Unilateral lung edema: effects on pulmonary gas exchange, hemodynamics, and pulmonary perfusion distribution

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LUNG EDEMA ACCOMPANIES VARIOUS types of acute heart and respiratory failure. Different types of lung edema, e.g., hydrostatic and permeability edema, have different pathogenic mechanisms and are associated with different diseases. They contribute differently to the outcome of patients. An elevated pulmonary microvascular pressure remains the driving force for the development of hydrostatic lung edema. Inflammation is crucial for the development of permeability edema.

However, inhomogeneities exist, which prevent simplistic membrane models from explaining the development of both types of lung edema (31). In addition, different types of lung edema may have different impacts on pulmonary circulation and gas exchange. Pulmonary gas exchange, hemodynamics, and distribution of pulmonary blood flow during the course of different types of equivalent lung edema have not been systematically evaluated.

We developed an animal model to induce two types of equivalent unilateral lung edema in sheep. In the first set of experiments, lung edema was induced with aerosolized HCl, which was delivered selectively into the left lung to produce unilateral, homogeneous tissue damage. We chose the application of HCl solution as a model for the aspiration of gastric content, a major cause of the acute respiratory distress syndrome (ARDS) in adult patients (8, 12). In the second set of experiments, lung edema was induced with aerosolized NaCl, which was also delivered into the left lung. NaCl solution was selected because we anticipated that aerosolized saline would create approximately the same amount of edema in the lung as aerosolized HCl (9).

We characterized regional lung edema caused by aerosolized HCl or NaCl. 1) morphologically, 2) using in vivo and ex vivo measures for extravascular lung water (EVLW), and 3) by imaging techniques. We systematically evaluated the influence of the two types of lung edema on pulmonary gas exchange, hemodynamics, and distribution of pulmonary blood flow. We found that the worsened oxygenation in acid-injured lungs was related to a greater distribution of blood flow to the injured lung. In contrast, the NaCl-treated lungs had equivalent degrees of edema from saline aerosolization but had no tissue injury and maintained oxygenation, which was related to a shift of pulmonary blood flow away from the saline-aerosolized lung.
METHODS

Animal preparation. Healthy adult sheep (n = 28; mean weight 33 kg) were anesthetized with 20 mg/kg body wt thiopental and paralyzed with 0.1 mg/kg body wt pancuronium bromide. General anesthesia was maintained during the study using a continuous infusion of methohexitol sodium and fentanyl (15 mg·kg⁻¹·h⁻¹ each). The sheep were paralyzed using intermittent applications of pancuronium bromide (0.1 mg/kg) via an intravenous catheter placed in a peripheral vein. The sheep were orally intubated with a cuffed endotracheal tube (9-mm ID) and connected to a ventilator (Servo 900 C, Siemens-Elema, Sweden). They were placed in supine position and were mechanically ventilated in the volume-controlled mode. A tracheotomy was performed and, after ventilation for 2 min with 100% O₂, the orotracheal tube was removed, and a modified, cuffed double-lumen endobronchial tube (Broncho-cath, 41 charrière, Mallinckrodt, Athlone, Ireland) was positioned in the trachea through the tracheostoma to ventilate the right and left lungs separately. In sheep, the right upper bronchus originates directly from the lower third of the trachea. This specific anatomy required modification of the double-lumen endobronchial tube to enable ventilation of the right upper lobe of the lung. Proper tube positioning was verified by bronchoscopy and during unilateral ventilation with simultaneous flow measurements in the contralateral lung. The sheep were now mechanically ventilated in the volume-controlled mode using two synchronized Servo 900 C ventilators. At a fixed respiratory rate of 12 breaths/min and a positive end-expiratory pressure of 10 cmH₂O, the tidal volume was set to maintain an arterial partial pressure of CO₂ (PaCO₂) between 35 and 40 Torr. This was achieved with tidal volumes of 10–12 ml/kg, creating peak and mean airway pressures of ~29 and 19 cmH₂O at baseline, respectively. The ventilator settings were then kept constant throughout the experiments. Catheters were placed in the aorta and in the superior vena cava, and a 7-Fr Swan-Ganz thermodilution catheter (Edward Laboratories, Palo Alto, CA) was placed in the pulmonary artery for hemodynamic monitoring, blood sampling, and injection of colored microspheres. A fiberoptic thermistor catheter (PV 2024, Pulsion, Munich, Germany) was placed into one of the femoral arteries for measurements of EVLW, intrathoracic blood volume (ITBV), and right ventricular end diastolic volume (REDV). Ringer solution was administered via the femoral vein (8–10 ml·kg⁻¹·h⁻¹) to replace undetected water and volume loss during the acquisition of blood samples. Correct placement of the catheters was confirmed by fluoroscopy.

