemoglobin (MetHb), CO-hemoglobin (COHb), and oxygen saturation (HbO_2) were measured using species-specific spectroscopy (OSM 3, Radiometer Copenhagen, Denmark). Mixed expired gas was collected simultaneously at each study point during several respiratory cycles and analyzed for mean expiratory PCO_2 ($PeCO_2$).

The secondary parameters arterial (CaO_2), mixed venous (CvO_2) and arterial capillary oxygen content (CcO_2) and venous admixture (Q_{VA}/Q_T) were calculated:

$$CaO_2\,[ml/dl] = (Hb \cdot 1.36) \cdot \frac{\mathrm{HbaO_2}}{100} + (PaO_2 \cdot 0.0031)$$

$$CvO_2\,[ml/dl] = (Hb \cdot 1.36) \cdot \frac{\mathrm{HbvO_2}}{100} + (PvO_2 \cdot 0.0031)$$

$$CcO_2\,[ml/dl] = (Hb \cdot 1.36) \cdot \left(1 - \frac{\mathrm{COHb}}{100} - \frac{\mathrm{MetHb}}{100}\right) + (P_{alv}O_2 \cdot 0.0031)$$

$P_{alv}O_2$ (alveolar oxygen partial pressure) [mmHg] = $P_B - P_{H2O} - P_{alv}CO_2$
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] = $PaCO_2 : 0{,}8$ [16]

$$Q_{VA}/Q_T\,[\%] = \frac{CcO_2 - CaO_2}{CcO_2 - CvO_2}$$

Additionally, conventional dead space ($\dot{V}_D/\dot{V}_T^{cal}$) was calculated:

$$\dot{V}_D/\dot{V}_T^{cal}\,[\%] = \frac{PaCO_2 - PeCO_2}{PaCO_2}$$

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

Multiple inert gas elimination technique (MIGET)

Ventilation-perfusion distributions were analyzed using the MIGET. Briefly, the solubility of six inert gases (sulfur hexafluoride, ethane, cyclopropane, halothane, ether and acetone) was determined for each animal. Subsequently, 45 min before the first blood sampling, an isotonic saline solution equilibrated with these inert gases 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. [17]. The duplicate samples were processed separately resulting in two $\dot{V}_A/\dot{Q}$ distributions for each condition investigated in this study. The data presented 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 standard deviation 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.

Experimental protocol

Acute lung injury (ALI) was induced by surfactant depletion due to repeated lung lavage with saline as previously described and evaluated by Lachmann et al. [18]. 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 for less than 1 min. Baseline values for untreated ALI were collected after the PaO_2 remained persistently below 100 mmHg for 1 h without any additional lavage. Subsequently, for a time period of 30 min each, 10 ppm inhaled NO alone (NO), 10 ppm inhaled NO in combination with 1 μg/kg per min intravenous ALM (NO + ALM) and 1 μg/kg per min intravenous ALM alone (ALM) were sequentially administered. With regard to the long plasma half-life time of ALM [19], the sequence of treatments was not randomized to avoid a residual effect of ALM: in each animal NO inhalation was the first, combined NO and ALM the second, and ALM alone the third intervention. NO was administered during inspiration from a cylinder of nitrogen with a NO concentration of 800 ppm. NO and nitrogen dioxide (NO_2) concentrations in the inspiratory limb of the ventilator circuit were continuously measured by the control device integrated in the ventilator. Concentrations of NO_2, a product of the spontaneous oxidation of NO in the presence of oxygen, never reached probably toxic values. Almitrine 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.

All hemodynamic and gas exchange parameters as well as MIGET data were determined after each intervention (NO, NO + ALM, ALM). At the end of the study, all animals were killed with an intravenous application of potassium chloride.

Statistical analyses

All values are expressed as means ± SDs. Statistical analyses were performed using the SigmaStat for Windows 5.0 (Jandel, San Rafael, USA) software package. Each parameter was analyzed by one-way analysis of variance for repeated measures (ANOVA) followed by the Student-Newman-Keuls test for all pairwise comparison when ANOVA revealed significant results. Probability values less than 0.05 were considered significant.

Results

All animals survived the entire study period. Examination of all animals by a veterinary surgeon prior to the study confirmed the absence of any sign of infection or pulmonary disease. No differences in baseline parameters were observed among the animals. Total Hb, MetHb and COHb remained unchanged throughout the study. A mean of 10 ± 3 lavages had to be performed to obtain a stable ALI with a decrease of PaO_2 from 532 ± 22 mmHg to 63 ± 18 mmHg.

