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Amelioration of lung reperfusion injury by L- and E- selectin blockade ☆

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Abstract

Objective: Reperfusion injury is the main reason for early graft failure after lung transplantation. Inhibition of the adherence of polymorphonuclear leukocytes to activated endothelium by blocking L- and E-selectins (antibody EL-246) could potentially inhibit reperfusion injury. **Methods**: Reperfusion injury was induced in a left lung autotransplant model in sheep. After hilar stripping the left lung was flushed with Euro–Collins solution and preserved for 2 h in situ at 15°C. After reperfusion right main bronchus and pulmonary artery were occluded leaving the animal dependent on the reperfused lung (control, $n = 6$). Pulmonary function was assessed by alveolo-arterial oxygen difference ($AaDO_2$) and pulmonary vascular resistance (PVR), the chemiluminescence of isolated neutrophils, as well as the release of beta-*N*-acetyl-glucosaminidase (β-NAG) served as indicator of neutrophilic activation. Extravascular lung water was an indicator for pulmonary edema formation. EL-246 group animals ($n = 6$) were treated additionally with 1 mg/kg BW of EL-246 given prior and during reperfusion. **Results**: After 3 h of reperfusion five control animals developed alveolar edema compared to one animal in the EL-246 group ($P = 0.08$). $AaDO_2$ (mm Hg) was significantly higher in the control compared to the EL-246 group (510 ± 148 vs. 214 ± 86). PVR (dyn × s × cm^{-5}) was significantly increased in the control compared to the EL-246 group (656 ± 240 vs. 317 ± 87). Neutrophilic activation was significantly lower in the EL-246 group. Extravascular lung water was significantly lower compared to control (6.88 ± 1.0 vs. 13.4 ± 2.8 g/g blood-free lung weight). **Conclusions**: Treatment with EL-246 results in improved pulmonary function and less in vivo PMN activation in this experimental model. Further studies are necessary to evaluate the possible role of selectin blockade in amelioration of reperfusion injury in human lung transplantation.

Keywords: Reperfusion injury; Lung transplantation; Sheep; Selectin; Chemiluminescence; Experimental

1. Introduction

During the past decade lung transplantation has evolved into a clinically accepted treatment option for patients with end-stage pulmonary disease. Graft dysfunction, however, remains one of the leading causes of early morbidity and mortality. The factors leading to impairment of graft function include unrecognized donor pathology, inadequate preservation, infection, and pathologic changes occurring during reperfusion, generally termed as 'reperfusion injury'.

The clinical picture of reperfusion injury includes increased pulmonary vascular resistance, interstitial and alveolar pulmonary edema and impaired gas exchange. These alterations are consistent with dysfunction of the pulmonary vascular endothelium. In addition, vasodilatation and intravascular hypovolemia in the face of 'third space loss' indicate a systemic component of this pathologic process.

The exact mechanism of this disorder is not completely understood, but migration, activation and respiratory burst production of toxic oxygen radicals of polymorphonuclear neutrophilic leukocytes (PMN) into the pulmonary tissue are part of the initial steps in its development. A key factor for the initiation of the extravascular PMN migration is interaction with the endothelium. This interaction is mediated in large part by surface molecules called selectins. Selectins are a three-member family of leukocyte, platelet, and endothelial cell adhesion proteins that mediate leukocyte traffic into normal and inflamed tissues. P-selectin is

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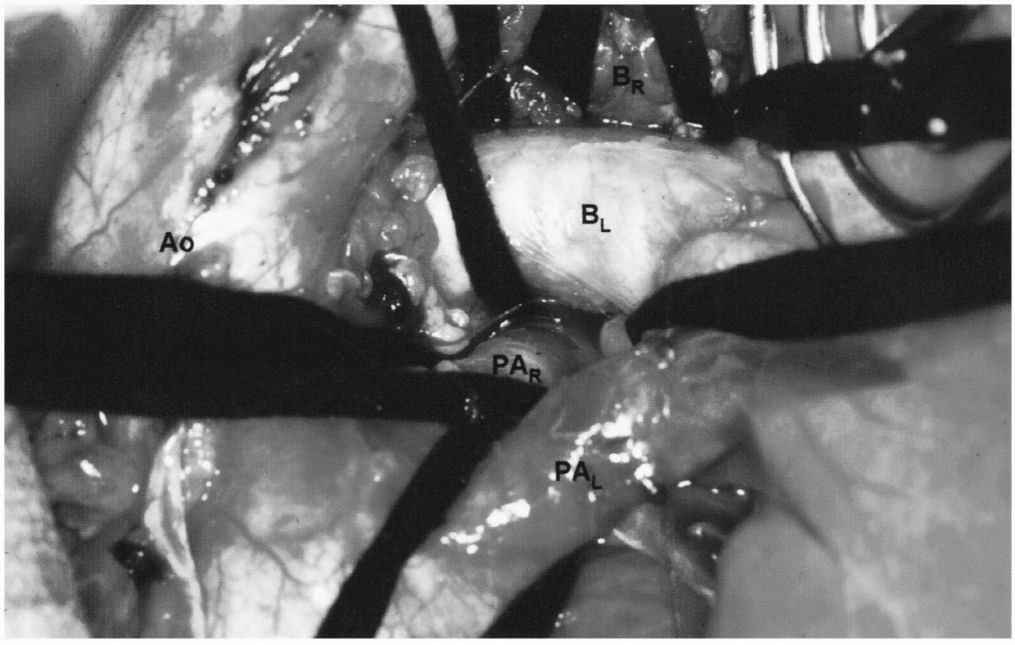

