Low-Dose Inhalation of an Endothelin-A Receptor Antagonist in Experimental Acute Lung Injury: ET-1 Plasma Concentration and Pulmonary Inflammation

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Inhalation of endothelin (ET)-A receptor antagonists has been shown to improve gas exchange in experimental acute lung injury (ALI) but may induce side effects by increasing circulating ET-1 levels. We investigated whether the inhaled ET_A receptor antagonist, LU-135252, at low doses, improves gas exchange without affecting ET-1 plasma concentrations and lung injury in an animal model of ALI. Twenty-two piglets were examined in a prospective, randomized, controlled study. In anesthetized animals, ALI was induced by surfactant depletion. Animals received either LU-135252 at a dose of 0.3 mg/kg during 20 mins (LU group; $n = 11$), or nebulization of saline buffer (control group; $n = 11$). The Mann-Whitney *U* test was used to compare groups ($P < 0.05$). In the LU group, arterial partial pressure of oxygen (PaO_2) and mean pulmonary artery pressure (MPAP) improved compared with the control group (PaO_2, 319 ± 44 mm Hg vs. 57 ± 3 mm Hg; MPAP, 32 ± 2 mm Hg vs. 41 ± 2 mm Hg; values at 6 hrs after induction of ALI; $P < 0.05$). Mean arterial pressure and cardiac output were not different between groups. ET-1 plasma concentrations increased from 0.96 ± 0.06 fmol/ml after induction of ALI to a maximum of 1.17 ± 0.09 fmol/ml at 3 hrs after ALI onset in the LU group and did not differ significantly from the control group (1.21 ± 0.08 fmol/ml, not significant). On histologic examination, we found no differences in total lung injury score between groups. However, the LU group revealed significantly reduced interstitial inflammation and hemorrhage ($P < 0.05$ vs. control group). In this animal model of ALI, inhalation of LU-135252 at a dose of 0.3 mg/kg induced a significant and sustained improvement in gas exchange, whereas there were no changes in ET-1 plasma concentrations. Furthermore, our data indicate a trend toward decreased pulmonary inflammation in the group receiving the inhaled ET_A receptor antagonist Exp Biol Med 231:960–966, 2006

Key words: acute lung injury; endothelin-1; endothelin-A receptor antagonist; inflammation

Introduction

Endothelial damage, pulmonary hypertension, intrapulmonary right-to-left shunt (Q_S/Q_T), and consecutive deterioration in pulmonary gas exchange are main characteristics of both experimental acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS). Recently, it has been suggested that endothelins (ETs) are involved in the pathogenesis of ALI (1). Marked increases in plasma and tissue concentration of ET have been found in lungs of patients who died from ARDS (2–4). Among the different isoforms, ET-1 is the main subtype (5). ET-1 is a potent vasoconstrictor peptide, a mitogen, and may induce pulmonary hypertension and bronchoconstriction (1). Additionally, it has been suggested that ET-1 is involved in pulmonary inflammation (6, 7). Therefore, the ET system may contribute to many of the symptoms and pulmonary structural changes seen in ARDS. Stimulation of pulmonary ET_A receptors mediates airway and vascular smooth-muscle contraction and proliferation, mediator release (leukotrienes, platelet activating factor, and cytokines), edema formation, and enhancement of nerve-induced airway contraction (8). ET receptor blockers are usually administered intravenously or orally. Their effectiveness has been shown particularly in

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animal models of airway inflammation (7, 9) and pulmonary hypertension (10). In a previous study (11), in an experimental model of ALI, we demonstrated that *inhalation* of the ET_A receptor antagonist, LU-135252, caused vasodilation in ventilated lung regions, thereby reducing pulmonary hypertension and improving gas exchange, similar to inhaled nitric oxide (NO; Ref. 12). However, at the dose of 3.0 mg/kg used, inhalation of LU-135252 also induced systemic vasoconstriction and possibly contributed to a reduction in cardiac output (CO). This was associated with increased ET-1 plasma levels, which might have contributed to the hemodynamic changes (11). Moreover, it could be argued either that the increased ET-1 levels itself may enhance lung tissue damage, or that ET_A receptor blockade may prevent a further increase in lung injury; however, there was no histologic analysis to answer this question. Recently, we demonstrated comparable effects on hemodynamics and gas exchange in experimental ALI using either a 10-fold lower dose of inhaled LU-135252 or 30 ppm inhaled NO (13). In particular, there were no significant effects on the systemic circulation.