Hemodynamic parameters

All hemodynamic parameters are summarized in Table 1. Systemic hemodynamics (HR, MAP, CVP, PCWP, CO) remained unchanged throughout the entire study period, while MPAP revealed significant changes due to experimental procedures: inhaled NO induced a decrease in MPAP when compared to untreated ALI, ALM and NO + ALM ($p < 0.05$). In contrast, ALM increased MPAP when compared to untreated ALI, NO and NO + ALM ($p < 0.05$). With NO + ALM no changes in MPAP were observed when compared to untreated ALI.

Gas exchange

Gas exchange parameters are summarized in Table 2. None of the experimental interventions had any influence on $PaCO_2$. Inhalation of NO, infusion of ALM as well as the combination of NO + ALM caused an increase in PaO_2 and a decrease in $\dot{Q}_{VA}/\dot{Q}_T$ when compared to untreated ALI ($p < 0.05$). Changes in PaO_2 and $\dot{Q}_{VA}/\dot{Q}_T$ with NO + ALM exceeded improvements obtained with NO or ALM alone ($p < 0.05$). After induction of ALI $\dot{V}_D/\dot{V}_T^{cal}$ remained unchanged over the entire study period.

Multiple inert gas elimination technique

Over 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 $\dot{Q}_{lqw}$ and $\dot{V}_D/\dot{V}_T$ due to either intervention. A decrease in $\dot{Q}_S/\dot{Q}_T$ and an increase in $\dot{Q}_{normal}$ was observed with NO, ALM and NO + ALM ($p < 0.05$). According to the improvements in gas exchange, blood flow redistribution from unventilated lung areas towards those with normal $\dot{V}_A/\dot{Q}$ distributions was higher with NO + ALM than with either NO or ALM alone ($p < 0.05$). 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. As a representative

Table 1 NO and ALM in 10 pigs with acute lung injury; hemodynamic parameters

	Baseline	Untreated ALI	NO	NO + ALM	ALM
HR [bpm]	91 ± 10	86 ± 16	81 ± 14	76 ± 13	80 ± 18
MAP [mm Hg]	99 ± 15	95 ± 9	95 ± 12	97 ± 10	93 ± 12
MPAP [mm Hg]	18 ± 3	29 ± 5	$27 \pm 4^{\#BC}$	28 ± 3^{AC}	$33 \pm 3^{\#AB}$
CVP [cm H_2O]	7 ± 2	8 ± 2	8 ± 2	8 ± 2	8 ± 2
PCWP [mm Hg]	8 ± 2	9 ± 3	9 ± 3	8 ± 2	9 ± 3
CO [l/min]	4.2 ± 0.6	3.8 ± 0.8	3.5 ± 0.9	3.2 ± 0.7	3.2 ± 0.8

Values are means ± SD. Untreated ALI = untreated acute lung injury, NO = inhalation of nitric oxide, ALM = infusion of Almitrine, NO + ALM = combined application of NO and ALM, HR = heart rate, MAP = mean artery pressure, MPAP = mean pulmonary artery pressure, CVP = central venous pressure, PCWP = pulmonary capillary wedge pressure, CO = cardiac output
$^{\#}$ = $p < 0.05$ for comparison with untreated ALI values, ^{A} = $p < 0.05$ for comparison with NO values, ^{B} = $p < 0.05$ for comparison with ALM values, ^{C} = $p < 0.05$ for comparison with ALM + NO values

Table 2 NO and ALM in 10 pigs with acute lung injury; gas exchange

	Baseline	Untreated ALI	NO	NO + ALM	ALM
PaO_2 [mm Hg]	532 ± 22	63 ± 18	$134 \pm 67^{\#B}$	$202 \pm 97^{\#AC}$	$100 \pm 64^{\#B}$
$PaCO_2$ [mm Hg]	35 ± 4	54 ± 11	49 ± 12	49 ± 13	54 ± 16
$\dot{Q}_{VA}/\dot{Q}_T$ [%]	6 ± 4	49 ± 14	$30 \pm 7^{\#B}$	$23 \pm 9^{\#AC}$	$36 \pm 12^{\#B}$
$\dot{V}_D/\dot{V}_T^{cal}$ [%]	58 ± 4	73 ± 4	72 ± 5	72 ± 5	73 ± 6