Fig. 1. Surgical field after complete preparation. Left and right main bronchus (B_L and B_R), as well as left and right pulmonary arteries (PA_L and PA_R) are isolated. Ao, aorta.

expressed by endothelial cells and platelets, E-selectin by endothelial cells, and L-selectin by circulating leukocytes. Blocking this initial interaction should be able to reduce PMN migration and its sequelae.

We studied the effects of L- and E-selectin blockade to ameliorate lung reperfusion injury in an experimental model of left-lung autotransplantation in sheep.

2. Material and methods

A model of left lung in situ autotransplantation combined with hilar stripping was designed for this investigation. The left lung was flushed with Euro–Collins solution and preserved for 2 h in situ at 15°C. During reperfusion right main bronchus and pulmonary artery were occluded leaving the animal dependent on the reperfused lung.

Female Merino sheep with a body weight between 25 and 35 kg were used for the experiments. All animals received humane care in compliance with the 'principles of laboratory animal care' formulated by the National Society of Medical Research and the 'guide for the care and use of laboratory animals' prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH Publication No 80-23, revised 1978). The experimental protocol was approved by the local regulatory authorities.

2.1. Experimental groups

Two experimental groups were studied: In group A (control) the complete in situ left lung autotransplantation was performed including flush perfusion and cold storage. In group B (EL-246) the EL-246 antibody was administered intravenously directly prior and during the first 10 min of reperfusion (1 mg/kg). Each group consisted of successful experiments.

The antiselectin antibody EL-246 used in this study was shown to recognise and block both human L- and E-selectin and to cross react in sheep [1,2].

2.1.1. Anaesthesia

The animals were premedicated with azaperon (Stresnil, Janssen, Neuss, Germany, 200 mg) and atropine sulfate (atropine sulfate, B. Braun, Melsungen, Germany, 0,5 mg) both given by i.m. injection. A venous line was established by puncturing an auricular vein. Induction of anesthesia was performed with sodium thiopental (Trapanal, Byk Gulden, Konstanz, Germany, 250 mg i.v.). The animals were intubated with an orotracheal tube (8.5 mm internal diameter, Rüsch, Germany). Volume controlled mechanical ventilation was instituted (Siemens Servo 900 C respirator, Siemens, Erlangen, Germany). Initially tidal volume was set to 10 ml/kg BW, respiratory rate to 14 breaths/min with an FiO_2 of 0.5. The respirator settings were subsequently adjusted to achieve a pCO_2 of 40–45 mmHg and arterial oxygen saturation of more than 90%.

Anaesthesia was maintained with sodium thiopental and fentanyl (300 mg Trapanal, Byk Gulden, Konstanz, Germany and 0.2 mg Fentanyl, Janssen, Neuss, Germany) both given as i.v. bolus injections every 15–30 min, for muscular relaxation pancouronium bromide (4 mg i.v., Pancuroniumbromid, Organon Teknika, Eppelheim, Germany) was added as appropriate. The experiment was

terminated by i.v. injection of T61 (10 ml, Hoechst, Frankfurt/Main, Germany).

2.2. Surgical technique

The animal was placed in right lateral position. A central venous catheter was inserted in the left external jugular vein percutaneously using the Seldinger technique. An additional central venous port for subsequent placement of a Swan Ganz catheter was introduced in the same fashion. An arterial catheter for invasive blood pressure monitoring was placed in the left carotid artery in the same fashion.

