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Cardiopulmonary effects of iloprost in experimental acute lung injury

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ABSTRACT: Iloprost, a prostacyclin analogue with a prolonged plasma half-life has beneficial effects in chronic pulmonary hypertension, whereas the effects in acute lung injury (ALI) are unknown. The present study was performed to evaluate the cardiopulmonary effects of iloprost in experimental ALI.

ALI was induced in 18 pigs by repeated lung lavage. Animals were randomised to controls, *i.v.* or inhaled iloprost for 15 min. Haemodynamics, gas exchange and ventilation–perfusion distribution were measured at the end of iloprost application and after 1 and 2 h.

As a short-term effect, both *i.v.* and inhaled iloprost significantly decreased pulmonary artery pressure without major effects on gas exchange or systemic haemodynamics. After 1 and 2 h, a reduction of pulmonary hypertension was no longer present. As a long-term effect, inhaled, but not *i.v.*, iloprost decreased pulmonary shunt and significantly improved gas exchange after 1 and 2 h.

In conclusion, the single application of iloprost revealed short-term pulmonary vasodilation without other major cardiopulmonary effects. However, inhaled iloprost improved gas exchange due to a decrease of pulmonary shunt as a long-term effect, possibly as a result of a reduction of lung oedema formation.

KEYWORDS: Acute lung injury, animal model, haemodynamics, prostacyclin, pulmonary gas exchange

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Acute lung injury (ALI) is defined by hypoxaemia as a result of a ventilation–perfusion ($V'A/Q'$) mismatching, mainly characterised by intrapulmonary shunt in atelectatic lung areas. Furthermore, hypoxic pulmonary vasoconstriction and a widespread occlusion of the pulmonary microvasculature may cause pulmonary hypertension [1].

Inhaled short-acting vasodilators, such as nitric oxide (NO) or prostacyclin (*i.e.* prostaglandin I_2 (PGI_2)), may reduce intrapulmonary shunt, improve oxygenation and reduce pulmonary hypertension in ALI due to selective pulmonary vasodilation [2, 3]. Although randomised controlled trials failed to reveal improved outcome [4–7], inhaled vasodilators are still recommended as a rescue therapy in severe hypoxaemia and pulmonary hypertension [8]. However, short-acting vasodilators have to be administered continuously and their sudden withdrawal may even increase pulmonary arterial pressure due to a rebound phenomenon [9, 10].

Iloprost is a prostacyclin analogue with an increased plasma half-life time of ~20–30 min [11, 12], which has been used successfully to induce a prolonged reduction of pulmonary artery pressure in chronic pulmonary hypertension of different origin by *i.v.* [13–15] or inhalational [12, 16, 17] administration. In contrast, the effects of iloprost in ALI have remained unknown until recently.

In ALI, the administration of iloprost may be advantageous when compared with short-acting vasodilators, because of prolonged pulmonary vasodilation without the need for continuous application and the risk of a rebound phenomenon. Conversely, nonselective pulmonary and systemic vasodilation may impair gas exchange and cause systemic hypotension.

The present study was performed to investigate the effects of *i.v.* and inhaled iloprost on haemodynamics, gas exchange and $V'A/Q'$ distribution in experimental ALI.

MATERIALS AND METHODS

Animal preparation

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

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A total of 18 female pigs weighing 29.8±1.9 kg (mean±SD) were included in the study. A veterinarian examined all of the animals to exclude any pre-existing diseases.

Intramuscular azaperone (5–7 mg·kg^{-1}) and atropine (0.01 mg·kg^{-1}) were administered 1 h prior to the start of anaesthesia. Anaesthesia was induced with thiopental (5 mg·kg^{-1}) and maintained with a continuous infusion of thiopental (6–10 mg·kg^{-1}·h^{-1}), fentanyl (0.1 μg·kg^{-1}·min^{-1}) and pancuronium (4–5 μg·kg^{-1}·min^{-1}). All animals were positioned supine, intubated orally with an endotracheal tube and mechanically ventilated (Servo 900 Ventilator; Siemens Elema, Lund, Sweden). The animals were ventilated with a respiratory rate of 25 breaths·min^{-1}, a positive end-expiratory pressure of 10 mmHg and an inspiration to expiration ratio of 1:1. A tidal volume of 8 mL·kg^{-1} body weight was used. The supine position and the ventilator setting were not changed throughout the experiment.