Application of HCl or NaCl. HCl (0.15 M, pH 1.0) or NaCl (0.15 M, pH 7.4) was aerosolized using an ultrasonic nebulizer (U 804, Medap, Germany). Aerosolized fluids were nebulized selectively into left lungs through the lumen of the endobronchial tube, which was directed to the left lung. No aerosols were given to the right lungs. HCl or NaCl was delivered continuously into left lungs while the right lungs were ventilated for computed imaging. These analyses utilized magnetic resonance imaging and computer tomography. Finally, we performed selective gravimetric measurements (tissue dry:wet weights) to verify the regional distribution of lung edema.

Baseline measurements were obtained after animal preparation and after a 30-min period of ventilation using the double-lumen endobronchial tube and the two synchronized ventilators. After the baseline period, either aerosolized HCl or NaCl was delivered continuously into left lungs while the controls received no treatment. Repeated measurements were performed 2 and 4 h after the onset of HCl or NaCl application in both treatment groups and the controls.

In vivo measurements included evaluations of pulmonary gas exchange, hemodynamic variables, EVLW, and pulmonary perfusion distribution. The first set of in vivo data was obtained at baseline in 28 sheep. The second set of in vivo data was obtained in 24 sheep 2 h after HCl or NaCl treatment or in controls (n = 8 in each group). The third set of in vivo data was obtained in 12 sheep 4 h after HCl or NaCl treatment or in controls (n = 4 in each group).

Ex vivo measurements included morphological analysis, computed imaging, and gravimetric total lung water based on lung tissue dry-to-wet ratio (dry:wet) weights. The first set of ex vivo data was obtained from four sheep after the baseline period. The second set of ex vivo data was obtained from 12 sheep after 2 h of HCl or NaCl treatment or controls (n = 4 in each group). The third set of ex vivo data was obtained from 12 sheep after 4 h of HCl or NaCl treatment or controls (n = 4 in each group). After biopsies from representative right and left lung areas were obtained for morphological analysis, lungs were explanted via a median thoracotomy. Heart-lung explants were continuously perfused and ventilated for computed imaging. These analyses utilized magnetic resonance imaging and computer tomography. Finally, we performed selective gravimetric measurements (tissue dry:wet weights) to verify the regional distribution of lung edema.

The local animal research committee approved the study.

Pulmonary gas exchange measurements. For pulmonary gas exchange measurements, blood was sampled in heparinized syringes after withdrawing the volume of catheter dead-space three times. Minute ventilation and frequency were measured with a calibrated Wright’s respirometer. Barometric pressure was measured using a calibrated barometer. Blood samples (2 ml) were analyzed at 37°C for pH and oxygen and carbon dioxide tensions with standard blood-gas electrodes (ABM 3, Radiometer, Copenhagen, Denmark). Hemoglobin and methemoglobin were measured by the light absorption technique using a photometer (OSM3, Radiometer) adjusted for sheep’s blood. The pulmonary gas exchange...
was evaluated using the ratio of partial pressure of oxygen in arterial blood and the fraction of inspired oxygen (\(P_{aO_2}/FIO_2\)).