A lateral thoracotomy was performed in the left fourth intercostal space. The left main pulmonary artery and bronchus were isolated in the pulmonary hilum. The pericardium was opened and the origin of the right pulmonary artery dissected after preparing the pulmonary trunc bifurcation. Dissecting the space between right pulmonary artery and tracheal bifurcation a tape was passed around the right main bronchus (Fig. 1). The pulmonary veins were dissected at their entrance into the left atrium. During these steps of the surgical procedure particular care was taken to minimise manipulation of the ventilated left lung.

A Swan–Ganz catheter was inserted through the left jugular vein and placed in the main pulmonary artery, the correct position was verified by palpation. An additional catheter was inserted into the left atrial appendage for continuous monitoring of left atrial pressure.

Heparine was given intravenously (300 IU/kg). A cannula was placed in the pulmonary artery and the artery was cross-clamped proximally. A side biting clamp was placed on the left atrium central to the left pulmonary veins and an incision was made for fluid drainage. The left lung was then flushed with cold modified Euro–Collins solution (60 ml/kg). Pulmonary pressure was monitored during flushing and was kept between 12 and 15 mm Hg. Ventilation was continued during flush perfusion.

After completion of perfusion, the main left bronchus was transected between two vascular clamps with the lung kept semi-inflated. The lung was left in situ and covered with cold towels. The temperature was measured in the left interlobar space. When the temperature exceeded 15°C additional cold saline was applied to the towels.

Total ischemic time of the left lung was set at 2 h. The transected left bronchus was reconstructed at the end of the ischemic period with a continuous 4-0 Prolene (Ethicon, Hamburg, Germany) suture with the left lung deflated. The incision of the left atrium was closed and reperfusion begun with removing the clamp from the pulmonary artery. Hemodynamics were allowed to achieve a steady state during the initial 15 min of reperfusion. Right pulmonary artery and right main bronchus were then occluded by vascular clamps, thus making the animal dependent on left lung only.

2.3. Experimental protocol

2.3.1. Cardiopulmonary assessment

Assessment of cardiopulmonary function consisted of:

- measurement of cardiac output by thermodilution (Cardiac Output Computer, Hoyer, Bremen, Germany), registration of pulmonary artery, left atrial, central venous and arterial pressures,
- measurement of arterial blood gases (Blood Gas Analyzer Model 178, CIBA Corning, Oberlin, USA), measurement of work of breathing (Bicore CP 100 Pulmonary Monitor Computer, Bicore, Irvine, CA, USA).

Subsequently the arterio-alveolar oxygen difference ($AaDO_2$), the systemic and pulmonary vascular resistance (SVR, PVR) were calculated according to following formulas:

Effective $AaDO_2 = FiO_2 \times (P_{bar} - 47) - PaCO_2\text{-}PaO_2$

where P_{bar} is the barometric pressure, FiO_2 is the inspiratory oxygen fraction, PaO_2, $PaCO_2$ are the arterial partial pressures for O_2 and CO_2.

$$SVR = (MAP - CVP) \times 80/CO$$

where MAP is the mean arterial pressure, CVP is the central venous pressure and CO is cardiac output.

$$PVR = (PAP - PCWP) \times 80/CO$$

where PAP is the pulmonary artery mean pressure and PCWP is the pulmonary capillary wedge pressure.

The evaluation time points were at the start of the experiment, after completion of instrumentation and hilar preparation and 60, 120 and 180 min after reperfusion.

Hemodynamic stability (i.e. mean arterial pressure above 60 mmHg) was maintained by careful infusion of electrolyte solutions and/or continuous epinephrine infusion (0.1–1.0 μg/kg per min epinephrine hydrochloride, Hoechst, Frankfurt/Main, Germany) guided by hemodynamic parameters.

2.4. Biochemical assessment of leukocyte activation

2.4.1. Zymosan-enhanced chemiluminescence (ZE-CL)

The zymosan-induced and luminol-enhanced chemiluminescence of isolated polymorphonuclear neutrophilic leukocytes (PMN), as parameter for the ability of PMN to produce reactive oxygen metabolites, was determined in a six-channel Biolumat LB 9505 (Bethold, Wildbad, Germany) according to standard described methods [3]. The photon emission was recorded for at least 60 min. Peak maximum values were measured for isolated granulocyte suspensions, corrected for the corresponding blanks by subtraction and normalised to 25 000 cells. The PMN granulocytes were isolated from citrate-blood, which was drawn after hilar preparation prior to preservation and 60, 120 and 180 min after reperfusion.