An 18-gage arterial line (Vygon, Ecouen, France) and an 8.5-French venous sheath (Baxter, Irvine, CA, USA) were placed into a femoral vessel percutaneously. A right heart catheter was positioned into a pulmonary artery under transducer pressure guidance.

Fluid replacement was provided by administration of hydroxyethyl starch (Fresenius Kabi, Bad Homburg, Germany), according to haemodynamics, with an average of 9±3 mL·kg^{-1}·h^{-1}. Urine output was recorded *via* a transurethral catheter.

Data acquisition

Haemodynamic parameters were obtained by routine clinical monitoring. Mean arterial blood pressure (MAP), mean pulmonary artery pressure (MPAP), central venous pressure (CVP), and pulmonary capillary wedge pressure (PCWP) were measured with disposable transducers and a monitoring system (AS/3 Compact; Datex Ohmeda, Helsinki, Finland). The zero reference level for the supine position was the midaxilla. Cardiac output (CO) was measured using thermodilution technique. Heart rate (HR) was traced and counted by the blood pressure curve. Systemic (SVR) and pulmonary vascular resistance (PVR) were calculated by standard formulae.

For arterial and mixed-venous blood gases (partial pressure of oxygen and carbon dioxide), blood samples were collected simultaneously in duplicate and analysis was performed immediately. Blood gases were measured with standard blood-gas electrodes (ABL 510; Radiometer, Copenhagen, Denmark). The other parameters were determined by species-specific spectroscopy (OSM 3; Radiometer).

V'_A/Q' distributions were evaluated using the multiple inert gas elimination technique (MIGET), as previously described in detail [18–20]. The presented data are the mean values of V'_A/Q' distributions taken in duplicate. Shunt (Q'_S/Q'_T) was defined as the fraction of total pulmonary blood flow perfusing unventilated alveoli (V'_A/Q' <0.005). Low V'_A/Q' regions were defined as those with V'_A/Q' ratios ranging 0.005–0.1, normal V'_A/Q' regions as those with V'_A/Q' ratios ranging 0.1–10, and high V'_A/Q' regions as those with V'_A/Q' ratios ranging 10–100. Data for perfusion distribution are presented as percentages of total pulmonary blood flow and expressed as blood flows to regions with low, normal and high V'_A/Q' ratios. Data for ventilation distribution are presented as percentages of total minute ventilation and expressed as ventilation to regions with low, normal (V'_{normal}) and high V'_A/Q' ratios. Dead space ventilation (V_D/V_T) was defined as the fraction of gas entering unperfused lung units (V'_A/Q' >100). Quality control was performed by calculating the residual sum of squares (RSS) between measured and calculated V'_A/Q' distributions.

Experimental protocol

Induction of experimental ALI was performed by repeated lung lavages, as described previously [21]. The experimental protocol was started when an arterial oxygen tension (P_{a,O_2}) <150 mmHg was achieved for ⩾60 min without additional lavages.

After induction of ALI, the animals were randomly assigned to three groups. As there is no information about inhalational or *i.v.*-applied dosages of iloprost in pigs in the current literature, pilot studies were performed to determine effective dosages of *i.v.* and inhaled iloprost. The effective dosage to produce ⩾20% reduction of MPAP 15 min after application was 80 ng·kg^{-1}·min^{-1} *i.v.* and 220 ng·kg^{-1}·min^{-1} inhalational iloprost, respectively.

Therefore, application of either 80 ng·kg^{-1}·min^{-1} *i.v.* iloprost (Ilomedin; Schering, Berlin, Germany) for a period of 15 min in the first group of animals or 220 ng·kg^{-1}·min^{-1} inhalational iloprost for a period of 15 min in the second group of animals took place. The third group had no administration of iloprost at any point. Inhalational iloprost was applied with a continuous ultrasonic nebulisation system (Model 6302595 E 400 E; Siemens Elema). Haemodynamics, pulmonary gas exchange and V'_A/Q' distributions were measured at baseline, after induction of ALI, immediately after iloprost application, and 1 and 2 h thereafter.

