EXPERIMENTAL

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PEEP has beneficial effects on inflammation in the injured and no deleterious effects on the noninjured lung after unilateral lung acid instillation

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Abstract *Objective:* In clinical lung injury areas of inflammation and structural alveolar alteration are unevenly distributed and interspaced between healthy or less injured lung areas. Positive end-expiratory pressure (PEEP) applied with mechanical ventilation (MV) may affect injured and healthy lung areas differently. We compared the effects of PEEP on the inflammatory response in injured and noninjured regions of the lung in an animal model of unilateral lung acid instillation. *Subjects:* Anesthetized, paralyzed, and ventilated rats. *Interventions:* Rats underwent left-endobronchial instillation with either hydrochloric acid or isotonic saline and were randomized 24 h later to MV using constant tidal volume (16 ml/kg) with either ZEEP, PEEP at 5 mmHg, or PEEP at 10 mmHg. After 4 h of MV the animals ($n = 9$ or 10 per group) were killed and inflammatory markers assessed in left- and right-lung lavage fluid samples. In four additional animals per group differential lung perfusion was assessed. *Results:* Unilateral acid injury alone worsened oxygenation, decreased left-lung perfusion, and increased left-lung lavage neutrophil and macrophage counts and cytokine levels. MV with ZEEP further impaired oxygenation and further decreased left-lung perfusion in acid-injured animals. MV with high PEEP preserved oxygenation and significantly decreased left-lung lavage protein content and cell counts in acid-injured animals and had no deleterious effect on the right (noninjured) lung. *Conclusion:* In this model of unilateral lung acid injury high PEEP attenuates the inflammatory cell response in the acid-injured lung, preserved oxygenation and has no deleterious effects in the opposite lung.

Keywords Ventilator-associated lung injury · Oxygenation · Lung lavage · Lung perfusion · Microspheres · Cytokines

Introduction

Chest computed tomography studies show that acute lung injury is morphologically characterized by inhomogeneous pulmonary infiltrates [1, 2]. These studies suggest that the distribution of lung injury is not diffuse, and that areas of severe structural lung injury are interspaced between areas of almost normal lung morphology. Patients with severe lung injury frequently require mechanical ventilation (MV) to improve oxygenation or support failing respiratory muscle function. MV, although life saving in these cases, may by itself

worsen existing lung injury or injure normal lung tissue. The mechanisms of ventilator-associated lung injury involve cyclic overdistension of the alveoli while using large tidal volumes (VT) and cyclic alveolar and small airway collapse during exhalation while ventilating with inappropriately low PEEP levels [3, 4, 5]. Data from experimental and clinical studies support the application of appropriate PEEP levels in patients with acute lung injury or ARDS [6, 7, 8].

In the setting of patchy lung infiltration both VT and PEEP may distribute unevenly between the injured and healthy lung regions [9]. Effects of PEEP may therefore differ between healthy and injured regions of the lung. On the one hand, PEEP may theoretically decrease or reduce periodic alveolar collapse in the injured lung and lead to a decrease in ventilator-associated lung injury. On the other hand, increasing PEEP levels may contribute to overdistension of the noninjured lung areas and be injurious in these areas.

While difficult in a clinical scenario, experimental unilateral lung injury, by separately obtaining samples from the injured and the opposite (noninjured) lung, offers the possibility of differentiating the effects of PEEP on healthy and injured lung areas. Acid aspiration continues to be an important cause of acute lung injury [10] and therefore is a relevant experimental model.

Accordingly, in this study, while ventilating with constant tidal VT, we investigated the effects of increasing levels of PEEP on the pulmonary inflammatory response in unilateral acid-induced lung injury in rats [11].

Materials and methods

This study was approved by the institutional and local Committee on the Care and Use of Animals (Thüringer Landesamt für Lebensmittelsicherheit und Verbraucherschutz, Weimar, Germany). Male Wistar rats weighing 350–380 g were used in the experiments and handled according to the National Institutes of Health guidelines.

Induction of lung acid injury

Animals received inhalational anesthesia with 1.5% isoflurane in 100% oxygen, and tail artery blood (150 µl) was collected for leukocyte counts and blood gas analysis (ABG) (ABL 50, Radiometer, Copenhagen). Laryngoscopy (size 0 laryngoscope) was performed; a specially designed blunt cannula was advanced through the trachea into the left main bronchus, and 0.4 ml 0.1 N hydrochloric acid (HCl) or 0.4 ml isotonic saline (NaCl) was instilled. Animals were kept in the left lateral position for 10 min and at emergence from anesthesia transferred to their cages with free access to water and food. Preliminary studies using hydrochloric acid labeled with black ink

(1%) had demonstrated that with this technique acid instillation was confined to the left lung only (see Electronic Supplementary Material S1).

Twenty-four hours after treatment acid-injured and control animals were further allocated to undergo MV with either zero end-expiratory pressure (ZEEP), PEEP at 5 mmHg (6.7 cmH$_2$O; PEEP5 group), PEEP at 10 mmHg (13.3 cmH$_2$O; PEEP10 group), or no MV ($n = 14$ per group).

Experiments and measurements in nonventilated animals

At 6 and 24 h after the treatment inhalation anesthesia was repeated to obtain ABG. After the last ABG animals were anesthetized with ketamine (70 mg) and midazolam (4 mg) and (without instrumentation) killed as described below. Lung lavage was performed and samples were collected and processed identically as in ventilated animals (see below).