Table 1
Cardiac output (CO) and systemic vascular resistance (SVR) of both groups (mean ± SD)

	Group A(control)		Group B (EL-246)	
	CO (l/min)	SVR (dyn × s × cm^{-5})	CO (l/min)	SVR (dyn × s × cm^{-5})
Base	3.7 ± 1.3	2205 ± 620	2.7 ± 1.3	2227 ± 720
60 min reperfusion	3.5 ± 1.0	1516 ± 350	4.7 ± 1.7	1209 ± 302
120 min reperfusion	3.0 ± 1.1	1858 ± 558	3.8 ± 1.5	1327 ± 320
180 min reperfusion	2.2 ± 1.1	2067 ± 833	4.1 ± 1.9	1337 ± 324

2.4.2. Beta-N-acetyl-glucosaminidase (β-NAG)

The release of β-NAG was chosen as parameter of PMN and macrophage activation and was measured fluorimetrically in citrated blood, with 4-methylumbelliferyl-*N*-acetyl-β-D-glucosaminide as substrate and 4-methylumbelliferone as standard. Fluorescence was measured with a Model RF-510 spectrofluorophotometer (Shimadzu, Japan). Blood samples were drawn after hilar preparation prior to preservation and 60, 120 and 180 min after reperfusion.

2.5. Extravascular lung water

Two lung biopsies (approximately 20 g of weight each) were taken at the end of ischemic time and after termination of the experiment. Extravascular lung water (in g per g blood-free dry lung weight) was measured according to the method published by Drake [4].

2.6. Statistical analysis

Values are presented as means ± standard deviation. Normally distributed values between groups were compared by the Student's *t*-test or in case of repeated measurments over the time by analysis of variance (ANOVA) for repeated measures. Non-normally distributed data were compared either the Fisher's exact test (comparison of pulmonary edema between groups) or the Mann–Whitney *U* test (with Bonferroni correction). Data distribution was controlled by performing box-plot analyses and subsequent judgement. A statistical test for normality (Shapiro–Wilks) was performed in addition. In one case of non-normally distributed values for repeated measures (zymosan-enhanced chemiluminescence) decadic logarithm was introduced, in order to transform the non-normal to normal distribution. For all but one parameters (β-NAG) the native values were used for analysis. Because of substantial differences in the base values for β-NAG, values after reperfusion are expressed and analysed as percent of the base value. Analyses were performed with the SPSS/Mac statistical software (version 6.1).

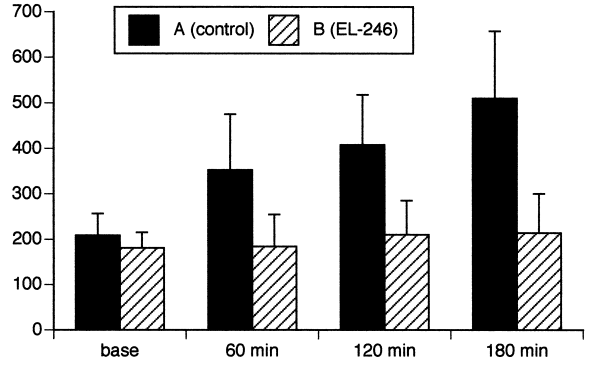

Fig. 2. Values for alveolo-arterial oxygen difference over the time (means ± SD

3. Results

3.1. Cardiac output (CO) and systemic vasvular resistance (SVR)

Mean cardiac output ranged in group A (control) from 3.7 ± 1.3 to 2.2 ± 1.1 l/min. In group B (EL-246) mean CO ranged between 2.7 ± 1.3 and 4.7 ± 1.7 l/min. The differences between groups were not statistically significant ($P = 0.11$), despite a recognisable trend towards lower CO values in group A with ongoing reperfusion. Means (±SD) for the different time points are provided in Table 1.

Systemic vascular resistance (dyn × s × cm^{-5}) ranged from 1516 ± 350 to 2205 ± 620 in group A (control) and from 1209 ± 302 to 2227 ± 720 in group B (EL-246). The differences between the groups were statistically not significant ($P = 0.37$). Means (±SD) for the different time points are stated in Table 1.

3.2. Alveolo-arterial oxygen difference ($AaDO_2$)

The $AaDO_2$ values in the control group (group A) increased significantly during reperfusion (range from 209 ± 48 to 510 ± 148 mmHg). The $AaDO_2$ in the EL-246 group remained remarkably stable throughout the experiment. The differences between both groups were statistically significant ($P = 0.0078$). Means and standard deviations are displayed in Fig. 2.