Values are means ± SD. Untreated ALI = untreated acute lung injury, NO = inhalation of nitric oxide, ALM = infusion of Almitrine, NO + ALM = combined application of NO and ALM, PaO_2 = arterial oxygen partial pressure, $PaCO_2$ = arterial carbon dioxide partial pressure, $\dot{Q}_{VA}/\dot{Q}_T$ = venous admixture, $\dot{V}_D/\dot{V}_T^{cal}$ = conventionally calculated dead space
$^{\#}$ = $p < 0.05$ for comparison with untreated ALI values, ^{A} = $p < 0.05$ for comparison with NO values, ^{B} = $p < 0.05$ for comparison with ALM values, ^{C} = $p < 0.05$ for comparison with ALM + NO values

Table 3 NO and ALM in 10 pigs with acute lung injury; MIGET data

	Baseline	Untreated ALI	NO	NO + ALM	ALM
$\dot{Q}_S/\dot{Q}_T$ [%]	4 ± 3	50 ± 15	$32 \pm 9^{\#B}$	$26 \pm 12^{\#AC}$	$37 \pm 13^{\#B}$
$\dot{Q}_{low}$ [%]	0.4 ± 1.1	1.3 ± 2.9	1.8 ± 3.3	2.4 ± 6.8	4.3 ± 8.9
$\dot{Q}_{normal}$ [%]	96 ± 3	49 ± 16	$65 \pm 15^{\#B}$	$72 \pm 15^{\#AC}$	$59 \pm 19^{\#B}$
Mean $\dot{Q}$	0.62 ± 0.15	1.46 ± 0.68	0.99 ± 0.25	1.06 ± 0.43	1.39 ± 0.98
Log SD $\dot{Q}$	0.42 ± 0.14	0.80 ± 0.54	0.72 ± 0.49	0.67 ± 0.51	0.89 ± 0.75
$\dot{V}_D/\dot{V}_T$ [%]	66 ± 7	67 ± 8	68 ± 8	68 ± 9	68 ± 9
Mean $\dot{V}_A$	0.73 ± 0.18	2.16 ± 0.81	1.64 ± 0.79	1.67 ± 0.66	2.29 ± 1.23
Log SD $\dot{V}_A$	0.36 ± 0.09	0.43 ± 0.1	0.48 ± 0.14	0.47 ± 0.14	0.47 ± 0.14

Values are means ± SD. Untreated ALI = untreated acute lung injury, NO = inhalation of nitric oxide alone, ALM = infusion of Almitrine alone, NO + ALM = combined application of NO and ALM, $\dot{Q}_S/\dot{Q}_T$ = 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)
$^{\#}$ = $p < 0.05$ for comparison with untreated ALI values, ^{A} = $p < 0.05$ for comparison with NO values, ^{B} = $p < 0.05$ for comparison with ALM values, ^{C} = $p < 0.05$ for comparison with ALM + NO values

example, $\dot{V}_A/\dot{Q}$ distributions of one animal for each experimental condition are presented in Figs. 1, 2, 3, 4, 5.

Discussion

The purpose of this study was to determine the effects of the combined application of inhaled NO and intravenous ALM on the $\dot{V}_A/\dot{Q}$ distributions in experimental lung injury. Our major finding was that combined NO and ALM improved gas exchange due to a redistribution of blood flow from non-ventilated regions towards ventilated lung areas when compared to untreated ALI and NO or ALM alone, although the effects of both drugs alone also reached statistical significance compared to ALI values. The percentage of $\dot{Q}_{low}$ remained low and played only a minor role in the $\dot{V}_A/\dot{Q}$ mismatching.