Experiments and measurements in mechanically ventilated animals

Instrumentation

Twenty-four h after treatment animals were anesthetized with an intraperitoneal injection of ketamine (70 mg) and midazolam (4 mg). Cefuroxime (12.5 mg) was injected subcutaneously for antibiotic prophylaxis (Cefuroximratiopharm, Ratiopharm, Ulm, Germany). The right external jugular vein and right carotid artery were surgically exposed and catheters (ID 0.5 mm) for fluid infusion and to transduce central venous (CVP) and arterial blood pressure (AP; monitor: SMU 611, PPG Hellige, Freiburg, Germany) were inserted. The trachea was exposed and incised, and a blunt cannula (outer diameter 2 mm) was placed and secured in the lumen.

Ventilation period

Volume-controlled MV was started with respiratory rate 40 breaths/min, VT 16 ml/kg, inspiration-to-expiration ratio 1:1 (Animal Respirator Advanced 4601-1, Technical and Scientific, TSE Systems, Bad Homburg, Germany). FIO$_2$ was 1.0 at beginning and end of MV, but reduced to 0.4 throughout the ventilation period. Pancuroniumbromide (0.2 mg) was injected intravenously for muscle relaxation. PEEP was applied using an external water column connected to the expiratory port of the ventilator and increased in steps of 2–3 mmHg to avoid hemodynamic deterioration. Cardiorespiratory variables and ABG were recorded every 30 min throughout the ventilation period. Body temperature was maintained

at 38°C using a feed-back warming system (Theraterm de Luxe, 250 W, Osram, Munich, Germany with HSE temperature regulator, Hugo Sachs Elektronic, March, Germany). Continuous infusion of balanced electrolyte solutions at a rate of 10 ml/h (Thomaejonin, Delta Pharma GmbH, Pfullingen, Germany) and intravenous anesthetics (18 mg/h ketamine and 0.18 mg/h midazolam) at a rate of 0.6 ml/h was maintained throughout the ventilation period.

After 4 h of MV animals were exsanguinated by collecting 8–10 ml blood from the inferior vena cava. Sternotomy was performed, and the lungs were removed en bloc from the thorax and visually evaluated for macroscopic effects caused by pretreatment to confirm left-sided acid lung injury. Animals with bilateral or no visible acid lung injury were excluded from the study.

Lung lavage

Right and left lungs were lavaged separately with 10 ml PBS using aliquots of 2.5 ml. The pooled effluents (7.5–8.5 ml) from each side were processed separately by centrifugation at 3,000 rpm for 10 min. The resulting cell pellet was suspended in 100 µl PBS, and absolute numbers of neutrophils and macrophages were counted using a hemocytometer and corrected for the total amount of bronchoalveolar lavage fluid (BALF).

Lung lavage protein content

Protein content in BALF supernatant was measured using turbidimetry (assay: Roche Diagnostics; analyzer: Hitachi 717).

Blood neutrophil counts

The proportion of blood neutrophils was obtained from a cell smear (May-Gruenwald stain; 100 white blood cells were counted at a magnification of $\times 500$), and absolute neutrophil numbers were calculated using the total white blood cell count which was determined using a hemocytometer.

Cytokines

Cytokine levels in the supernatant of BALF were assessed by enzyme-linked immunosorbent assay using commercially available kits specific for rat (interleukin, IL-6: KRC0062; macrophage inflammatory protein 2, MIP-2: KRC1022; BioSource, Solingen, Germany). Kits were used according to manufacturer guidelines. The detection threshold was 8 pg/ml for IL-6 and 1 pg/ml for MIP-2.

Additional experiments

Lung perfusion

In four rats per group lung perfusion was measured by central venous injection of color-coded microspheres (no lung lavage was performed in these animals). The technique has been presented in detail elsewhere [12, 13]. Briefly, 10^5 colored microspheres with a nominal diameter of 15 µm (Dye Trak, Triton Technology, San Diego, Calif., USA) were injected via the central venous catheter. Different microsphere colors were used at the beginning (after PEEP application) and at the end of MV. In nonventilated animals only one injection was performed (24 h after treatment).

Left and right lungs were weighed and digested separately in 4 N concentrated solution of KOH, and samples were processed as previously described [14]. Each resulting dye sample was analyzed using a spectrophotometer at wavelengths of 190–820 nm. The number of microspheres was calculated using the specific photometric absorbance value of the different dyes. The proportion of the left- and right-lung perfusion was then calculated as the proportion of the microsphere number on the total number of microspheres.

Computed tomography of the lungs

Computed tomography (General Electrics, LightScan) was performed in two additional anesthetized and spontaneously breathing animals 24 h after left-sided lung injury.

Statistical analysis

Data are presented as mean $\pm$ SEM. Analysis of variance was performed to assess the effects of group, lung side, PEEP level, and time on markers of lung injury and lung function. A repeated measures term was used where appropriate. Bonferroni's correction was applied in the case of multiple comparisons. The t test was used to assess differences between two parameters. Differences at the level of $p < 0.05$ were considered statistically significant. The statistics software SPSS version 11 (Carey, N.J., USA) was used for data analysis.