3.3. Pulmonary vascular resistance (PVR)

The PVR values in group A (control) increased substantially during reperfusion (range from 210 ± 58 to 656 ± 240 dyn × sec × cm^{-5}). The PVR values in the EL-246

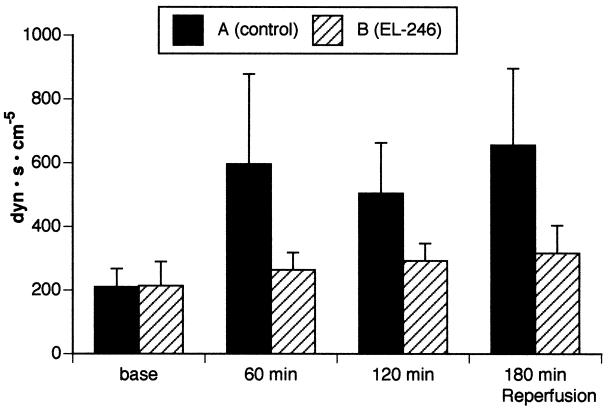

Fig. 3. Values for pulmonary vascular resistance over the time (means ± SD).

group (group B) remained stable throughout the experiment ranging between 214 ± 76 and 317 ± 87 dyn × s × cm^{-5}. The differences between both groups were statistically significant ($P = 0.0118$) (Fig. 3).

3.4. Alveolar pulmonary edema

In group A (control) five out of six animals and in group B (EL-246) one out of six animals developed frank pulmonary edema. This difference did not reach statistical significance ($P = 0.08$).

3.5. Work of breathing

In both other groups all values increased significantly after reperfusion ranging from 2.25 ± 0.2 to 4.01 ± 0.84 J/l in the reference group and from 1.74 ± 0.18 to 2.43 ± 0.38 J/l in the EL-246 group. The differences between both groups were statistically significant ($P = 0.0287$).

3.6. Extravascular lung water

Extravascular lung water (in g per g blood-free dry lung weight) was 13.4 ± 2.8 in group A (control), and 6.88 ± 1.02 in group B (EL-246). The differences between groups A and B were statistically significant ($P = 0.029$).

3.7. Biochemical assessment of leukocyte function

The results of biochemical assessment of leukocyte function are summarised in Table 2.

3.7.1. ZE-CL

With ongoing reperfusion values decreased in group A (control) but remained stable in group B (EL-246). Decadic logarithm was introduced to obtain adequate distribution, since values were not normally distributed. The differences between the groups (after logarithmic transformation) were statistically significant ($P = 0.0709$).

3.7.2. β-NAG

Substantial enzyme release took place in both groups in reperfusion. Mean enzyme release referred to the base value ranged from 149 ± 59 to 199 ± 86% in group A (control) and from 135 ± 59 to 223 ± 294% in group B (EL-246). Statistically significant differences between groups A and B could be not be detected ($P = 0.4590$).

4. Discussion

A major cause of early morbidity after lung transplantation is initial graft dysfunction, also termed as reperfusion injury [5–7]. This is associated with the complex pathophysiology of ischemia, organ preservation and reperfusion despite well established organ preservation techniques. The reperfusion injury usually involves the lungs first, but its further course mounts into a systemic inflammatory response syndrome [8]. The exact mechanism has not yet been clarified, but activation of PMN granulocytes seems to be a step of strategic importance. Several experimental studies and clinical observations suggest involvement of almost every existing inflammatory cascade [9–13].

Neutrophil migration across the endothelial cell layer is a multistep process involving sequential engagement of specific adhesion receptors. According to the current understanding endothelial cells are stimulated by cytokines to synthesise ELAM-1 and ICAM-1.These inducible adhesion molecules provide position-specific information for PMN. The adhesion molecules on PMN and endothelium mediate the initial interaction between the non-activated PMN and the endothelium. PMN rolling on endothelial cells is mediated by the interaction of E- and P-selectin with their

Table 2
Zymosan-enhanced chemiluminescence and β-*N*-acetyl-glucosaminidase (β-NAG) (mean ± SD)