Statistical analyses

All data are expressed as mean±SD. The data were analysed within the groups in comparison to ALI and between the groups comparing *i.v.* and inhaled iloprost with controls by two-way ANOVA for repeated measurements, followed by the Student-Newman-Keuls test for all pairwise comparison when ANOVA revealed significant results. A value of $p<0.05$ was considered to indicate statistical significance. Baseline values were controlled to exclude major cardiopulmonary dysfunction prior to the induction of experimental ALI. Therefore, baseline values were not included in the statistical analysis.

RESULTS

Baseline parameters revealed physiological values in all animals at the beginning of the study. To obtain a stable lung injury, 18±9 lavages had to be performed with a decrease of mean P_{a,O_2} from 481±37 mmHg to 90±25 mmHg, and an increase of MPAP from 22±3 mmHg to 41±3 mmHg. The mean time interval from baseline to ALI was 185±46 min. Mean urine output was 156±5 mL·h^{-1}. All animals survived until the end of the study.

Changes in CO, MAP, MPAP, Q'_S/Q'_T and P_{a,O_2} are presented in figure 1. Other haemodynamics and gas exchange

parameters are summarised in table 1. After induction of ALI, statistical analysis revealed a decreased HR and an increased SVR in animals randomised to *i.v.* iloprost when compared with controls ($p<0.05$). The difference in HR remained unchanged until the end of the study ($p<0.05$). After 2 h, HR was lower in both intervention groups when compared with controls ($p<0.05$). SVR decreased immediately after *i.v.* iloprost ($p<0.05$).

In both intervention groups, MPAP and PVR decreased immediately after application of iloprost ($p<0.05$), whereas differences in comparison with ALI were no longer revealed after 1 and 2 h. CVP and PCWP remained unchanged within physiological ranges in all groups.

MIGET data are demonstrated in table 2. Acceptable quality of V'_A/Q' distribution analysis was confirmed by calculating the RSS, which should be <5.348 in ⩾50% and <10,645 in ⩾90% of all experimental runs [22]. In the present study, the RSS was <5.348 in 71% and <10,645 in 91% of all experimental runs.

In controls, gas exchange and V'_A/Q' distribution remained unchanged after induction of ALI until the end of the study. In animals randomised to *i.v.* iloprost, the induction of ALI caused a lower percentage of Q'_S/Q'_T when compared with controls ($p<0.05$). This difference remained present until the end of the study and was accompanied with a higher P_{a,O_2} in comparison with controls after 2 h. However, when compared to ALI within this group, Q'_S/Q'_T and P_{a,O_2} remained unchanged until the end of the study.

Inhaled iloprost increased V_D/V_T and decreased V'_{normal} immediately after application ($p<0.05$). However, in contrast to *i.v.* iloprost, Q'_S/Q'_T decreased and P_{a,O_2} increased after 1 and 2 h in this group ($p<0.05$).

DISCUSSION

The aim of the present study was to examine the effects of *i.v.* and inhaled iloprost on haemodynamics, gas exchange and V'_A/Q' distribution in an animal model of ALI. There were three major findings. First, the reduction of MPAP due to *i.v.* and inhaled iloprost was not accompanied by major changes in systemic haemodynamics, gas exchange or V'_A/Q' distribution. Secondly, neither *i.v.* nor inhaled iloprost had a long-term effect on reducing MPAP after 1 or 2 h. Thirdly, inhaled iloprost improved oxygenation due to a decrease of Q'_S/Q'_T after 1 and 2 h.

From these data, it can be concluded that iloprost does not offer major advantages when compared with short-acting vasodilators with regards to a long-term reduction of pulmonary hypertension over several hours. These results are in accordance with the haemodynamic effects of iloprost in chronic pulmonary hypertension. Likewise, in several studies, the single application of inhaled iloprost had no prolonged beneficial effects over several hours, whereas repeated applications six times per day decreased pulmonary arterial pressure permanently within weeks [16, 17, 23, 24]. In contrast, MACHHERNDL *et al*. [25] found no haemodynamic improvement in 12 patients with severe pulmonary hypertension after long-term treatment with aerosolised iloprost. However, these results might have been caused by several limiting factors of this investigation, such as the small number of patients and the