Results

Eight animals were excluded from the experiment: Two saline instilled animals died during ventilation with PEEP10. Three animals had no macroscopically visible left side lung injury after acid instillation (one each in the ZEEP, PEEP10, and nonventilated groups) and three animals had bilateral lung injury (one each in the
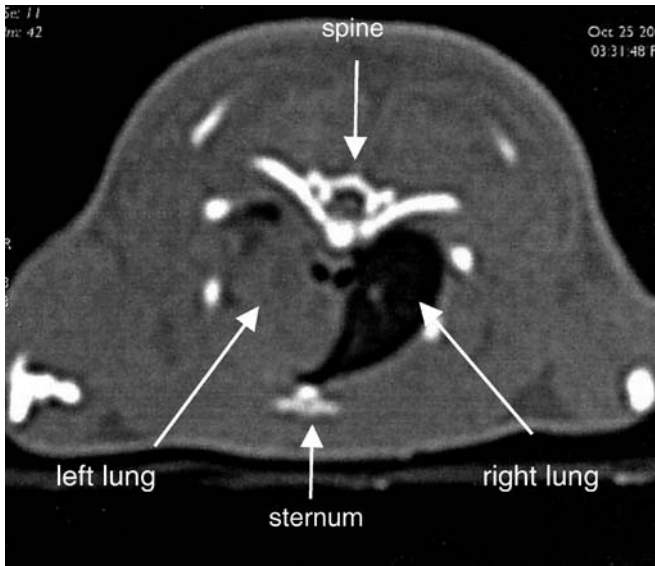
Fig. 1 Computed tomography section of the lungs of a rat obtained 24 h after instillation of hydrochloric acid into the left lung. The animal is in prone position and breathing spontaneously. Note the consolidation of large areas of the left lung

ZEEP, PEEP5, and nonventilated group). Acid instillation caused transient symptoms of illness (reduced locomotion, piloerection, tachypnea). All acid-injured left lungs (while excluding the above animals) looked similar with consolidated areas comprising approx. 50% of the lung surface. Noninjured right lungs appeared to be unaffected and macroscopically comparable to the lungs of the control group. Computed tomography showed consolidation of parts of the left lungs and aerated right lungs (Fig. 1).

Effects of unilateral acid injury in nonventilated animals

Acid-injured left lungs were heavier than control left lungs (0.85 ± 0.03 vs. 0.48 ± 0.03 g; $n = 4$ per group). In control animals perfusion (proportion of total lung perfusion) was evenly distributed between the left ($51.3 \pm 1.3\%$) and the right lung ($48.7 \pm 1.4\%$). In acid-injured animals perfusion of the left lung was significantly lower than that of the right lung ($29.5 \pm 1.3\%$ vs. $70.5 \pm 1.4\%$; $p < 0.05$). PaO_2 (in mmHg) at 6 and 24 h was significantly lower in acid-injured than in control animals (before treatment: 330 ± 13 vs. 327 ± 12, n.s.; 6 h: 255 ± 8 vs. 323 ± 13, $p < 0.05$; 24 h: 272 ± 11 vs. 344 ± 10; $p < 0.05$). Neutrophil counts (cells/μl) in the two groups were comparable before (900 ± 87 vs. 897 ± 104) but higher in the acid injury group 24 h after treatment (1298 ± 131 vs. 828 ± 70; $p < 0.05$).

Effects of mechanical ventilation on cardiorespiratory variables

Increasing PEEP depressed heart rate and blood pressure and this effect was more pronounced in control animals (Fig. 2). PaO_2 decreased significantly during MV with ZEEP, and this effect was stronger in acid instilled animals. Oxygenation was maintained during MV with PEEP5 and PEEP10 (Fig. 3). After initiation of MV left-lung perfusion was higher in acid treated animals ventilated with PEEP than in animals ventilated with ZEEP. Left lung perfusion further decreased over time in all acid-instilled animals ventilated with ZEEP but increased during ventilation with PEEP (Fig. 3). No statistical analysis was carried out because of the small number of animals in each group.

Lung lavage

In nonventilated animals acid injury resulted in significantly higher protein content, neutrophil and macrophage counts, and IL-6 and MIP-2 levels in the left- than the right-lung BALF (Fig. 4). Compared to control animals, left-lung acid injury also resulted in significantly higher neutrophil and macrophage counts in right-lung BALF. In control animals no differences were found between left- and right-lung BALF in any of these markers.

In ventilated acid-injured animals at each PEEP level protein content, neutrophil and macrophage counts were significantly higher in left- than in right-lung BALF (Figs. 5, 6). In left-lung BALF increasing PEEP resulted in significantly lower neutrophil and macrophage counts and protein content than with ZEEP. In right-lung BALF neutrophil counts and protein content were not affected by PEEP, but there was a trend towards lower macrophage counts ($p < 0.1$) in animals ventilated with PEEP5 or PEEP10 than in animals ventilated with ZEEP. In acid-injured animals at each PEEP level IL-6 levels in BALF were higher in left- than in right-lung BALF with the highest levels seen in animals ventilated with ZEEP. However, there was considerable variability in these levels, and no significant effect of PEEP was seen. No differences were noted between MIP-2 levels in left- and right-lung BALF, and there was no significant effect of PEEP. No significant effects of PEEP were seen on cytokine levels in control animals. In ventilated control animals there were no differences between left- and right-lung BALF in any of these markers at any PEEP level, and, except that macrophage counts were significantly higher in both left- and right-lung BALF from control animals ventilated with ZEEP than with PEEP, no further effects of PEEP were seen.