**Hemodynamic measurements.** The pulmonary artery, systemic arterial, and central venous catheters were connected to calibrated, fluid-filled pressure transducers (P23ID, Statham-Gould Instruments, Oxnard, CA) and were flushed continuously. The catheters were referenced to the midheart level before each measurement. Heart rate (HR) was determined from the arterial blood pressure wave. Pulmonary arterial pressure (Ppa), aortic pressure (Pao), central venous pressure (\(P_{cv}\)), HR, electrocardiogram, and rectal temperature were displayed and recorded continuously on a multichannel Brush recorder (Gould). Pulmonary arterial wedge pressure (Ppw) was determined at end-expiration after inflating the balloon of the Swan-Ganz catheter with the appropriate volume (0.5–1.0 ml of air). Cardiac output (Q_t) was calculated by a cardiac output computer (Edwards Laboratories, Palo Alto, CA) and averaged from four or five consecutive thermodilution measurements. Body surface area was calculated as 0.869 body wt (in kg)^{0.5} (21). Pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) were calculated using standard formulae.

**EVLW, ITBV, and REDV measurements.** We measured EVLW, ITBV, and REDV with the thermal-dye method (3, 20). We used the pulmonary artery catheter to inject ice-cold indocyanine green dye. The fiberoptic thermistor catheter (PV 2024, Pulsion, Munich, Germany) placed in one of the femoral arteries registered double-indicator dilution curves. EVLW, ITBV, and REDV were computed using the Pulsion Cold Z-021 (Munich, Germany).

**Pulmonary blood flow distribution.** To evaluate pulmonary blood flow distribution, we injected different colored microspheres of 15 μm diameter (Dye-Trac, Triton Technology, San Diego, CA) through the proximal port of the Swan-Ganz catheter into the right atrium at baseline and at 2 and 4 h later. Microspheres were extracted from the right and left lung tissue at the end of the study, according manufacturer instructions (Triton Technology). The various colors were spectrophotometrically quantified using a Beckman DU 600 spectrophotometer (Beckman, Munich, Germany) and multicomponent analysis (18). In a pilot set of three sheep, we determined the optimal amount of microspheres for quantitative blood flow measurements, obtained calibration curves for multiple component analysis, and compared blood flow data obtained with the thermodilution technique. Blood flow data obtained with the two independent techniques differed by ~3%. We chose the thermodilution method for determining total blood flow at each measurement point because we anticipated that the average of four to five consecutive measurements using this technique would give a more correct value compared with the single measurement that could be obtained using the microsphere technique.

**Computed imaging, morphological analysis, and gravimetric measurements.** To evaluate regional distributions of lung edema, we performed magnetic resonance imaging and computer tomography (Magnetom and Somatom, respectively, Siemens, Erlangen, Germany) on heart-lung explants that were continuously perfused and ventilated as described previously (4, 5). After a median thoracotomy, the lungs were perfused blood-free and examined macroscopically. Then we obtained representative tissue samples in situ from the left treated lung and the right untreated lung. These tissue samples were examined using standard histological techniques to evaluate regional distribution of lung tissue injury. After tomography, the right and left lungs were weighed and then homogenized separately for total lung water measurement. These measurements were based on the dry and wet weights of aliquots obtained from the homogenized lungs and using the following formula

\[
LW_t = M_{tw} - (M_{tw} \times M_{sw}/M_{sw})
\]

with \(LW_t\) being the total lung water, \(M_{tw}\) as the mass of the total of the wet right or left lung, \(M_{sw}\) as the mass of homogenized wet aliquot of this lung, and \(M_{sw}\) as the mass of the same sample after drying.

**Statistics.** All data are presented as means ± SE. Comparisons of variables among baseline and experimental intervals and comparisons between experimental and control groups were made using a repeated measures ANOVA, with Scheffe's exact t-test as a post hoc test. Differences were considered significant at \(P < 0.05\).

**RESULTS**

Pulmonary gas exchange deteriorated from baseline throughout the 4-h period of HCl treatment. Although \(P_{aCO_2}\) was stable, \(P_{aO_2}/FIO_2\) decreased from 254 to 187 mmHg. In NaCl-treated sheep and controls, pulmonary gas exchange remained constant over the entire 4-h observation period (Table 1).