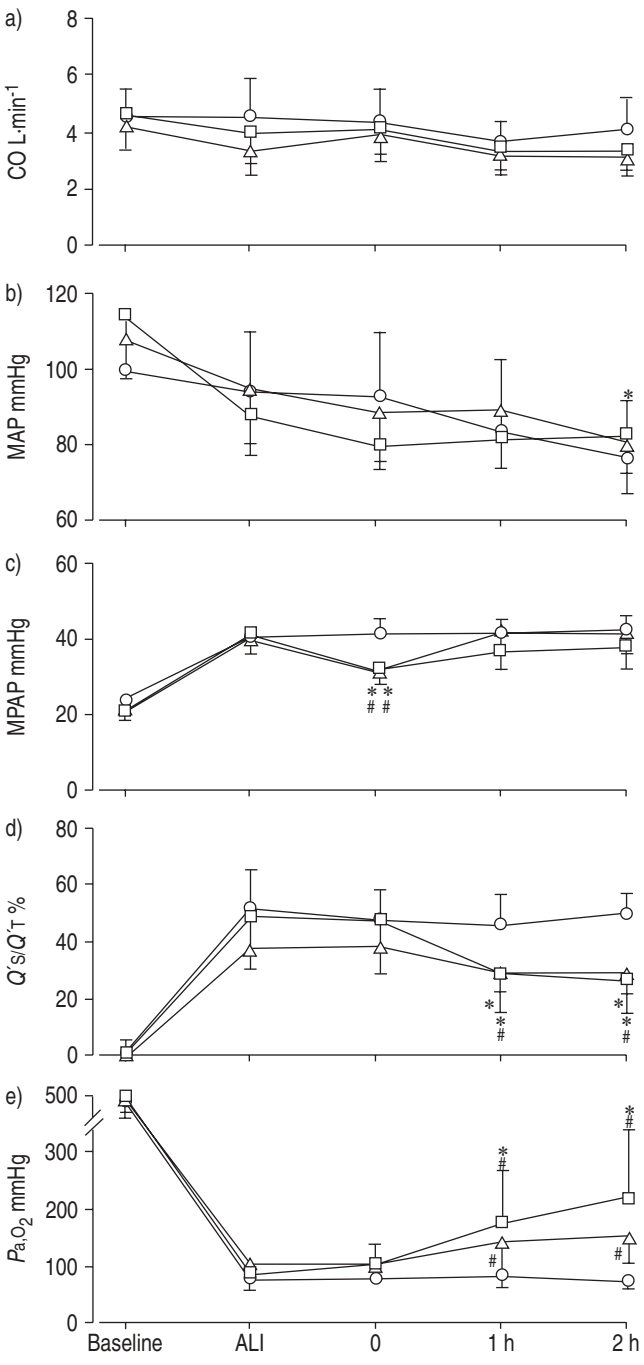

FIGURE 1. Haemodynamics and gas exchange were measured before (baseline) and immediately after induction of acute lung injury (ALI), immediately after 80 ng·kg^{-1}·min^{-1} *i.v.* or 220 ng·kg^{-1}·min^{-1} inhalational iloprost for 15 min each (0), 1 h and 2 h after administration of iloprost in the control (○), *i.v.* (△) and inhalational (□) iloprost groups. Data are presented as mean±SD. The following were measured: a) cardiac output (CO), b) mean arterial blood pressure (MAP), c) mean pulmonary arterial pressure (MPAP), d) pulmonary shunt (Q'_S/Q'_T), and e) arterial oxygen partial pressure (P_{a,O_2}). *: $p<0.05$ compared with ALI within the group; #: $p<0.05$ compared with controls.

open, uncontrolled nature of the study. Thus, according to most of the clinical results, it can be assumed that a long-term haemodynamic effect over several hours probably depends on

