Partial Liquid Ventilation Reduces Fluid Filtration of Isolated Rabbit Lungs with Acute Hydrochloric Acid–induced Edema

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Background: Hydrochloric acid aspiration increases pulmonary microvascular permeability. The authors tested the hypothesis that partial liquid ventilation has a beneficial effect on filtration coefficients in acute acid-induced lung injury.

Methods: Isolated blood-perfused rabbit lungs were assigned randomly to one of four groups. Group 1 (n = 6) served as a control group without edema. In group 2 (n = 6), group 3 (n = 6), and group 4 (n = 6), pulmonary edema was induced by intratracheal instillation of hydrochloric acid (0.1 N, 2 ml/kg body weight). Filtration coefficients were determined 30 min after this injury (by measuring loss of perfusate after increase of left atrial pressure). Group 2 lungs were gas ventilated, and group 3 lungs received partial liquid ventilation (15 ml perfluorocarbon/kg body weight). In group 4 lungs, the authors studied the immediate effects of bronchial perfluorocarbon instillation on ongoing filtration.

Results: Intratracheal instillation of hydrochloric acid markedly increased filtration coefficients when compared with noninjured control lungs. Partial liquid ventilation reduced filtration coefficients of the injured lungs (to 0.9 ± 0.3 ml · min⁻¹ · mmHg⁻¹ · 100 g⁻¹ wet lung weight, P < 0.01). Neither pulmonary artery nor capillary pressures (determined by simultaneous occlusion of inflow and outflow of the pulmonary circulation) were changed by hydrochloric acid instillation or by partial liquid ventilation. During ongoing filtration, bronchial perfluorocarbon instillation (5 ml/kg body weight) immediately reduced the amount of filtered fluid by approximately 50% (P = 0.027).

Conclusions: In the acute phase after acid injury, partial liquid ventilation reduced pathologic fluid filtration. This effect started immediately after bronchial perfluorocarbon instillation and was not associated with changes in mean pulmonary artery, capillary, or airway pressures. The authors suggest that in the early phase of acid injury, reduction of fluid filtration contributes to the beneficial effects of partial liquid ventilation on gas exchange and lung mechanics.

ASPIRATION of acid gastric contents is recognized as a major cause of morbidity and mortality in clinical anesthesia. Aspirated hydrochloric acid increases pulmonary microvascular permeability with subsequent influx of plasma-derived, protein-rich edema fluid into the alveolar space. during the acute respiratory failure after acid aspiration, partial liquid ventilation has been shown to improve gas exchange and lung mechanics.

Part of these beneficial effects of partial liquid ventilation may result from a reduction of the acid-induced increase in fluid filtration. According to the Starling equation, fluid filtration across the pulmonary capillaries depends on the balances of hydrostatic and colloidal osmotic pressures across the pulmonary capillary membrane, as well as on its protein reflectance coefficient and the area of perfused capillary bed. It is possible that partial liquid ventilation influences one or more of these variables in permeability edema. For example, bronchial instillation of perfluorocarbons with a higher density than blood may alter the balance of regional hydrostatic pressures in favor of the interstitial pressure. Furthermore, intrapulmonary blood flow may be redistributed from dependent to nondependent lung regions, as shown previously for normal lungs in vivo as well as in in vivo experiments. Such redistribution effects may alter the area of perfused capillary bed and might be of relevance in situations in which permeability edema predominantly affects dependent lung regions, particularly in cases of acid aspiration. In addition, because of their physicochemical characteristics, perfluorocarbons may lavage hydrochloric acid and edema fluid from the alveolar membrane. Based on these considerations, we tested the hypothesis that partial liquid ventilation influences filtration coefficients after acid-induced permeability edema in isolated rabbit lungs.