In this study, we attempted to confirm whether, in an experimental model of ALI, inhalation of 0.3 mg/kg LU-135252 improves arterial oxygenation without affecting mean arterial pressure (MAP) and CO. In addition, we hypothesized that low-dose inhaled LU-135252 does not alter ET-1 plasma concentrations. Based on histologic analysis, we further compared progression of pulmonary inflammation between animals receiving the inhaled ET_A receptor antagonist and the control group.

Materials and Methods

This investigation was approved by the Berlin Animal Protection Committee in accordance with the German Animal Protection Law (approval no. G0260/97), and conforms with the Guide for the Care and Use of Laboratory Animals (DHHS, PHS, NIH publication no. 85-23, revised 1985).

General Procedure. Twenty-two piglets with a body weight of 23–27 kg were studied. Anesthesia was induced with intravenous (iv) administration of 10 mg/kg thiopental and 1 μg/kg remifentanil followed by an infusion of 0.1 μg/kg/min remifentanil. For muscle relaxation, 0.15 mg/kg iv bolus, followed by a continuous infusion of 2.5 μg/kg/min of pancuronium bromide was used. Immediately after induction, the animals were tracheotomized and intubated with a 7.5- to 8.0-mm outer diameter tracheal tube, fitted with a heat moisture exchanger with a bacterial filter.

Throughout the experiments, the piglets were ventilated in a volume-controlled mode (tidal volume, 10–14 ml/kg; respiratory rate, 16 breaths/min; FiO_2, 1.0; inspiratory/expiratory ratio, 1:1; and positive end-expiratory pressure, 6 cm H_2O) using an EVITA 2 ventilator (Dräger AG, Lübeck, Germany). The body temperature was maintained using a heating pad to within ±0.5°C of the prestudy range. During the experiments, no further cardiovascular agents were administered.

For the experiments, the animals were instrumented with a pulmonary artery catheter (model 93A-431-7.5 F; Baxter Healthcare Corporation, Irvine, CA) advanced from the femoral vein, and an arterial line (18 G; Vygon, Ecouen, France) inserted into the femoral artery. The arterial line and the pulmonary artery catheter were used for blood sampling and hemodynamic measurements. Heart rate (HR), central venous pressure (CVP), MAP, mean pulmonary artery pressure (MPAP), and pulmonary capillary wedge pressure (PCWP) were recorded using a Hewlett-Packard monitoring system (Model 66 S; Böblingen, Germany). Measurements were taken in supine position, with the zero reference at the midaxilla level. CO was determined as the mean of four measurements, with standard thermodilution techniques using injections of saline (10 ml at 1°–5°C) during different phases of the respiratory cycle. Intrapulmonary shunt was calculated using standard formulas.

Blood samples (arterial and mixed venous) were collected anaerobically and analyzed within 5 mins (ABL 520; Radiometer, Copenhagen, Denmark). Arterial oxygen saturation (SaO_2) and mixed venous oxygen saturation (SvO_2) were measured by spectrophotometry with the analyzer adjusted to pig blood (OSM 3 Hemoximeter; Radiometer).

ET was determined in plasma using an enzyme-linked immunosorbent assay kit (Biomedica, Vienna, Austria). The samples were collected in aprotinin-coated, cooled containers. After centrifugation, plasma was stored at −20°C in uncoated vials and stored until analysis.