TABLE 1 Haemodynamics and gas exchange

	Baseline	ALI	0	1 h	2 h
HR min^{-1}					
Control	102±13	106±40	108±47	100±34	106±38
i.v.	98±9	87±9¶	92±14¶	86±15¶	80±11¶
Inhalational	110±14	104±16	105±17	97±23	91±12¶
PCWP mmHg					
Control	13±1	11±1	12±1	11±2	12±1
i.v.	11±2	11±1	10±2	11±2	9±3
Inhalational	11±1	13±1	13±2	12±2	13±2
SVR dyn·s·cm^{-5}					
Control	1665±404	1639±546	1642±518	1681±581	1372±447
i.v.	1937±343	2026±378¶	1699±499#	2035±364¶	1856±356¶
Inhalational	1809±234	1568±402	1332±234	1687±363	1755±313
PVR dyn·s^{-1}·cm^{-5}					
Control	150±63	547±116	571±135	668±130	631±179
i.v.	263±35	727±221	456±96#	817±245	810±231
Inhalational	170±29	584±111	369±98#,¶	596±158	630±171
P_{a,CO_2} mmHg					
Control	38±8	55±13	55±13	53±13	59±17
i.v.	38±4	49±11	50±12	49±13	49±8¶
Inhalational	37±5	57±8	58±10	52±8	51±8¶

Data are presented as mean±SD. Haemodynamics were measured before (baseline) and immediately after induction of acute lung injury (ALI), immediately after 80 ng·kg^{-1}·min^{-1} *i.v.* or 220 ng·kg^{-1}·min^{-1} inhalational iloprost for 15 min each (0), 1 h and 2 h after administration of iloprost. HR: heart rate; PCWP: pulmonary capillary wedge pressure; SVR: systemic vascular resistance; PVR: pulmonary vascular resistance; P_{a,CO_2}: arterial carbon dioxide tension. #: $p<0.05$ compared with ALI within the group; ¶: $p<0.05$ compared with controls.

repeated administration over a number of weeks. Nevertheless, in the present study, iloprost reduced MPAP without major effects on systemic haemodynamics or gas exchange, whereas inhaled iloprost even improved oxygenation as a long-term effect. Therefore, iloprost may offer an alternative to NO and PGI_2 in ALI.

However, some limitations of the current study have to be noted. Most importantly, experimentally induced ALI was less severe in animals randomised to *i.v.* iloprost. Although MPAP increased equally, statistical analysis revealed differences in $Q'S/Q'T$ when compared with controls and those animals submitted to inhaled iloprost. Moreover, SVR was higher in this group. Therefore, the effects of *i.v.* iloprost may only be estimated by the comparison with ALI within this group. With this restriction, *i.v.* iloprost is suggested to reduce MPAP efficaciously with only minor changes of systemic haemodynamics. Thus, a slight systemic vasodilation caused a decrease of SVR, whereas CO and MAP remained unchanged. Furthermore, P_{a,O_2} and $V'A/Q'$ distribution remained unchanged within this group, probably due to nonselective pulmonary vasodilation without beneficial intrapulmonary perfusion redistribution.

In contrast to this group, animals submitted to inhaled iloprost were comparable with controls, with regards to the severity of ALI. However, there is a trend of increased VD/VT and decreased V'_{normal} when compared with controls, which might, in part, be responsible for a slight, but statistically significant difference of V'_{normal} and VD/VT immediately after application of inhaled iloprost. Conversely, these changes in ventilation distribution may be artificially caused by a loss of the more soluble inert gases ether and acetone, which have been used for the MIGET analysis [18], during iloprost nebulisation. Although the expiratory tubing and the mixing box for the expired gas samples were heated above body temperature in order to avoid such a loss in condensed vapour, a certain loss of these gases in the endotracheal tube seems probable.

However, the overall short-term effect of inhaled iloprost was comparable with *i.v.* iloprost. Thus, MPAP decreased without major changes in haemodynamics or gas exchange. It can be concluded that inhaled iloprost caused nonselective intrapulmonary vasodilation, in contrast to short-acting vasodilators, due to its prolonged plasma half-life time. Furthermore, the dosage chosen to obtain a significant decrease of MPAP was possibly too high to exert intrapulmonary selective vasodilation, but caused vasodilation in ventilated and nonventilated lung areas in addition, due to its active percentage in circulating blood. Therefore, oxygenation remained unchanged during inhaled iloprost, whereas inhaled NO or PGI_2 may improve gas exchange in ALI.