Materials and Methods

Isolated Lung Preparation, Perfusion, and Ventilation

With approval of the Institutional Review Board for the care of animal subjects (Bezirksregierung, Düsseldorf, Germany) and in accordance with the guidelines of the National Institutes of Health (Bethesda, MD), we anesthetized New Zealand white rabbits (n = 24; body weight between 2.2 and 3.3 kg) of either sex with 30 mg/kg pentobarbital sodium intravenously. After tracheostomy, the animals’ lungs were ventilated with air at a tidal volume of 10 ml/kg body weight and at a rate of 30 breaths/min (Harvard Respirator, model 683; Harvard Apparatus, South Natick, MA). Heparin (1,000 IU/kg body weight) was injected intravenously 3 min before the rabbits were exsanguinated rapidly via a carotid artery. After midline sternotomy, the trachea, heart, and lungs were removed en bloc and perfusion cannulas were tied into the pulmonary artery and the left atrium via the left ventricle. Care was taken to avoid pulmonary

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air embolism during preparation. Only the rabbits' autologous blood (hematocrit, 32-36%) was used to fill the extracorporeal circulation circuit, and perfusion was instituted at a constant flow of 100 ml/min (calibrated roller pump, model 102000; Stöckert Inst., Munich, Germany). Perfusate temperature was maintained at 37°C with a water bath, and pH was maintained between 7.5 and 7.5 by means of addition of sodium bicarbonate, if necessary. After the lungs were removed from the chest, they were inflated for a short time with positive pressures up to 10 cm H2O until any visible atelectases had resolved. Thereafter, they were ventilated with 5% CO2 in air at a tidal volume of 10 ml/kg body weight, a respiratory rate of 30 breaths/min, and an inspiration/expiration ratio of 1:1. A positive end-expiratory pressure of 2 cm H2O was maintained by means of a water seal in the expiratory limb. Premixed gas (5% CO2 in air at a tidal volume of 10 ml/kg body weight, a respiratory rate of 30 breaths/min, and an inspiration/expiration ratio of 1:1. A positive end-expiratory pressure of 2 cm H2O was maintained by means of a water seal in the expiratory limb. Premixed gas (5% CO2 in air) was supplied by Messer Griesheim GmbH (Duisburg, Germany).

Measurements

Pulmonary arterial, left atrial, and airway pressures were measured continuously with electromanometers (P23 ID, Statham; Gould, Oxnard, CA). Total lung weight was measured with use of a force transducer (model FT 03; Grass Instruments, Quincy, MA). Per fusate oxygen and carbon dioxide tensions, pH (CMS 3MK2; Radiometer, Copenhagen, Denmark), plasma oncotic pressure (Onkometer BMT 921; Dr. Karl Thomae GmbH, Biberach an der Riss, Germany) and hematocrit (Haematokrit-Zent rifuge, Hettich, Germany) were obtained at the beginning and the end of the experiments.

Filtration Coefficients

As indices of transcapillary fluid filtration, we determined changes in lung weight as well as perfusate volume, which is not influenced by potential evaporative loss of perfluorocarbon via the bronchial space. For this purpose, we measured blood reservoir volume of the perfusion circuit with an ultrasound reflection device (5 MHz piezoelectric crystal) designed to determine the height of the blood column in the reservoir. This device allowed measurement of volume changes with an accuracy of 0.1 ml. During conditions of constant intrapulmonary blood volume and absent extrapulmonary loss of perfusate from the circuit, any decrease in reservoir volume reflects transcapillary fluid filtration. Capillary filtration coefficients were obtained from the slopes of changes in reservoir volume after increase of left atrial pressure. Capillary pressures were determined before and during reservoir increase by simultaneous occlusion of inflow and outflow tract of the pulmonary vasculature.10 The increase in left atrial pressure was maintained for 7 min, and the tangent to the slow phase of the reservoir volume curve between the second and seventh minute was used for calculating filtration coefficients. These coefficients were related to wet lung weight and expressed in ml · min⁻¹ · mmHg⁻¹ · 100 g⁻¹ wet lung weight. Wet lung weight was assumed to be 0.24% of total body weight of the animal, which has been proposed for estimation of wet lung weight of New Zealand white rabbits.11,12