Fig. 2 Blood pressure, heart rate and peak airway pressure in rats ventilated with ZEEP, PEEP at 5 or 10 mmHg, and constant VT. **A** Animals with left-lung acid injury. **B** Control animals with left-lung saline instillation 24 h prior to ventilation ($n = 9–10$ per group). Variables were obtained after application of the corresponding PEEP level at the beginning (0.5 h) and before the end of the ventilation period (3.5 h). Values are given as mean ± SEM. All changes over time within group were significant ($p < 0.05$) except heart rate in acid-injured and control animals ventilated with ZEEP and except peak airway pressure in control animals ventilated with PEEP5 (Please note that airway pressures are given in mmHg)
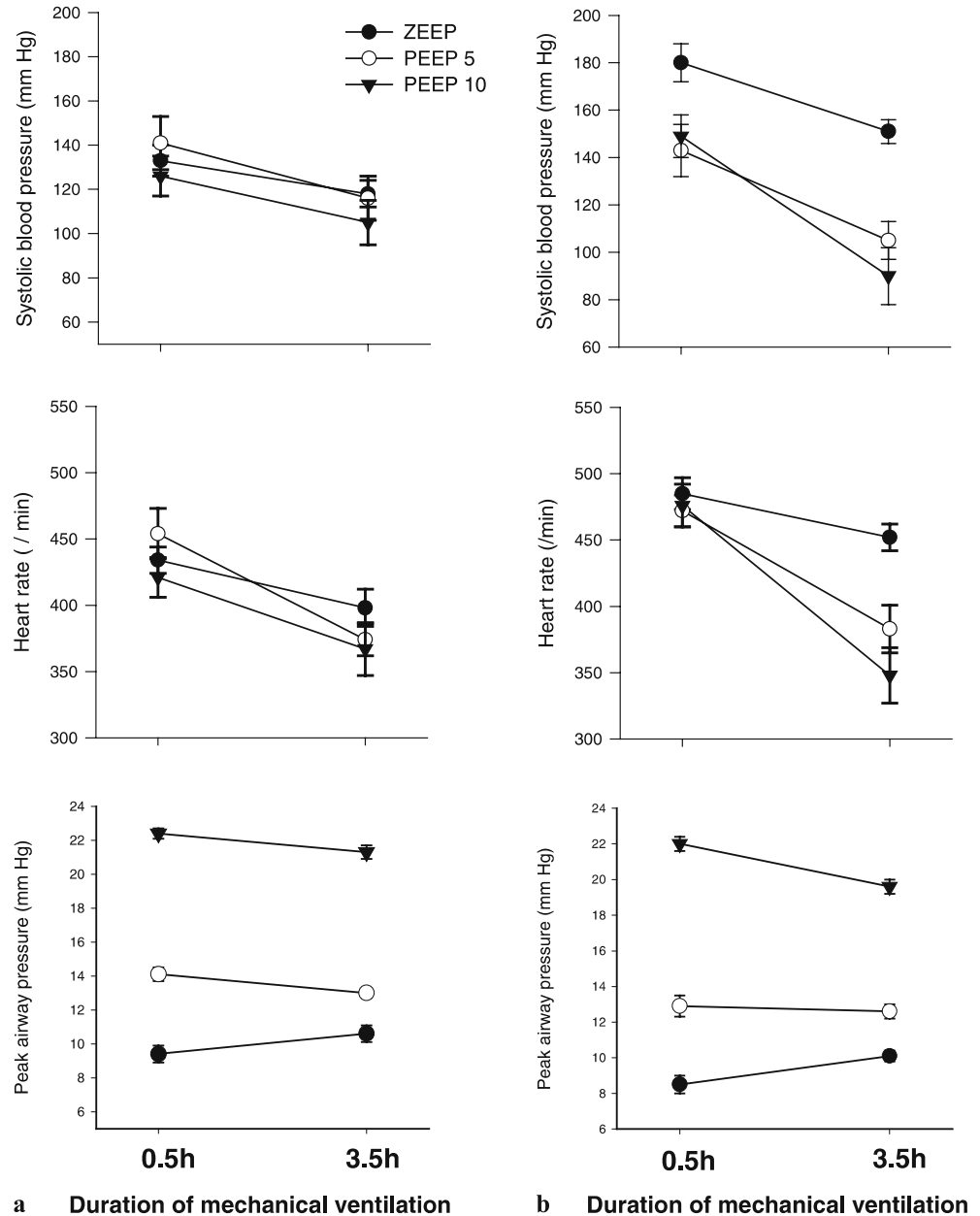
Systemic markers of inflammation after MV

In all groups blood neutrophil counts (Table 1) increased significantly during MV. Analysis according to PEEP levels revealed no differences between groups in either treatment arm.