**Pulmonary and systemic hemodynamics.** At baseline, animals had normal pulmonary and systemic hemodynamics, as shown in Table 1. In the control sheep, pulmonary and systemic hemodynamics did not change during the observation period. During the course of HCl or NaCl treatment, some hemodynamic variables changed compared with baseline and controls. The mean Ppa increased from 16.0 to 18.3 (at 2 h) and 18.8 mmHg (at 4 h) in HCl-treated animals. Ppa increased in NaCl-treated animals as well but without statistical significance. Ppw slightly increased over time in both groups, but this increase reached no statistical significance. Pcv increased in both animal groups during treatment, but a statistically significant level was reached only in the NaCl group. The systemic hemodynamic variables, including Pao, HR, QT, and SVR were constant in both treatment groups over the entire observation time. PVR in the whole lungs increased in animals treated with HCl but remained unchanged after NaCl. PVR in the left, treated lungs decreased after HCl and increased after NaCl. In the right, untreated lungs, PVR increased after HCl but decreased after NaCl (Fig. 1).

EVLW measurements in vivo revealed increasing values over time for both treatment groups but no changes in the control group. At baseline, EVLW was 8 ml/kg body wt. In the HCl treatment group, EVLW was 14 and 16 ml/kg after 2 and 4 h, respectively. EVLW was significantly higher after 2 and 4 h in the HCl-treated group compared with the baseline measurement and measurements from the control group without any treatment. In animals treated with NaCl, EVLW increased from 8 ml/kg to over 10–15 ml/kg and became significantly higher at the 4-h measurement point compared with baseline and the control group (Table 2). ITBV did not change during HCl treatment but increased from 22 to 24 ml/kg during NaCl treatment. This change was not significant. REDV showed a
Table 1. Hemodynamic and pulmonary gas exchange during the course of HCl or NaCl treatment and in control sheep without treatment

<table>
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<th>Baseline</th>
<th>HCl Treatment</th>
<th>NaCl Treatment</th>
<th>Control</th>
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<tr>
<td></td>
<td>2 h</td>
<td>4 h</td>
<td>2 h</td>
<td>4 h</td>
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<tr>
<td>No. of animals</td>
<td>28</td>
<td>8</td>
<td>4</td>
<td>8</td>
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<tr>
<td>Mean Ppa, mmHg</td>
<td>16.0 ± 0.9</td>
<td>18.3 ± 0.9†</td>
<td>18.8 ± 1.1†</td>
<td>17.7 ± 1.5</td>
</tr>
<tr>
<td>Mean Ppw, mmHg</td>
<td>8.2 ± 0.9</td>
<td>8.2 ± 1.1</td>
<td>8.7 ± 1.4</td>
<td>10.3 ± 1.3</td>
</tr>
<tr>
<td>Mean Pcv, mmHg</td>
<td>6.8 ± 0.8</td>
<td>8.3 ± 1.0</td>
<td>8.0 ± 1.1</td>
<td>9.0 ± 1.0†</td>
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<tr>
<td>Mean Pao, mmHg</td>
<td>107 ± 4</td>
<td>100 ± 5</td>
<td>119 ± 8</td>
<td>108 ± 6</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>111 ± 6</td>
<td>110 ± 5</td>
<td>119 ± 8</td>
<td>103 ± 24</td>
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<tr>
<td>Qv/body surface area</td>
<td>3.85 ± 0.09</td>
<td>4.53 ± 0.08</td>
<td>4.16 ± 0.12</td>
<td>4.44 ± 0.04</td>
</tr>
<tr>
<td>PVR, dyn·s·cm⁻¹⁻¹</td>
<td>133 ± 12</td>
<td>138 ± 16</td>
<td>154 ± 13†</td>
<td>128 ± 21</td>
</tr>
<tr>
<td>SVR, dyn·s·cm⁻¹⁻¹</td>
<td>1,493 ± 112</td>
<td>1,244 ± 159</td>
<td>1,249 ± 149</td>
<td>1,646 ± 261</td>
</tr>
<tr>
<td>PacO₂, Torr</td>
<td>35.9 ± 0.2</td>
<td>37.2 ± 0.3</td>
<td>36.6 ± 0.2</td>
<td>33.9 ± 0.4</td>
</tr>
<tr>
<td>PaO₂/FIO₂</td>
<td>254 ± 14</td>
<td>197 ± 11†</td>
<td>187 ± 13†</td>
<td>266 ± 16</td>
</tr>
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</table>

Values are means ± SE. Ppa, pulmonary artery pressure; Ppw, pulmonary-arterial wedge pressure; Pcv, central venous pressure; Pao, aortic pressure; HR, heart rate; Qv, cardiac output; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; PacO₂, arterial CO₂ pressure; PaO₂, arterial O₂ pressure. *Significantly different compared with baseline (P < 0.05); †significantly different compared with control group (P < 0.05).