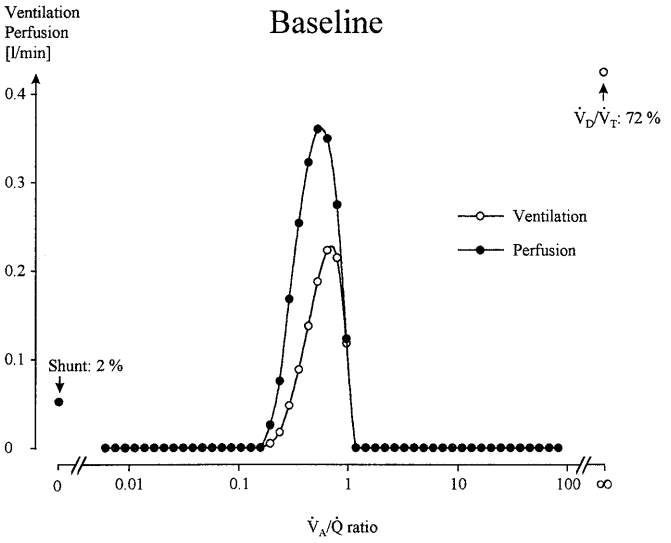

Fig. 1 Ventilation-perfusion distribution in one animal at baseline conditions (Pulmonary ventilation and perfusion plotted against 50 lung compartments with different $\dot{V}_A/\dot{Q}$ ratios by the multiple inert gas elimination technique. *(Shunt:* blood flow to lung regions with $\dot{V}_A/\dot{Q} = 0$, *Dead space ventilation* ($\dot{V}_D/\dot{V}_T$): ventilation to lung regions with $\dot{V}_A/\dot{Q} > 100$)

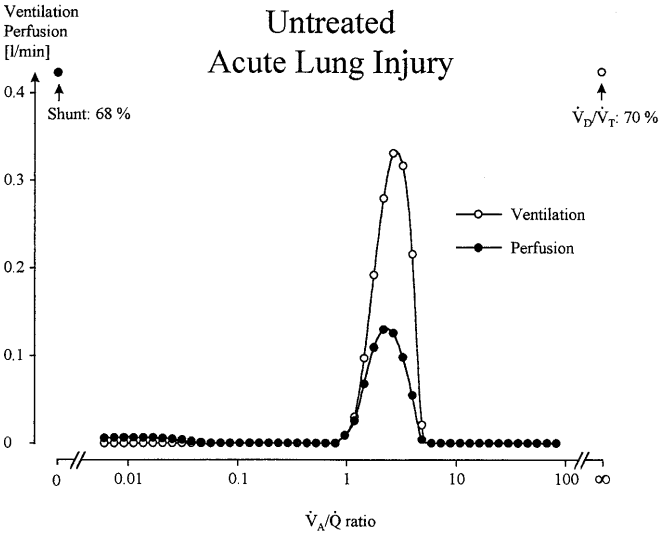

Fig. 2 Ventilation-perfusion distribution in one animal after induction of acute lung injury (see Fig. 1 for details)

In ARDS the pulmonary gas exchange is reduced by a mismatching of ventilation and perfusion in the lung [2]. MIGET analyses of $\dot{V}_A/\dot{Q}$ distributions in ARDS patients as reported by other authors showed an increased $\dot{Q}_S/\dot{Q}_T$ of about 30–40 %, a decreased $\dot{Q}_{normal}$ of about 50–60 % and a small amount of $\dot{Q}_{low}$ of about 10 % [6, 7]. In contrast to these findings, we observed a higher fraction of $\dot{Q}_S/\dot{Q}_T$ (50 ± 15 %) while the portion of $\dot{Q}_{low}$

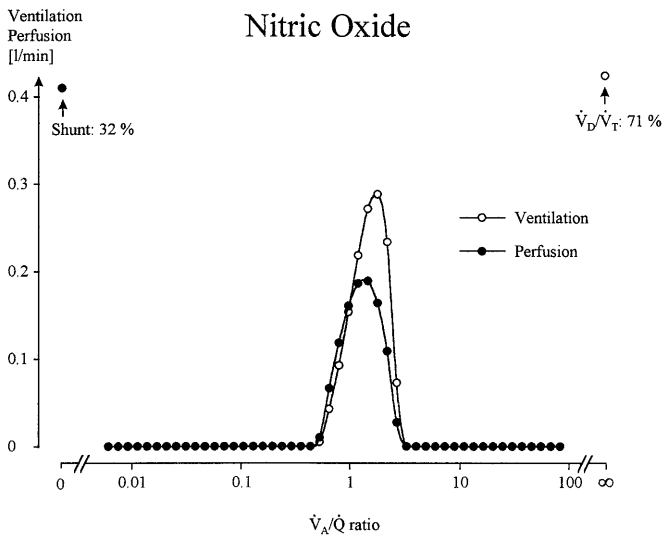

Fig. 3 Ventilation-perfusion distribution in one animal with 10 ppm nitric oxide (see Fig. 1 for details)