Within this context, it should be noted that experimentally and clinically applied dosages of inhaled iloprost are usually much lower when compared with those used in the present study. Thus, in patients with chronic pulmonary hypertension, a dosage of ~10–20 ng·kg^{-1}·min^{-1} was demonstrated to provide beneficial effects [12, 16, 17, 23, 24], while 40–70 ng·kg^{-1}·min^{-1}

TABLE 2 Ventilation–perfusion (V'_A/Q') distribution

	Baseline	ALI	0	1 h	2 h
Q'_S/Q'_T % Q'_T					
Control	2±4	52±14	48±11	46±11	50±8
i.v.	0±0	38±7[¶]	39±9	30±7[¶]	29±7[¶]
Inhalational	1±1	49±13	48±9	29±13[#,¶]	27±11[#,¶]
Q'_{low} % Q'_T					
Control	9±10	9±7	11±8	12±6	11±7
i.v.	13±15	16±10	18±6	21±8	19±10
Inhalational	21±25	13±8	20±6	25±12[¶]	21±13
Q'_{normal} % Q'_T					
Control	89±9	39±14	41±9	43±10	39±8
i.v.	87±15	46±10	43±11	49±11	51±13
Inhalational	77±26	36±12	32±8	46±12	51±14
Q'_{high} % Q'_T					
Control	0±0	0±0	0±0	0±0	0±0
i.v.	0±0	0±1	0±0	0±0	1±3
Inhalational	0±0	2±4	0±0	0±0	0±0
Mean Q'					
Control	0.4±0.2	0.7±0.4	0.7±0.3	0.7±0.3	0.6±0.3
i.v.	0.4±0.2	0.7±0.7	0.5±0.3	0.5±0.4	0.7±0.5
Inhalational	0.5±0.2	1.3±1.9	0.3±0.1	0.5±0.4	0.7±0.6
Log $_{SD}$ Q'					
Control	1.0±0.2	1.9±0.7	2.0±0.6	2.2±0.3	2.1±0.7
i.v.	1.2±0.3	2.1±0.5	2.4±0.1	2.4±0.2	2.3±0.2
Inhalational	1.5±0.7	2.1±0.4	2.3±0.1	2.3±0.2	2.0±0.6
V'_{low} % V'_E					
Control	0±1	0±0	0±0	0±0	0±0
i.v.	0±1	0±0	0±0	0±0	0±0
Inhalational	0±0	0±0	0±0	0±0	0±0
V'_{normal} % V'_E					
Control	38±8	42±3	44±5	44±5	44±5
i.v.	36±3	45±5	47±5	49±4	46±6
Inhalational	41±7	38±8	36±4[¶]	42±5	41±6
V'_{high} % V'_E					
Control	2±4	0±0	0±0	0±0	0±1
i.v.	0±0	2±2	1±2	1±2	2±5
Inhalational	0±1	5±11	0±0	0±0	0±0
V_D/V_T % V'_E					
Control	60±8	58±3	56±5	56±5	56±5
i.v.	64±3	53±4	51±6	51±5	52±4
Inhalational	58±7	57±10	64±4[#,¶]	58±5	59±6
Mean V'_A					
Control	1.2±0.5	2.1±0.2	2.3±0.3	2.4±0.4	2.3±0.7
i.v.	1.3±0.2	2.6±0.8	2.7±0.7	2.6±0.7	3.2±1.7
Inhalational	1.5±0.4	3.3±2.9	1.7±0.3	2.2±0.8	2.2±0.8
Log $_{SD}$ V'_A					
Control	0.9±0.5	0.5±0.1	0.5±0.1	0.5±0.1	0.6±0.1
i.v.	0.8±0.3	0.7±0.1	0.6±0.2	0.6±0.1	0.6±0.1
Inhalational	0.7±0.4	0.6±0.1	0.6±0.1	0.5±0.1	0.5±0.1

Data are presented as mean±SD. V'_A/Q' distribution before (baseline) and immediately after induction of acute lung injury (ALI), immediately after 80 ng·kg^{-1}·min^{-1} *i.v.* or 220 ng·kg^{-1}·min^{-1} inhalational iloprost for 15 min each (0), 1 h and 2 h after administration of iloprost. Q'_S/Q'_T: shunt (V'_A/Q' <0.005), Q'_{low}: blood flow to regions with low (>0.005–<0.1) V'_A/Q' ratio; Q'_{normal}: blood flow to regions with normal (>0.1–<10) V'_A/Q' ratio; Q'_{high}: blood flow to regions with high (>10–<100) V'_A/Q' ratio; mean Q': mean V'_A/Q' ratio of perfusion; log $_{SD}$ Q': logarithmic standard deviation of perfusion; V'_{low}: ventilation to regions with low (>0.005–<0.1) V'_A/Q' ratio; V'_{normal}: ventilation to regions with normal (>0.1–<10) V'_A/Q' ratio; V'_{high}: ventilation to regions with high (>10–<100) V'_A/Q' ratio; V_D/V_T: dead space ventilation; mean V'_A: mean V'_A/Q' ratio of ventilation; log $_{SD}$ V'_A: logarithmic standard deviation of ventilation. [#]: p<0.05 compared with ALI within the group; [¶]: p<0.05 compared with controls.