Discussion

In this study we used a modified version of acid aspiration-induced lung injury, which warrants some comments. By acid instillation in the left lung only our model offers the prospects of studying effects of ventilation in injured lung tissue and in lung areas, which are not directly injured (i.e., the opposite lung), separately. In contrast, most experimental studies instill acid into the trachea, thereby producing (mostly) bilateral lung injury. Further, we ventilated animals 24 h after the insult when the inflammatory response was clearly established, whereas in most previous experimental studies the period of observation or ventilation is usually within 0–6 h after acid aspiration, a period during which recruitment of cells may not be complete [4, 15].
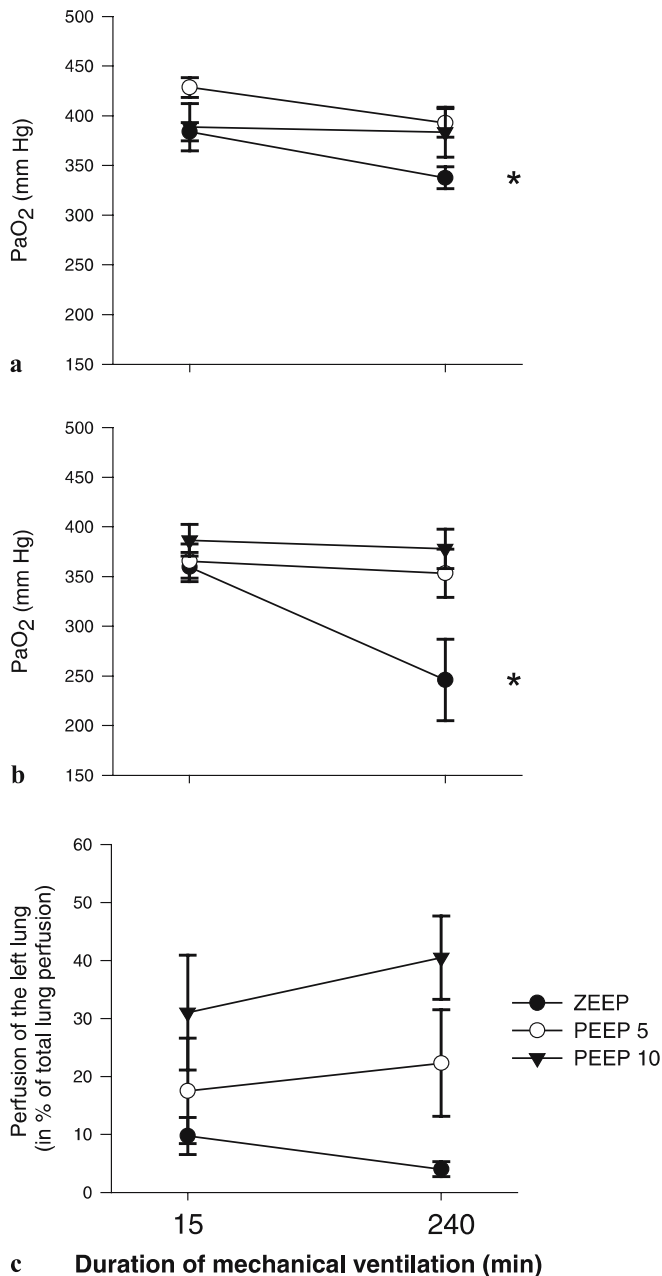
Fig. 3 Oxygenation and left-lung perfusion in rats during mechanical ventilation with ZEEP, PEEP at 5 or 10 mmHg, and constant VT. Variables are shown after application of the corresponding PEEP level at the beginning (0.5 h) and before the end of mechanical ventilation (3.5 h). **A** Control animals with left-lung saline instillation. **B**, **C** Animals with left-lung acid injury 24 h prior to ventilation ($n = 9$–10 in **A** and **B**, $n = 4$ in **C**). Left lung perfusion is given as percentage of total lung perfusion. Values are given as mean ± SEM. * $p < 0.05$ vs. 15 min at the same PEEP level

Table 1 Blood neutrophil (PMN) counts (cells/µl) before and at the end of mechanical ventilation (*MV*) with ZEEP, PEEP at 5 mmHg, and PEEP at 10 mmHg in acid-injured and control animals; within all groups $p < 0.05$ for values before vs. end of MV

|	Before MV	End of MV
Acid injury		
ZEEP	1369 ± 245	3075 ± 699
PEEP5	1217 ± 95	3326 ± 317
PEEP10	1329 ± 306	3587 ± 436
Controls		
ZEEP	790 ± 129	4339 ± 453
PEEP5	1014 ± 132	4164 ± 458
PEEP10	958 ± 142	4321 ± 657

pairs oxygenation. We also found a systemic response to the pulmonary insult, as indicated by a moderate increase in blood neutrophil count. Our results are in agreement with previous studies documenting a cellular inflammatory response in the injured lung accompanied by a systemic inflammatory response [15, 16] and increased alveolar levels in proinflammatory cytokines [17, 18].

Although not macroscopically visible, evidence of a mild inflammation was also present in the noninjured right lung. The type and fit of the cannula that we used to intubate the left main bronchus to induce unilateral lung injury makes spillage of acid from the injured to the noninjured lung unlikely (hence the most likely explanation for bilateral injury found in three animals being acid injection in the trachea). These animals were excluded from the study. Since we also found evidence of systemic inflammation following acid instillation, the response in the noninjured lung is probably due to systemic dissemination of inflammation. Previous studies of other groups support our findings [19, 20, 21].

The main findings in the ventilation study are that increasing levels of PEEP reduced the inflammatory response in the injured lung, did not result in detrimental effects on inflammation in the opposite lung, and preserved oxygenation during the ventilation period. In contrast, ventilation with ZEEP aggravated inflammation in the injured lung and impaired oxygenation. In addition, during MV the perfusion of the injured lung increased with PEEP and decreased with ZEEP.