Induction of ALI. The lavage procedure was performed according to the method of surfactant depletion through repetitive lung lavages with isotonic saline, as previously described (14). Induction of ALI was assumed when the animal's arterial partial pressure of oxygen (PaO_2) to FiO_2 ratio was persistently below 100 mm Hg (13 kPa) during a period of 1 hr.

Experimental Protocol. After induction of ALI, the animals were randomly assigned to either receive an aerosolized ET_A-receptor antagonist (LU-135252; Knoll AG, Ludwigshafen, Germany; 0.3 mg/kg dissolved in 5–10 ml buffer, nebulized during 30 mins; LU group; $n = 11$), or to receive nebulization of the buffer (5–10 ml, inhaled during 30 mins) and no further intervention (control group; $n = 11$). In both groups, a pneumatic drug nebulizer (Venturi principle; part no. 8405000; Dräger; capacity, ~1 ml/min; and pneumatic resistance, 1 mbar/100 l/min) was placed between the tracheal tube and the inspiratory limb of the standard ventilator tubing. The aerosol produced by the nebulizer consisted of more than 80% of particles having diameters between 0.3 and 5 μm.

Histologic Examination. After the experiment, tissue biopsies were taken from the ventrocranial, medial, and dorsocaudal part of each lung. The lung specimens were embedded in paraffin, and conventional slices were

performed and stained with hematoxylin and eosin. These slices were evaluated by a pathologist (M.E.), who was blinded to the animal's group assignment, according to a modified score (15). Variables scored were atelectasis, alveolar and interstitial inflammation, alveolar and interstitial hemorrhage, alveolar and interstitial edema, necrosis, and overdistension. Each variable was scored using a 0- to 4-point scale with injury in 0%, 25%, 50%, 75%, or 100% of the investigated tissue, scoring 0, 1, 2, 3, and 4, respectively. Furthermore, the severity of alveolar and interstitial inflammation was scored in the visual field, including the maximum number of inflammatory cells (0–4 point scale, corresponding to 0%, 25%, 50%, 75%, or 100% of involved alveoli). A total lung injury score was calculated as the sum of the variables and averaged for both groups.

Statistical Analysis. Results are expressed as means ± SEM. Data presented were obtained at baseline (prelavage), after induction of ALI (postlavage), and at hourly intervals for 6 hrs thereafter. Statistical analysis was performed using SPSS for Windows 11.0 (SPSS Inc., Chicago, IL). Differences between groups were evaluated using the Mann-Whitney *U* test. Friedman's test was used to compare values at the onset of ALI with those during the consecutive 6 hrs. For *post hoc* testing, the Wilcoxon-Wilcox test was used. Statistical significance was assumed at $P < 0.05$.

Results

Before lavage, the baseline data of pulmonary gas exchange and hemodynamics were comparable between the LU group and the control group (Table 1). In all animals, induction of ALI decreased PaO_2 from 564 ± 15 mm Hg (prelavage) to 57 ± 4 mm Hg, and increased Q_S/Q_T from 13 ± 2% to 54 ± 4%. Pulmonary artery pressure increased from 22 ± 1 mm Hg to 27 ± 1 mm Hg in both groups, whereas CO remained stable at 4.7 ± 0.5 l/min. HR, PCWP, CVP, and MAP were not different from baseline (Table 1). In the LU group, all 11 animals survived the 6-hr observation period with improved gas exchange, whereas 6 of 11 control piglets died between 3 and 6 hrs after induction of ALI (Table 1).