inhaled iloprost were found to effectively provide selective pulmonary vasodilation in animal experiments with isolated rabbit lungs [26, 27]. However, besides species-related differences, it is well known that nebulisers differ with regards to their efficacy [28, 29]. Thus, the effective alveolar drug deposition by ultrasonic nebulisation depends on the percentage of the aerosolised drug with an optimal particle size of 3–5 μm. As this fraction varies between different nebulisers and continuous online measuring of inhaled drug concentrations is not possible in daily routine, dosage has to be adjusted with regards to physiological response, possibly resulting in different dosages. In the present study, the dosage was adjusted in order to obtain a reliable decrease of MPAP, but not to improve gas exchange, because the current authors aimed to investigate whether the significant reduction of MPAP is accompanied by gas exchange effects and not *vice versa*. Thus, it cannot be excluded that decreasing iloprost dosage would have caused selective pulmonary vasodilation without a significant decrease of MPAP. Nevertheless, during inhaled iloprost at least, pulmonary selectivity was more pronounced than during *i.v.* iloprost, as SVR remained unchanged in this group.

Most interestingly, inhaled iloprost caused a decrease of Q'_S/Q'_T, thereby improving oxygenation as a long-term effect after 1 and 2 h. With regards to a plasma half-life time of ~20–30 min [11], these changes were unlikely to be the result of a prolonged vasoactive effect of iloprost. Moreover, SCHERMULY *et al*. [30] showed that inhaled iloprost rapidly enters the intravascular compartment in healthy isolated rabbit lungs. Therefore, a retarded release of iloprost from out of the alveolar space, which might have contributed to a delayed selective vasodilation in the present study, seems to be improbable. Finally, after 1 h, no pulmonary vasodilation, as measured by MPAP or PVR, was present. In summary, active pulmonary vasodilation by iloprost at that time seems unlikely.

More likely, improved gas exchange was caused by reduced lung oedema formation. Thus, the short-term reduction of pulmonary hypertension by iloprost possibly decreased pulmonary oedema formation, thereby improving gas exchange within hours, but not immediately after iloprost application. A reduction of lung oedema formation due to iloprost is also reported by SCHERMULY *et al*. [27]. They investigated inhaled iloprost in isolated rabbit lungs with lung injury induced by perfusion with a thromboxane A_2-mimetic. In that trial, a significant decrease of MPAP and Q'_S/Q'_T was determined immediately after iloprost inhalation when compared with controls. However, similar to the current results, after 1 and 2 h, the differences in Q'_S/Q'_T seem to be more marked, whereas the haemodynamic effect decreased.

According to the hypothesis of a reduced lung oedema formation, *i.v.* iloprost should equally decrease Q'_S/Q'_T and increase oxygenation, but it failed to improve gas exchange in the present study. Thus, there was a trend towards a decrease of Q'_S/Q'_T and an increase of P_{a,O_2} after 1 and 2 h in this group, but this difference failed to reach statistical significance. However, as discussed previously, statistical analysis in this group was limited due to differences in comparison with the other groups after induction of ALI. Nevertheless, reduced lung oedema formation is a hypothesis to explain the beneficial effects of iloprost, but this can not be proven with the current data.

In conclusion, inhaled iloprost, especially, may offer an alternative to short-acting vasodilators to reduce mean pulmonary artery pressure in acute lung injury without major haemodynamic or gas-exchange effects. Furthermore, inhaled iloprost may cause an improvement of gas exchange over time, possibly due to reduced lung oedema formation. However, this study did not reveal advantages of iloprost in comparison with short-acting vasodilators. Further clinical studies are needed with regards to this.

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