Similar course; it did not change during HCl treatment but increased slightly during NaCl treatment. In the control sheep, no changes in ITBV and REDV were found during the observation period.

Pulmonary blood flow distribution to the right lung was 66%, compared with 34% of the total blood flowing to the left lung at baseline. During HCl or NaCl treatment this pattern changed differently in both treatment groups. HCl treatment shifted 6% of the total blood flow from the untreated right to the injured left lung. NaCl treatment shifted 5% of the total blood flow from the treated left to the untreated right lung (Fig. 1, Table 3). In the controls, pulmonary blood flow distribution did not change.

Presence and distribution of lung injury. Macroscopic evaluation of lungs after HCl or NaCl treatment revealed severe, unilateral lung injury due to HCl application but no signs of tissue damage after NaCl application (Fig. 2, A–C). These findings were confirmed by histological examinations of representative lung biopsies (Fig. 2, D, E). Biopsies obtained after 2 or 4 h of HCl treatment revealed normal lung tissue structures at all time points in the right lung but morphological changes in the left lungs. These changes included fibrin depositions after 2 h, neutrophil invasion after 4 h, and increasing interstitial edema from 2 to 4 h. After NaCl inhalation, no morphological indices of tissue injury or inflammation were found; however, some signs of interstitial edema were present.

Presence and distribution of lung edema. Magnetic resonance imaging and computer tomography performed on lung explants after 2 and 4 h of HCl or NaCl treatment demonstrated equivalent unilateral edema of the left lung in both treatment groups. The distribution of lung edema in both treatment groups, as analyzed on proton-density weighted axial magnetic resonance images, was nearly homogeneous and increased over time (Fig. 3). There were no predominant areas of edema location, e.g., in central or dependent lung structures. Instead, edema was distributed over the whole lung, accumulating close to bronchial and vascular structures. This observation was confirmed by high-resolution computer tomography (Fig. 4). Gravimetric evaluation of total lung water based on tissue dry:wet weights revealed equivalent, increased total lung water in the left lungs after HCl and NaCl treat-


Table 2. Extravascular lung water, intrathoracic blood volume, and right ventricular end diastolic volume during the course of HCl or NaCl treatment and in control sheep

<table>
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<th>Baseline</th>
<th>HCl Treatment</th>
<th>NaCl Treatment</th>
<th>Control</th>
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<tr>
<td></td>
<td>2 h</td>
<td>4 h</td>
<td>2 h</td>
<td>4 h</td>
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<tr>
<td>No. of animals</td>
<td>28</td>
<td>8</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>EVLW, ml/kg</td>
<td>8.1 ± 0.6</td>
<td>14.2 ± 0.7†‡</td>
<td>16.1 ± 1.4†‡</td>
<td>9.8 ± 1.6</td>
</tr>
<tr>
<td>ITBV, ml/kg</td>
<td>21.0 ± 2.4</td>
<td>20.0 ± 3.4</td>
<td>19.6 ± 0.2</td>
<td>22.3 ± 2.8</td>
</tr>
<tr>
<td>REDV, ml</td>
<td>163 ± 23</td>
<td>171 ± 26</td>
<td>149 ± 18</td>
<td>183 ± 35</td>
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</tbody>
</table>

Values are means ± SE. EVLW, extravascular lung water; ITBV, intrathoracic blood volume; REDV, right ventricular end-diastolic volume. *Significantly different compared with baseline (P < 0.05); †significantly different compared with the control group (P < 0.05).

ment but no changes in the right lungs of treated animals and right and left lungs of untreated animals compared with baseline (Table 4).