In the control group, PaO_2 and Q_S/Q_T deteriorated after induction of lung injury (PaO_2 varied between 59 and 51 mm Hg and Q_S/Q_T between 54% and 48%). During the experiment, MPAP increased from 28 ± 1 mm Hg (at ALI onset) to 41 ± 2 mm Hg (at 6 hrs after induction of ALI) in the control group. Inhalation of the ET_A receptor antagonist induced a sustained and substantial improvement in gas exchange during the subsequent 6-hr period. PaO_2 increased by approximately 400% (from 57 ± 3 mm Hg to 277 ± 28 mm Hg) within 2 hrs ($P < 0.01$ vs. control group; Fig. 1). Maximum effect on arterial oxygenation was reached at 4 hr with a PaO_2 value of 368 ± 36 mm Hg. Concomitantly, Q_S/Q_T decreased in the LU group from 53 ± 4% (at ALI onset) to 26 ± 2%, 2 hrs after inhalation of LU-135252. Six hours after LU inhalation, Q_S/Q_T was 22 ± 4%, which was significantly different from the value of 54 ± 3% in the control group ($P < 0.01$; Fig. 1).

Blood gas analysis demonstrated an increase in $PaCO_2$ in both groups after induction of ALI (Table 1). $PaCO_2$ increased by 15 mm Hg in the control group versus 10 mm Hg in the LU group. The pH was maintained close to 7.4 in the LU group and did not differ between groups after ALI. Mixed SvO_2 was low after induction of ALI in both groups (~44%) and was 18% higher after 6 hrs of LU-inhalation compared with the control group ($P < 0.05$; Table 1).

Arterial blood pressure and systemic vascular resistance (SVR) remained at baseline levels in both groups (Fig. 2; Table 1). MPAP increased in both groups, and values at 6 hr were significantly different from those measured at the onset of ALI ($P < 0.05$). However, 2 hrs after inhalation—until termination of the protocol—MPAP was significantly lower in LU animals compared with the control group ($P < 0.01$ vs. control group; Fig. 2). Accordingly, pulmonary vascular resistance (PVR) increased in both groups (Table 1). In the LU group, values of PVR were significantly lower between 2 and 4 hrs after inhalation of LU-135252 when compared with the control group (Table 1). In the LU group, CO was significantly reduced, by approximately 30%, 3 hrs after inhalation of the ET_A receptor antagonist compared to the onset of ALI ($P < 0.05$ vs. induction of ALI). However, changes in CO were not different between the LU group and the control group throughout the study period (Fig. 3).

Plasma concentrations of ET-1 were measured in all animals. During the protocol, arterial ET-1 plasma levels increased and values measured between 3 and 5 hrs were significantly higher when compared with values at onset of ALI in the LU group and in the control group ($P < 0.05$ vs. ALI; Table 2), but did not differ significantly between groups.

In histologic analysis, there were no differences in lung injury score regarding alveolar inflammation, alveolar and interstitial edema, atelectasis, overdistension, alveolar hemorrhage, and eosinophiles between groups (Table 3). The examination revealed interstitial inflammation and interstitial bleeding in both groups, but at a significantly lower rate in the LU group ($P < 0.05$ and $P < 0.01$; Table 3). The calculated lung injury score for different regions of the lung (ventral, medial, and dorsal) and the total lung injury score showed no differences between groups (Fig. 4).

Discussion

In our porcine model of ALI, inhalation of a low dose of the ET_A receptor antagonist, LU-135252, induced a significant and sustained improvement in arterial oxygenation and intrapulmonary shunt. Hemodynamic stability was well preserved in the LU group, and no significant differences in CO and MAP were observed between the treatment group and the control group. Concomitantly, pulmonary artery pressure was significantly lower in the LU

Table 1. Parameters of Hemodynamics and Gas Exchange[a]