was negligible after ALI was initiated (1 ± 3 %). As a consequence, the effects of NO and ALM, especially on this blood flow fraction, could not be demonstrated in this study. These differences in $\dot{Q}_S/\dot{Q}_T$ and $\dot{Q}_{low}$ indicate an increased number of atelectatic lung regions due to the more specific lung injury model used in our investigation, as repeated lung lavages cause primarily surfactant depletion. Moreover, the high amount of $\dot{Q}_S/\dot{Q}_T$ may indicate the development of absorption atelectasis due to the high FIO_2 used in this study, as described by Rodriguez-Roisin [20]. Therefore, the comparison of this model with clinical ARDS in patients is restricted. On the other hand, it has been shown that changes in lung mechanics, pulmonary gas exchange and hemodynamics as well as even histologic findings are comparable to those usually observed in patients with ARDS, and they remain stable for more than 2 h [18, 21]. Furthermore, previous studies revealed only a marginal influence of NO or ALM on pulmonary blood flow to low $\dot{V}_A/\dot{Q}$ regions [6, 7]. However, the effects of combined NO and ALM observed in this study might be particularly beneficial for ARDS patients without an increased blood flow to low $\dot{V}_A/\dot{Q}$ areas. Investigations in animals using another lung injury model or in patients may be more adequate to investigate the influence on $\dot{Q}_{low}$.

Another aspect of the MIGET data deserves comment: dead space values revealed by means of the conventional calculation ($\dot{V}_D/\dot{V}_T^{cal}$) as well as by MIGET ($\dot{V}_D/\dot{V}_T$) were rather high from the beginning and remained unchanged until the end of the study. It seems justified to speculate that this fact is due to the additional dead space represented by the endotracheal tube and the Y-piece of the ventilatory circuit, as can also be ob-

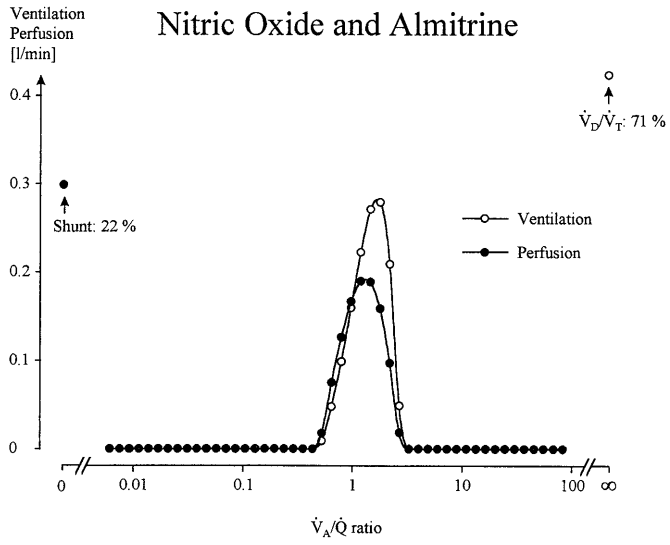

Fig. 4 Ventilation-perfusion distribution in one animal with 10 ppm nitric oxide and 1 μg/kg per min almitrine (see Fig. 1 for details)

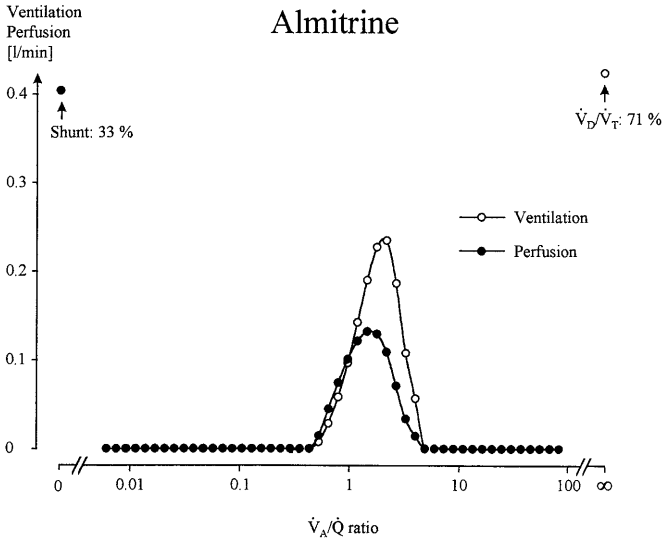

Fig. 5 Ventilation-perfusion distribution in one animal with 1 μg/kg per min almitrine (see Fig. 1 for details)

served in anesthesia in infants. However, based on the specific technique of MIGET to calculate $\dot{V}_A/\dot{Q}$ ratios, this problem should not exert a major impact on the results regarding the redistribution of blood flow.