**DISCUSSION**

The use of aerosolized saline as a treatment to achieve the same degree of lung edema as with aerosolized HCl results in data that can compare the effects of equivalent degrees of edema, with or without tissue injury, on gas exchange, hemodynamics, and pulmonary blood flow distribution. The most important finding in our study is that decreased oxygenation in the acid-injured lungs is related to a greater distribution of blood flow to the injured lungs. This is in contrast to the saline-treated lungs, which had equivalent degrees of edema from saline aerosolization but maintained oxygenation that was related to a shift of pulmonary blood flow away from the saline aerosolized lung. Our data support the view that different types of lung edema have distinct impacts on pulmonary gas exchange, hemodynamics, and pulmonary blood flow distribution.

Distinct changes of pulmonary blood flow distribution after HCl- or NaCl-induced lung edema in our study suggest that hypoxic pulmonary vasoconstriction may have been differently affected in the two types of equivalent lung edema, one with and the other without tissue injury. Whereas pulmonary blood flow was diverted from the better ventilated right lung to the HCl-aerosolized and -injured left lung, blood flow was distributed away from the saline-aerosolized left lung to the untreated right lung. Our finding that pulmonary blood flow to the HCl-injured lung increases is consistent with some reports and inconsistent with others in the literature. Consistent with our finding is the observation of Nieman et al. (28) that blood flow to smoke-exposed lungs increased gradually and became significantly higher than that to the contralateral normal lung after 2 h of smoke inhalation. Inconsistent is the observation by Prien et al. (29). However, they also reported that poor perfusion of the injured lung makes it difficult to detect lung edema using thermal-dye technique. One possible explanation for these inconsistencies comes from Takeda et al. (32), who found enhanced blood flow to HCl-injured lungs in dogs only during additional hypoxia. Mann et al. (22) also used fluorescently labeled microspheres to study the effects of unilateral alveolar hypoxia on pulmonary blood flow distribution. They found that hypoxic vasoconstriction alters the regional distribution of flow in the hypoxic, but not in the hyperoxic, lung (22). In our study, areas of hypoxia may have overlapped areas of lung edema and tissue injury, thus directing blood flow into the left, HCl-treated lungs. Finally, hypoxic pulmonary vasoconstriction seemed to be inhibited in acute lung injury caused by aerosolized HCl but remained intact after saline aerosolization. Such inhibition of hypoxic pulmonary vasoconstriction has been reported for several models of acute lung injury (7).

Lung injury caused by HCl increased pulmonary blood flow in injured lung areas, but NaCl treatment increased blood flow in better-ventilated lung areas. Whereas data from the latter treatment group are in line with the concept of hypoxic pulmonary vasoconstriction, by which blood flow is diverted from hypoxic to better-ventilated lung areas (6, 23), our data from the former group suggest inhibition of hypoxia-mediated blood flow regulation. However, blood flow redistribution after NaCl and HCl treatment was only moderate in the two treatment groups of our study and gas

Table 3. Pulmonary blood flow to the right and left lungs in % $Q_T$ and the corresponding PVR during the course of HCl or NaCl treatment and in control sheep

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<td></td>
<td>2 h</td>
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<td>2 h</td>
<td>4 h</td>
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<tr>
<td>No. of animals</td>
<td>28</td>
<td>8</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Blood flow, right lung</td>
<td>66.3 ± 2.1</td>
<td>64.8 ± 2.8</td>
<td>60.5 ± 2.5†‡</td>
<td>68.2 ± 3.4</td>
</tr>
<tr>
<td>PVR, right lung</td>
<td>214 ± 3.9</td>
<td>216 ± 6.2</td>
<td>254 ± 7.5†</td>
<td>188 ± 11.0†‡</td>
</tr>
<tr>
<td>Blood flow, left lung</td>
<td>33.7 ± 1.7</td>
<td>35.2 ± 1.9‡</td>
<td>39.5 ± 2.2†‡</td>
<td>31.8 ± 2.0‡</td>
</tr>
<tr>
<td>PVR, left lung</td>
<td>420 ± 7.6</td>
<td>403 ± 11.9‡</td>
<td>390 ± 11.5†‡</td>
<td>402 ± 19.8‡</td>
</tr>
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</table>

Values are means ± SE. *Significantly different compared with baseline (P < 0.05); †significantly different compared with the control group (P < 0.05); ‡significantly different compared with contralateral side (P < 0.05).
exchange alteration after HCl decreased by only 30% compared with baseline. One explanation for the only moderate changes of blood flow distribution in both treatment groups and the moderate alteration of pulmonary gas exchange after acid-induced lung injury is that gas exchange at baseline was not optimal. All sheep started with PaO$_2$/FIO$_2$ values that were much lower than normal. The reason for this abnormality is that we did the study with sheep in supine position.