Parameter	Protocol	Baseline	ALI	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr
HR (bpm)	Control group	84 ± 5	80 ± 3	84 ± 5	86 ± 6	82 ± 7	84 ± 7	82 ± 6	77 ± 5
	LU group	93 ± 4	91 ± 5	84 ± 6	80 ± 4	80 ± 4	80 ± 4	82 ± 4	83 ± 5
PCWP (mm Hg)	Control group	11 ± 1	13 ± 1	12 ± 0	13 ± 1	13 ± 1	13 ± 1	13 ± 1	13 ± 1
	LU group	10 ± 1	13 ± 1	13 ± 1	13 ± 0	13 ± 0	13 ± 0	13 ± 0	12 ± 1
CVP (mm Hg)	Control group	11 ± 1	12 ± 0	13 ± 1	13 ± 1	13 ± 1	13 ± 1	13 ± 1	11 ± 1
	LU group	10 ± 1	12 ± 1	12 ± 1	12 ± 1	12 ± 1	12 ± 1	12 ± 0	12 ± 0
$PaCO_2$ (mm Hg)	Control group	35 ± 2	44 ± 2	43 ± 2	47 ± 3	47 ± 3	52 ± 5	50 ± 4	50 ± 4
	LU group	42 ± 2*	50 ± 2*	46 ± 2	47 ± 3	46 ± 4	47 ± 4§	48 ± 5	50 ± 4
SvO_2 (%)	Control group	79 ± 3	44 ± 5	43 ± 3	40 ± 5	39 ± 5	36 ± 5	34 ± 5	41 ± 3
	LU group	78 ± 2	45 ± 5	55 ± 4*	63 ± 4**,§	62 ± 3**,§	62 ± 3**,§	60 ± 3**	59 ± 3**
SaO_2 (%)	Control group	98 ± 0	81 ± 3	81 ± 3	78 ± 6	79 ± 6	72 ± 7	72 ± 5	75 ± 3
	LU group	98 ± 0	79 ± 3	93 ± 2**	98 ± 1**,§	98 ± 0**,§	98 ± 0**,§	97 ± 1**,§	96 ± 2**,§
pH	Control group	7.53 ± 0.03	7.45 ± 0.01	7.45 ± 0.02	7.43 ± 0.02	7.41 ± 0.03	7.39 ± 0.04	7.41 ± 0.03	7.41 ± 0.03
	LU group	7.47 ± 0.02	7.39 ± 0.02*	7.42 ± 0.02	7.44 ± 0.03	7.45 ± 0.03§	7.46 ± 0.03§	7.45 ± 0.03§	7.45 ± 0.03
SVR ($dyn \cdot s/cm^{-5}$)	Control group	1629 ± 196	1595 ± 148	1536 ± 133	1651 ± 140	1604 ± 148	1660 ± 205	1600 ± 213	1798 ± 226
	LU group	1813 ± 168	1508 ± 156	1739 ± 162	1842 ± 113	2010 ± 126	1970 ± 158	2002 ± 131	2086 ± 126§
PVR ($dyn \cdot s/cm^{-5}$)	Control group	196 ± 20	282 ± 33	355 ± 38	441 ± 44	509 ± 43	561 ± 53§	549 ± 55§	605 ± 65§
	LU group	226 ± 29	228 ± 20	281 ± 36	317 ± 28*	360 ± 32*	379 ± 27*,§	410 ± 47§	461 ± 42§
Survivors (*n*)	Control group	11	11	11	11	10	8	7	5
	LU group	11	11	11	11	11	11	11	11

[a] Data are shown as mean ± SEM. Baseline, measurements before lavage; ALI, measurements at the onset of ALI (further measurements at hourly intervals); HR, heart rate; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure; $PaCO_2$, arterial partial pressure of carbon dioxide; SvO_2, mixed venous oxygen saturation; SaO_2, arterial oxygen saturation; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.
*$P < 0.05$ vs. control group; **$P < 0.01$ vs. control group; §$P < 0.05$ intragroup comparison vs. ALI.