One of the main favorable effects of PEEP may be the attenuation in the inflammatory response by reduction in cyclic atelectasis. Since the injured lung is more prone to atelectasis than the noninjured lung, the beneficial effects of PEEP may also be expected to occur predominantly in the injured lung. Our data regarding alveolar inflammatory cell counts and protein content in the study groups clearly support this. Our findings in cytokine levels in BALF are less clear. Ventilation with ZEEP was associated with the highest IL-6 concentrations (supporting our other results). However, effects of PEEP were insignificant regarding IL-6 and MIP-2. These findings may partially be explained

We show that in nonventilated animals unilateral acid instillation produces a strong inflammatory response in the injured and a modest inflammatory response in the noninjured lung, reduces perfusion of the injured lung, and im-

Fig. 4 Protein content and markers of inflammation in left and right-lung bronchoalveolar lavage fluid (*BALF*) obtained from nonventilated animals 24 h after instillation of 0.4 ml hydrochloric acid (*unilateral acid injury*) or normal saline (*control*) in the left lung. Values are given as mean ± SEM. * $p < 0.05$ vs. right side and vs. left side in controls, # $p < 0.05$ vs. right side in controls
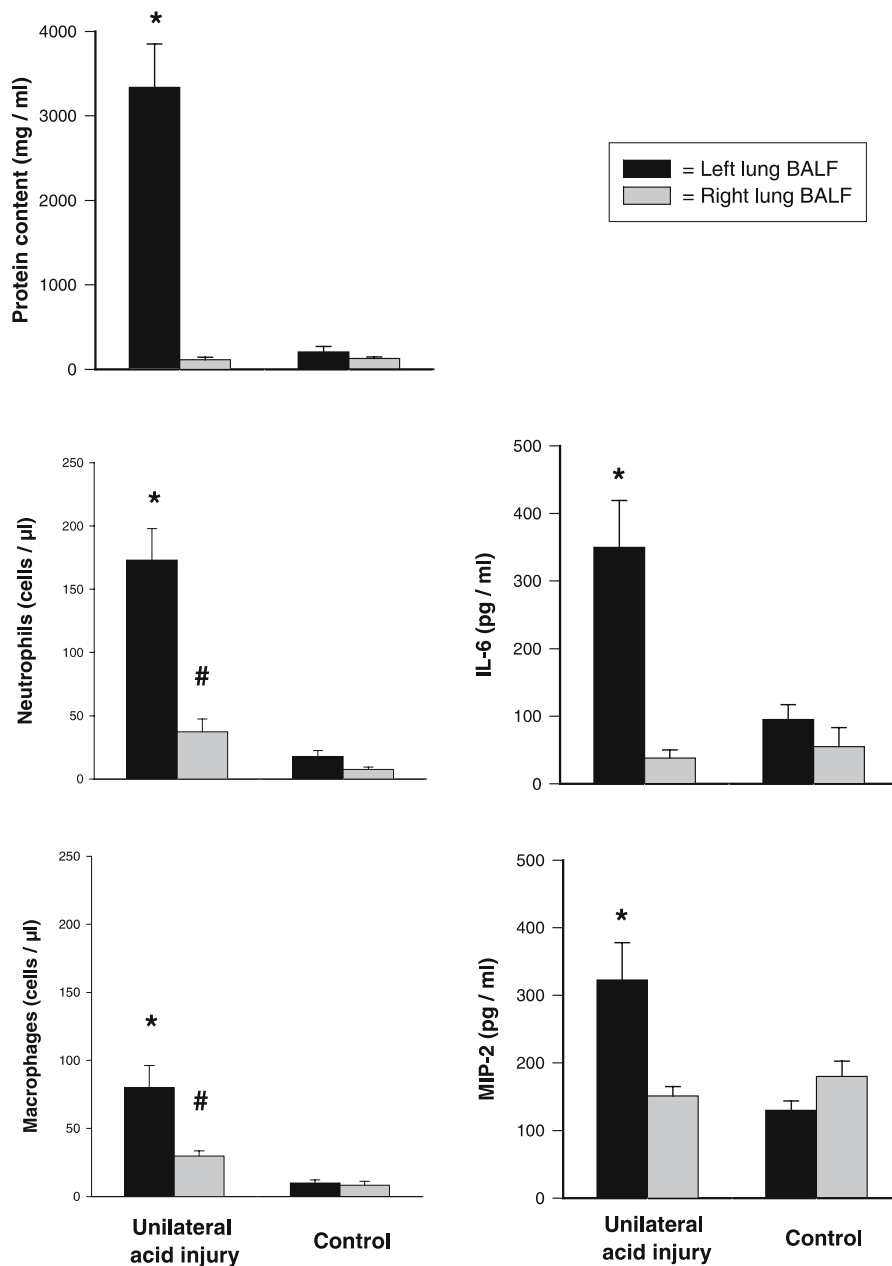
by high variability in cytokine levels and the relatively low number of animals per group, but may also reflect a still questionable relevance of these markers in ventilator associated lung injury [22].

Increasing levels of PEEP at constant VT may, by causing lung overdistention, also exert unfavorable effects including volutrauma, aggravated inflammation, reduced perfusion of the noninjured lung and worsened oxygenation [10, 23]. However, in a recent clinical trial in patients with acute respiratory distress syndrome and acute lung injury high vs. lower levels of PEEP were not associated with detrimental effects on biological markers

or clinical outcome [24]. In our study during ventilation with increasing levels of PEEP there were indications (disproportionate increase in Paw with PEEP10) of reduced lung compliance, which was not associated with an increase in inflammatory injury in the contralateral lung. The fact that right-lung macrophage counts were more increased during ZEEP ($p = 0.09$ vs. PEEP5 and PEEP10) may even reflect a weak beneficial effect of PEEP in the noninjured lung.