The efficacy of NO inhalation in improving the pulmonary $\dot{V}_A/\dot{Q}$ mismatch and reducing elevated MPAP has been described for several clinical and experimental lung disorders [22, 23, 24]: Thus, in previous studies NO was able to improve oxygenation in ARDS patients by selective vasodilation in ventilated lung areas [6]. It was revealed that the limited effect on ventilated regions due to the application mode and the fast inactivation of NO could cause a redistribution of blood flow from unventilated to ventilated regions and, therefore, a reduction of $\dot{Q}_S/\dot{Q}_T$. The results of the present study correspond with these findings, demonstrating an increased $\dot{Q}_{normal}$ and a reduced $\dot{Q}_S/\dot{Q}_T$. Regarding MPAP, we observed only a small, although significant decrease, which may be due to individual differences in the response to the single dose of 10 ppm NO used in our investigation. In clinical routine, a dose-response study is usually performed prior to the treatment with inhaled NO to reveal the dose with the best impact on gas exchange and pulmonary artery pressure [25, 26, 27, 28]. Intravascular NO is known to be rapidly bound to Hb, which is transformed to MetHb in the presence of oxygen. The unchanged MetHb concentration in our study confirmed observations that the application of up to 50 ppm NO to the inspiratory gas is generally considered safe [22, 29]. A potentially dangerous complication of NO inhalation can be a rebound pulmonary hypertension and bronchoconstriction following the withdrawal from NO [30, 31, 32, 33] but, as this complication is described only after long-term treatment with NO, we exclude any influence on the results of the following measurements with ALM.

Almitrine bismesylate is a peripheral chemoreceptor stimulant [34] which has also been reported to improve oxygenation in ARDS patients [7]. In contrast to NO, the mechanism by which ALM acts is not well understood but it is suggested that ALM may cause a pulmonary vasoconstriction preferentially in unventilated lung areas by affecting the pulmonary vessels directly [8, 35]. This mechanism of ALM could divert blood flow from non-ventilated to ventilated lung regions and therefore reduce $\dot{Q}_S/\dot{Q}_T$, as has been shown in the report of Reyes et al. in patients with ARDS receiving ALM [7]. In the present study ALM also reduced $\dot{Q}_S/\dot{Q}_T$ for the benefit of perfusion of better ventilated lung regions.

The fact that ALM produced an increase in MPAP is consistent with the hypothesis of pulmonary vasoconstriction caused by ALM. It has been observed that the negative effect on pulmonary hypertension is dose-dependent [11]. In recent trials reporting an effect of ALM in experimental and clinical lung injury, ALM was administered in different dosages ranging from 2 up to 16 μg/kg per min, demonstrating an improvement of pulmonary gas exchange with high-dose as well as with low-dose ALM infusion [7, 11, 14, 36, 37, 38]. To minimize the expected increase in MPAP, we previously performed a dose-response trial which revealed a dosage of 1 μg/kg per min ALM to be effective with regard to an improvement of gas exchange [39]. According to these data, we used this dosage in the present study. The efficacy of such a low dose may be explained by a

cumulative effect due to the high plasma protein binding and a possible almitrine-like activity of almitrine metabolites [19]. An increase in HR or CO, as reported by other investigators [40], was not observed.

Because the effects of NO and ALM are limited to different lung regions, an additive effect of NO + ALM has been suggested in ARDS where well ventilated and non-ventilated regions are present at the same time. Probably due to an enhancement of hypoxic pulmonary vasoconstriction (HPV) in non-ventilated lung areas, ALM may increase the respiratory response to NO. Thus, Benzing et al. demonstrated a decrease of $\dot{Q}_{VA}/\dot{Q}_T$ in ARDS patients inhaling NO due to a decrease of mixed venous oxygen partial pressure as a maneuver to enhance HPV [41]. In prospective clinical studies with ARDS patients, several authors have reported an improvement in gas exchange with NO + ALM [9, 10, 11, 12, 13, 14, 15]. As they did not perform MIGET, the physiologic mechanism by which the two drugs in association improved oxygenation remained unclear. MIGET data in the present study confirmed the hypothesis that the improvement in gas exchange with NO + ALM is a result of an increased blood flow redistribution from non-ventilated to better ventilated lung areas as compared with NO or ALM alone. The adverse influences of NO and ALM on MPAP eliminate each other, decreasing the risk of potential right heart failure when ALM is used alone.

Whether the combination of NO + ALM and its short-term effect on pulmonary gas exchange may have beneficial effects on mortality or the outcome of ARDS patients needs to be evaluated.

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