This position was required to perform the necessary surgery, but did not allow optimal gas exchange at baseline due to nonphysiological body position of the animal. Another explanation for the only moderate changes in our study is that positive pressure ventilation using positive end-expiratory pressure influences pulmonary blood flow distribution and gas exchange. By increasing lung volume in acute lung injury, positive end-expiratory pressure may recruit terminal air

Fig. 2. Morphology of sheep lungs after 4 h of unilateral HCl or NaCl treatment. A: surface of the left lung (top) shows severe tissue injury after HCl treatment, whereas the right, untreated lung appears normal (bottom). B: lung section after 4 h of HCl treatment. C: lung section after 4 h of NaCl treatment. D: representative photomicrograph of the left lung after HCl treatment. Note that HCl induces interstitial and alveolar edema, neutrophil infiltrates, and fibrin deposits. Original magnification is ×400. E: representative photomicrograph of the left lung after NaCl treatment. Note that NaCl induces neither inflammation nor tissue injury. Original magnification is ×400.

Fig. 3. Magnetic resonance images of a lung explant after 4 h of unilateral HCl treatment. The proton-density-weighted axial magnetic resonance image was calculated from a multispin-echo pulse sequence (TR = 5,000 ms, TE = 20, 35, 50, and 65 ms). The density of the left, HCl-treated lung (L) is very homogeneous and corresponds to the density of the water-filled reference tube, located at the bottom (gray circle). The right lung (R) was untreated and showed a normal lung tissue density.
spaces in the involved regions but may also distend noninvolved regions, thus increasing EVLW and worsening gas exchange (14). Positive end-expiratory pressure recruits additional lung units for gas exchange but may redistribute pulmonary blood flow to injured lung areas (13) or, as reported recently, to dependent lung regions in supine, but not in prone, anesthetized and mechanically ventilated sheep (33). A third explanation for only moderate blood flow redistribution and alteration of pulmonary gas exchange due to HCl treatment may be that the injury, though severe, was not extensive enough to abolish the entire gas exchange capacity of the treated lung. In analogy to our findings of blood flow and gas exchange alteration caused by HCl, Modelska and co-workers (27) reported recently that alveolar epithelial fluid transport capacity continued at ~50% after HCl-induced lung injury in rabbits. Preservation of some gas exchange capacity in the injured lung, together with the capacity in the untreated lung, may allow for a steady state with only moderate functional loss after HCl treatment in both studies. During NaCl treatment, pulmonary gas exchange remains unchanged, although there are significant pulmonary edema. Such findings indicate first that pulmonary edema alone does not cause pulmonary gas exchange deviation. Second, lungs have profound functional capacities to compensate for tissue injury and edema.

In addition to hypoxic pulmonary vasoconstriction, alveolar edema reabsorption may have been differently affected in the two types of lung edema in our study. The alveolar epithelium plays a critical role in alveolar edema reabsorption in the lung, and active ion transport across the alveolar epithelial barrier is the primary mechanism for clearance of edema fluid from the air spaces (25, 26). Alveolar type II epithelial cells actively transport sodium (24). Although we did not directly measure alveolar fluid transport, our hemodynamic and morphological data suggest that fluid transport mechanisms were intact after NaCl-induced edema, but damaged after HCl-induced lung edema. Pulmonary hemodynamics changed due to aerosolized HCl as well as NaCl, and these changes could both be attributed to preload indicators (20). However, the set of preload indicators that changes differs between the two treatment regimens. Whereas Ppa and PVR increased after HCl treatment, NaCl treatment increased Ppa, Pcv, REDV, and ITBV. The changes after HCl treatment could be attributed primarily to vasoconstriction, and changes after NaCl treatment could be attribute to additional volume that enters the circulation through alveoli, thus supporting the view that edema reabsorption in the saline-treated group could, conceivably, have been upregulated.