Compared to MV with ZEEP we saw a reduced perfusion of the noninjured lung and an increased perfusion of the injured lung shortly after PEEP was applied, an

Fig. 5 Protein content and neutrophil and macrophage counts in bronchoalveolar lavage fluid (*BALF*) in rats after 4 h of mechanical ventilation with ZEEP, PEEP at 5 or 10 mmHg, and constant VT. **A** Animals with left-lung acid injury. **B** Control animals with left-lung saline instillation 24 h prior to ventilation ($n = 9$–10 per group). **A** All variables obtained in left-lung BALF are significantly higher than in corresponding right-lung BALF. Values are given as mean ± SEM. * $p < 0.05$ vs. BALF from the same side and ventilation with ZEEP. # $p < 0.1$ vs. BALF from the same side and ventilation with ZEEP
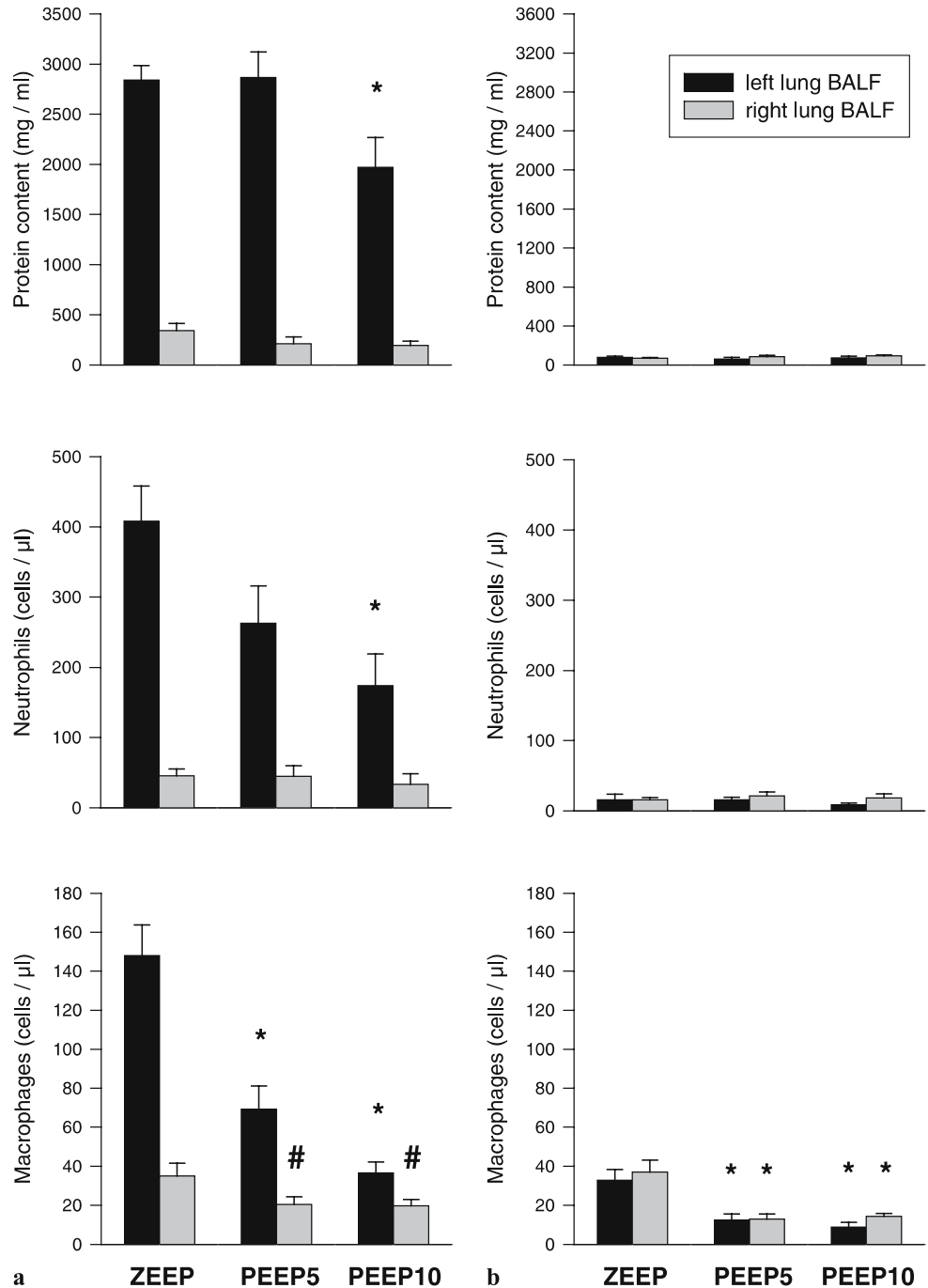
effect that was even more pronounced at the end of the ventilation period. We speculate that the perfusion of the injured lung has increased in response to the favorable effects of PEEP in increasing aerated lung volume, reducing hypoxic pulmonary vasoconstriction and thus decreasing the resistance to flow. Furthermore, oxygenation was preserved during MV with PEEP, suggesting that PEEP improved the ventilation/perfusion ratio, probably through recruitment. Our findings are in accordance with experiments conducted in animals with etchlorvynol-induced unilateral lung injury which showed an improvement in oxygenation and increased perfusion of the damaged lung [25]. In that study increasing PEEP from 5 to 12 cmH$_2$O improved oxygenation although blood flow was redistributed to the injured lung.