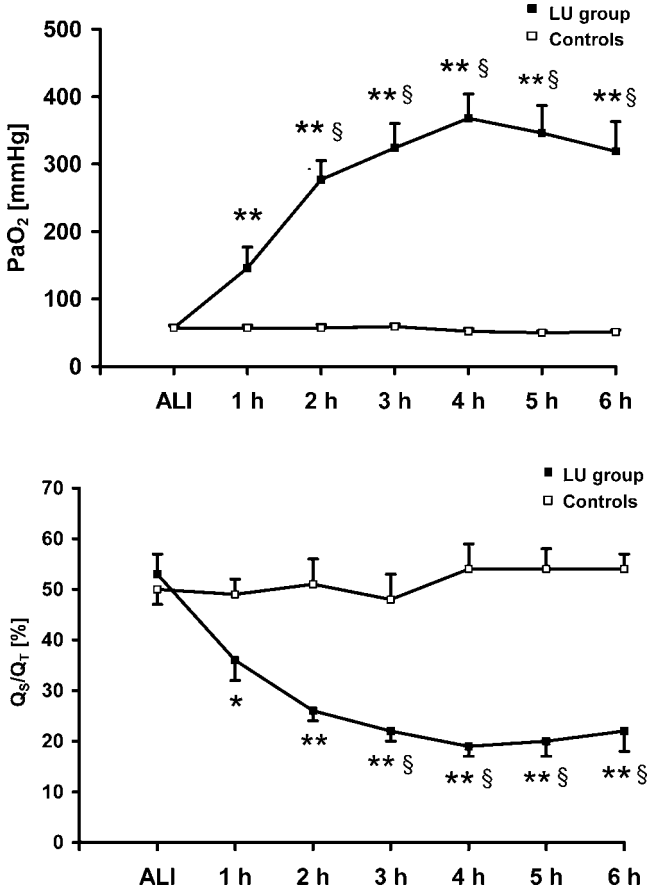

Figure 1. PaO_2 (mm Hg) and intrapulmonary Q_S/Q_T (%) during the protocol. Measurements were performed at the onset of ALI and at hourly intervals (solid squares, LU group; open squares, control group). Data are expressed as mean ± SEM. $^*P < 0.05$ vs. control group; $^{**}P < 0.01$ vs. control group; and §$P < 0.05$ in intragroup comparison vs. ALI.

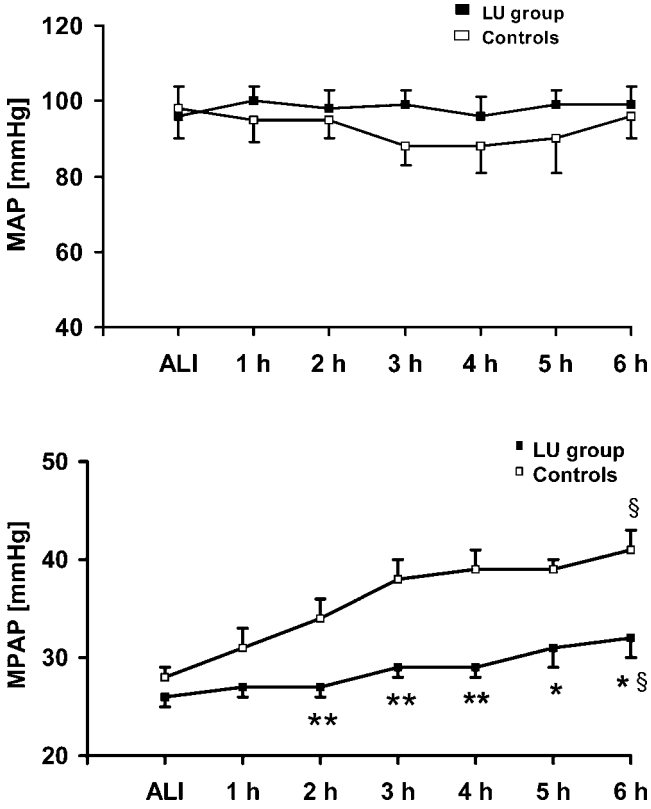

Figure 2. MAP (mm Hg) and MPAP (mm Hg) during the protocol. Measurements were performed at the onset of ALI and at hourly intervals (solid squares, LU group; open squares, control group). Data are mean ± SEM. $^*P < 0.05$ vs. control group; $^{**}P < 0.01$ vs. control group; and §$P < 0.05$ in intragroup comparison vs. ALI.

group in comparison with the control group, demonstrating selective pulmonary vasodilation. Plasma concentrations of ET-1 increased after the onset of ALI, but did not differ significantly between groups. In the treatment group, all animals survived the experiment, whereas in the control group, more than 50% of the animals died during the protocol. On histologic examination, we found a higher score for interstitial inflammation and interstitial hemorrhage in the control group, indicating an anti-inflammatory effect of inhaled LU 135252.