The time course of the morphological changes observed in our study is consistent with the findings of Kennedy et al. (16), who reported neutrophil accumulation in the interstitial lung space 4 h after HCl instillation in rats. Bachofen and co-workers reported recently that barrier leaks play a role in both hydrostatic and permeability lung edema (2). The differences between both types of edema may reflect the type and extent of injury to the alveolar epithelial barrier and the associated inflammatory reaction. In our case, HCl application induced tissue injury and inflammation indicated by neutrophil invasion; in contrast, NaCl did not. Acid aspiration-induced lung injury in rabbits was also mediated by neutrophils, which were primarily recruited by IL-8 (11).

The protocol used in this study to induce unilateral lung edema is unique. In contrast to all other studies of HCl-induced lung injury, we used aerosolization instead of an instillation technique for the delivery of HCl into the lung. We expected more homogeneous

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**Table 4. Total lung water development due to HCl or NaCl treatment and in the control sheep**

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<td></td>
<td>Baseline</td>
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<td>4 h</td>
</tr>
<tr>
<td>No. of animals</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Right lung</td>
<td>698 ± 24</td>
<td>712 ± 56</td>
<td>704 ± 43</td>
</tr>
<tr>
<td>Left lung</td>
<td>701 ± 35</td>
<td>801 ± 76†‡</td>
<td>868 ± 53†‡</td>
</tr>
</tbody>
</table>

Values are means ± SE. Total lung water was determined based on tissue dry-to-wet ratio weights and using the equation in Computed imaging, morphological analysis, and gravimetric measurements. *Significantly different compared with baseline (P < 0.05); †significantly different compared with the control group (P < 0.05); ‡significantly different compared with contralateral side (P < 0.05).
lung damage using aerosolized HCl compared with instilled HCl. Indeed, magnetic resonance imaging and computer tomography of the treated lungs revealed very homogeneous lung edema that was restricted to the left lung. Within the left, damaged lungs, we did not detect any predominant regions of lung edema formation after either HCl or NaCl application. Instead, lung water accumulated close to bronchial and vascular structures throughout the entire left lung after HCl or NaCl treatment. This observation indicates that the edema induced by the aerosolization technique is uniform and does not follow gravitational forces, i.e., is predominantly located in the dependent lung. This is inconsistent with predictions from the gravitationally based lung zone model but is in line with recent data regarding pulmonary blood flow distribution and edema formation reported by Hlastala and co-workers (15), and by Bachofen et al. (1). Further evidence for unilateral lung edema due to HCl and NaCl treatment came from gravimetric determination of total lung water in our study. Our wet-to-dry lung weight ratios for normal and edematous lungs are comparable with data reported in the literature (21, 27).

Lung edema induced with aerosolized HCl or NaCl and the lung tissue injury associated with HCl is strictly limited to the left lung in our study. Others reported crosstalk between the injured and healthy lungs, with contralateral lung damage as a secondary event caused by a systemic inflammatory reaction (10, 17, 21, 30). Such crosstalk did not occur in the 4-h time frame of our study. Kudoh and co-workers (19) reported that instillation of HCl in rabbits causes a dramatic increase in the alveolar epithelial permeability of the acid-instilled lung, but the permeability of the alveolar epithelium of the contralateral lung remains normal. However, they found unilateral acid instillation causes an increase in the permeability of the endothelium of both lungs. This contrasts with our findings that lung injury caused by aerosolized HCl in sheep is restricted to the acid-treated lung. It may well be that endothelial permeability in the contralateral lung did change in our study, but it was not detectable using imaging techniques and tissue wet/dry weights. Perhaps fluid transport capacities of the contralateral lung exceeded any signs for permeability changes in the experimental setting of our study.

In summary, the results of this experimental study in sheep indicate that equivalent and homogeneous lung edema can be induced with aerosolized HCl or NaCl. In contrast to aerosolized saline, aerosolized acid also induces tissue injury and worsens pulmonary gas exchange. The distribution of pulmonary blood flow changes specifically in the two types of lung edema and thus has a major impact on the gas exchange alteration common for acute lung injury. Alveolar epithelial transport may be maintained or even upregulated in portions of saline-treated lungs, thus accounting for why lung edema was not even worse in acid injury.

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REFERENCES