Fig. 6 Cytokine levels in lung lavage fluid (*BALF*) in rats after 4 h of mechanical ventilation with ZEEP, PEEP at 5 or 10 mmHg, and constant VT. **A** Animals with left-lung acid injury. **B** Control animals with left-lung saline instillation 24 h prior to ventilation ($n = 9$–10 per group). Values are given as mean ± SEM. * $p < 0.05$ vs. right side BALF at the same PEEP level
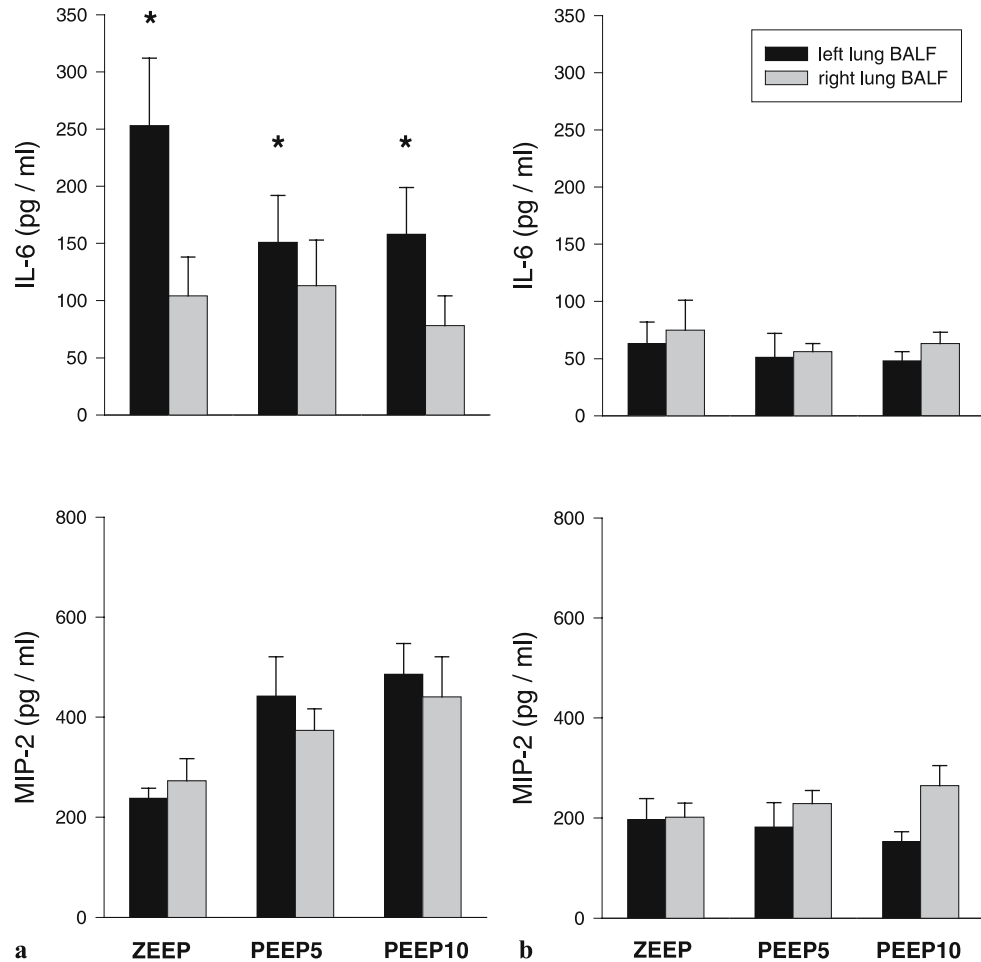
Our study has some limitations. First, in other causes of unilateral lung injury such as pneumonia and lung contusion the time course and intensity of the pulmonary response may differ from our findings in the setting of acid injury. Further, our observations may be only partly extended to the setting of bilateral injury. Although in bilateral lung injury areas of severe injury are interspaced with areas of near normal lung tissue similar to our model, the close proximity of injured and normal tissue areas may interact to produce effects not reproducible during unilateral lung injury, i.e., lung-lung interaction. Second, keeping VT constant in our study probably resulted in different levels of lung distension with increasing PEEP. However, aiming for comparable levels of lung distension in the different PEEP groups (e.g., by limiting peak airway pressure) would have resulted in lower VT in the PEEP groups. Because low VT per se may ameliorate the pulmonary inflammatory response [7, 26] a differentiation between effects of increasing PEEP and decreasing VT would have been difficult. Third, a VT of 16 ml/kg, as used in our study to achieve sufficient alveolar recruitment in animals ventilated with ZEEP may appear rather high when contemplating recent human studies. However, a VT of 16 ml/kg has been used in an acid aspiration lung injury model of the rat and has shown no detrimental effect as compared to 9 ml/kg [25]. We therefore conclude that a VT of 16 ml/kg as set on the ventilator was appropriate in this experimental setting.

In conclusion, in this model of unilateral pulmonary acid aspiration pneumonitis we found that increasing PEEP had beneficial effects on pulmonary inflammation markers in acid-injured and no negative effects on these markers in noninjured lung tissue. Preserved oxygenation during ventilation with PEEP and redistribution of lung perfusion to the injured lung indicated an improved functional capacity of the damaged lung.

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