Our results corroborate earlier findings concerning induction of selective pulmonary vasodilation by inhaled LU-135252 at a dose of 0.3 mg/kg in experimental ALI (13). The improvement in gas exchange we measured in this study is even higher than we found for inhalation of the 10-fold higher dose of LU-135252 (11), further confirming actual data obtained when comparing both doses (16). This provides arguments that the low dose of LU-135252 was already sufficient to block most of the pulmonary ET_A receptors.

The lack of systemic effects in the current study was paralleled by plasma ET-1 concentrations that did not differ significantly in the LU-135252–treated animals when compared with the control group. This is in contrast to previous results obtained during inhalation of LU-135252 at the higher dose of 3.0 mg/kg, which revealed systemic effects most likely induced by increased ET-1 levels in circulating blood (11). Although the affinity of LU-135252 for the ET_A receptor is approximately 130 times higher than

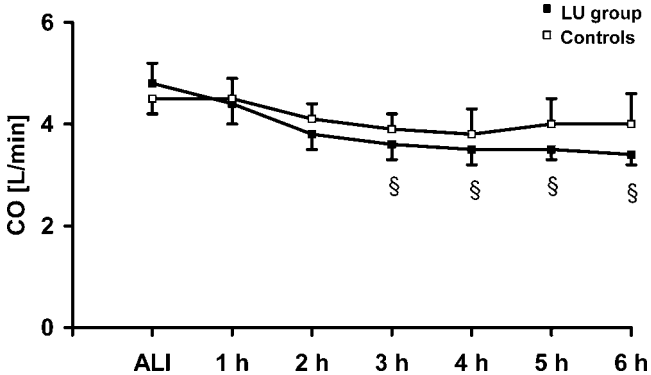

Figure 3. CO (l/min) during the protocol. Measurements were performed at the onset of ALI and at hourly intervals (solid squares, LU group; open squares, control group). Data are expressed as mean ± SEM; §$P < 0.05$ in intragroup comparison vs. ALI.

Table 2. Arterial Plasma Concentration of ET-1[a]

Group	Baseline	ALI	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr
LU group	0.78 ± 0.06	0.96 ± 0.06	1.03 ± 0.07	1.09 ± 0.08	1.17 ± 0.09§	1.15 ± 0.08§	1.14 ± 0.08§	1.15 ± 0.08
Control group	0.77 ± 0.03	0.83 ± 0.04	1.01 ± 0.07	1.03 ± 0.06	1.21 ± 0.08§	1.13 ± 0.08§	1.15 ± 0.07§	1.10 ± 0.05

[a] Measurements were performed before lavage (baseline), at the onset of ALI (ALI), and during the following 6 hrs. Values are given in fmol/ml and data are expressed as mean ± SEM.
§$P < 0.05$ in intragroup comparison vs. ALI.

Table 3. Results of Histologic Analysis[a]

Criteria	LU group	Control group	*P*
Alveolar inflammation (severity)	2.5 ± 0.4	2.8 ± 0.4	n.s.
Alveolar inflammation (tissue involvement)	3.0 ± 0.5	3.2 ± 0.5	n.s.
Interstitial inflammation (severity)	5.4 ± 0.3	6.4 ± 0.3	< 0.05
Interstitial inflammation (tissue involvement)	6.4 ± 0.3	6.4 ± 0.4	n.s.
Interstitial bleeding	2.6 ± 0.3	4.3 ± 0.4	< 0.01
Alveolar edema	0.3 ± 0.1	0	n.s.
Interstitial edema	0.6 ± 0.2	1.0 ± 0.4	n.s.
Atelectasis	4.1 ± 0.7	2.6 ± 0.3	n.s.
Necrosis	0	0	
Overdistension	3.1 ± 0.5	2.7 ± 0.4	n.s.
Alveolar bleeding	2.2 ± 0.3	2.9 ± 0.3	n.s.
Eosinophiles	0.1 ± 0.1	0.4 ± 0.2	n.s.
Bacteria	0	0	