	ZE-CL (× 10^3 counts/25 000 cells)		βNAG (units/l)	
	Group A (control)	Group B (EL-246)	Group A (control)	Group B (EL-246)
Base	1643 ± 454	1856 ± 381	0.52 ± 0.18	0.17 ± 0.04
60 mim reperfusion	1284 ± 270	1915 ± 1043	0.93 ± 0.4	0.44 ± 0.51
120 min reperfusion	1250 ± 339	1858 ± 724	0.94 ± 0.4	0.6 ± 0.76
180 min reperfusion	1026 ± 549	2233 ± 961	0.86 ± 0.6	0.98 ± 0.86

neutrophilic counterpart on cell surface glycoproteins. This event induces a rapid transition in PMN morphology and adhesiveness, adhesion strengthening, PMN aggregation and respiratory burst activation with production of toxic oxygen metabolites. Firm adhesion is thought to be achieved by PMN integrins (e.g. CD11b) binding to endothelial ICAM-1 as a necessary step for subsequent migration.

In our study we simulated the clinical transplantation setting including pulmonary preservation with cold modified Euro–Collins solution, as well as hypothermic storage throughout the ischemic period. Total ischemic conditions and denervation of the autograft can be achieved in situ: prior to crossclamping of the pulmonary artery and initiation of lung preservation, bronchial circulation and autonomic innervation of the lungs were interrupted through hilar stripping and transection of the left main bronchus. During storage the autograft was kept cold in a semi-inflated position with the left main bronchus clamped. Thus, a transplant was effectively simulated without the potential implications of early immunologic reactions.

The clinical and hemodynamic presentation of reperfusion syndrome in our model was reproducible in a reliable fashion: pulmonary gas exchange as well as hemodynamics deteriorated dramatically during reperfusion. The vast majority (five out of six) of animals in the control group developed frank alveolar edema. Many experimental models base on the high reactivity of sheep with regard to PMN-mediated pulmonary injury [14–18]. In sheep clamping of pulmonary artery alone does not cause significant changes in pulmonary function and/or hemodynamics [17]. The conditions of our model, i.e. total ischemia, denervation and preservation with modified Euro–Collins solution, however, were able to initiate a severe reperfusion injury despite the rather short ischemic time of 2 h.

Treatment with EL-246 proved to be very effective in ameliorating lung reperfusion injury in our experimental model. Pulmonary gas exchange, as well as pulmonary hemodynamics were significantly improved compared to the controls. Only one of the animals treated with EL-246 developed alveolar edema, compared to five in the control group. This corresponded with measurement of extravascular lung water: animals in group B (EL-246) showed statistically significant lower values compared to animals in group A (control). Consequently, the work of breathing was also significantly lower in group B compared to group A, reflecting higher lung compliance due to less interstitial fluid content.

Zymosan-enhanced chemiluminescence (ZE-CL) and β-NAG release were chosen as biochemical markers of PMN activation.

The in vitro chemiluminescence value reflects the amount of intracellular phagocytic and respiratory burst capacity of stimulated PMN. High values indicate unreleased granula and a low in vivo pre-stimulation of PMN, whereas low values indicate highly in vivo pre-activated and exhausted PMN. The time-dependent decrease of the chemiluminescence values in group A (control) suggests a profound in vivo PMN activation with ongoing reperfusion. The decline of the chemiluminescence values is most likely a sign of progressive PMN degranulation due to maximal activation. ZE-CL values in group B (EL-246) rose slightly and remained stable during reperfusion, indicating an in vivo protection of PMN by EL-246 against respiratory burst induced production of toxic oxygen derived radicals.

The activity of β-NAG in plasma, which biologically behaves similar to PMN elastase, suggests significant respiratory burst induced degranulation of PMN throughout reperfusion. This enzyme is located in the PMN azurophilic granula. It is not absolute specific for PMN, since it can also be released from platelets or macrophages. Due to the small number of circulating macrophages changes in β-NAG activity can be attributed predominantly to PMN activation.

This protective role of EL-246 was confirmed by β-NAG release, which was more intensive during reperfusion in group A (control), although this difference did not reach statistical significance.

Blocking the initial PMN interaction with the activated endothelium has been shown to reduce pulmonary reperfusion injury [1]. Studies with P- and E-selectin inhibition after single lung transplantation in dogs after 21 h of cold preservation with Euro–Collins solution showed similar results: oxygenation, as well as CO_2 elimination were significantly improved, PVR increased slowly after 2 h of reperfusion [19]. Our results are comparable to those of other groups indicating the potential benefits of this approach to reperfusion injury.

We conclude that in this experimental model our experimental set-up blockade of L- and E-selectin was effective in reducing reperfusion injury in sheep lungs. Selectin inhibition may thus represent a promising strategy to reduce post-transplant graft dysfunction.

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