[a] Data are presented as mean ± SEM. The variables were measured using a 0- to 4-point scale with injury in 0%, 25%, 50%, 75%, and 100% of the investigated lung tissue. The severity of alveolar and interstitial inflammation was scored in the visual field including the maximum number of inflammatory cells (0–4 point scale corresponding to 0%, 25%, 50%, 75%, and 100% of involved alveoli). All values are sum scores of ventral, medial, and dorsal contributions. n.s., not significant.

for the ET_B receptor, using too high of a dosage could make the ET_A receptor antagonist loose its selectivity for the ET_A receptor (17) and may also block pulmonary ET_B receptors, causing a reduction in clearance of circulating ETs (18). Thus, the stable ET-1 plasma levels in our actual study are possibly related to a high selectivity of LU-135252 to ET_A receptors when administered at the low dose of 0.3 mg/kg. The high selectivity for ET_A receptors contributes to enhance the beneficial effects of LU-135252 on gas exchange, because ET_B receptors on endothelial cells mediate vasodilation by the release of NO (19).

ET receptor blockade has the potential to reduce pulmonary inflammation. It may prevent or reduce activation of secondary mediators, such as thromboxane A_2, prostaglandins, and platelet activating factor (20); inhibit granulocyte infiltration (7); and may, thereby, reduce pulmonary edema (21). In fact, in our study, we found significantly reduced severity of interstitial inflammation and reduced interstitial hemorrhage in the LU group when compared with the control group. Other criteria of histologic analysis and total lung injury demonstrated no significant difference between groups. Nevertheless, our results indicate a trend toward decreased pulmonary inflammation in the group receiving the inhaled ET_A receptor antagonist at the low dose of 0.3 mg/kg. It should, however, be considered that the stable cardiopulmonary status in the LU group might also have contributed to the anti-inflammatory effect.

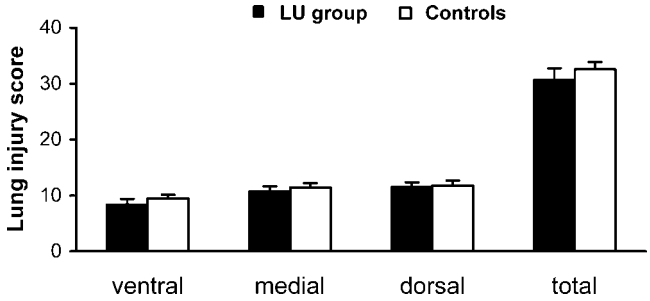

Figure 4. Total lung injury score. Sum of the individual variables of lung injury from separate lung regions. Ventral, nondependent lung regions; dorsal, dependent lung regions; medial, lung areas between dorsal and ventral. Total represents the sum of the three lung areas. Data are expressed as mean ± SEM.

In conclusion, our results confirm that the inhaled ET_A receptor antagonist, LU-135252, at a low dose of 0.3 mg/kg, significantly improves gas exchange in experimental ALI. At the dosage used, inhaled LU-135252 did not influence plasma ET-1 levels and this was paralleled by the absence of disadvantageous effects on systemic hemodynamics. Furthermore, our data indicate a trend toward decreased pulmonary inflammation in the group receiving the inhaled ET_A receptor antagonist. These findings underline the potential of inhaled ET_A receptor antagonists at low doses

for future clinical applications as selective pulmonary vasodilators in the treatment of patients with ALI.

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