Experiments

The perfused lungs were observed initially for 20 min to establish an isogravimetric state, with pulmonary arterial pressures between 15 and 30 cm H2O and a left atrial pressure adjusted at 4 cm H2O. After this stabilization period, the lungs were assigned randomly to one of four groups, and baseline filtration coefficients were determined. Lungs of group 1 (n = 6) served as control lungs without edema. In the lungs of group 2 (n = 6), group 3 (n = 6), and group 4 (n = 6), pulmonary edema was induced by intratracheal instillation of hydrochloric acid (0.1 N, 2 ml/kg body weight). Filtration coefficients were determined again 30 min after this injury. The lungs of group 2 were gas ventilated, and the lungs of group 3 received partial liquid ventilation. For this purpose, prewarmed (37°C) perfluorocarbon (15 ml/kg body weight) was instilled via the trachea over a period of 30 s with continued ventilation. Filtration coefficients were determined 30 min after initiation of partial liquid ventilation. In the lungs of group 4 (n = 6), we studied the immediate effects of perfluorocarbon on ongoing filtration. For this purpose, the lungs were exposed 30 min after the acid injury to a continuous hydrostatic challenge. Capillary pressure was increased by 20 cm H2O by appropriate increase of left atrial pressure. During ongoing filtration, the lungs repeatedly received 5 ml perfluorocarbon/kg body weight in intervals of 5 min up to a total dose of 15 ml/kg body weight.

The perfluorocarbon compound used (PF-5080; 3M, Neuss, Germany) had the following characteristics: chemical structure C8F18, specific gravity 1.77 g/ml, surface tension 15 dynes/cm, vapor pressure 44 mmHg (5.9 kPa) at 25°C, and dynamic viscosity 1.4 mPa · s.

Statistical Analysis

Data are presented as mean ± SD. We tested the following a priori null hypotheses: (1) Acid instillation has no effect on filtration coefficients, pulmonary artery and capillary pressures when compared with normal lungs. (2) In acid-injured lungs, partial liquid ventilation has no effect on filtration coefficients when compared with gas-ventilated acid-injured lungs. (3) During ongoing filtration (increased left atrial pressure), instillation of perfluorocarbon does not reduce the amount of filtered fluid. We used the Friedman test to analyze differences in variables within groups 1, 2, and 3. To test differences in variables between these groups, the Mann–Whitney U test was applied. In group 4, differences between gas ventilation and partial liquid ventilation were analyzed.
Partial Liquid Ventilation in Hydrochloric Acid Edema

Results

Intratracheal instillation of hydrochloric acid markedly increased filtration coefficients when compared with noninjured control lungs (2.3 ± 0.7 /min · mmHg · 100 g wet weight) without changing pulmonary artery, capillary, or airway pressures (table 1). At the same time, capillary filtration coefficients were reduced significantly (to 0.9 ± 0.3 /min · mmHg · 100 g wet weight, P = 0.022). However, they did not return to baseline values before hydrochloric acid instillation (fig. 1). This effect on filtration was observed immediately after perfluorocarbon had been instilled during ongoing filtration (increase in capillary pressure by 20 cm H2O, 1). The amount of filtered fluid per minute was reduced to approximately 50% with 5 ml perfluorocarbon/kg body weight (P = 0.027). This immediate effect on ongoing filtration was not further enhanced in a relevant fashion by additional instillations of perfluorocarbon (+5 ml/kg body weight). Ongoing filtration was not stopped, even with 15 ml perfluorocarbon/kg body weight.

Discussion

Hydrochloric acid causes a significant injury to the alveolo-capillary membrane with subsequent pulmonary edema.1–4 The resulting impairment in lung function within the first hour after injury is associated with direct chemical effects of the hydrochloric acid on the alveolar and capillary membranes, whereas changes in the second phase (after 6 h) are attributed mainly to inflammatory responses.13 In our study, we focused on the early phase after the injury and studied the effects of partial liquid ventilation on filtration.

The experiments were performed in isolated lungs because they allowed us to determine and control many variables of pulmonary filtration, especially capillary pressure, as one crucial determinant of lung fluid balance.14 Acid-induced injury resulted in a marked increase in pulmonary fluid filtration in accordance with previous observations in rabbits,1,2 dogs,3 and rats.4 The amount of filtered fluid could be measured directly as loss of perfusate and increase in lung weight when vascular volume was constant. Furthermore, isolated lungs have no lymph flow draining the pulmonary interstitial space into systemic veins. While in vivo increased microvascular filtration is compensated over a large range by an increase in pulmonary lymph flow, in isolated lungs, any filtration immediately increases lung weight. Therefore, the effects of partial liquid ventilation on transcapillary fluid transport could be studied independently of lymph flow. In addition, isolated lungs are free from neural and hormonal influences that may interfere with effects of partial liquid ventilation in vivo. These specific study conditions have to be considered when our observations from isolated lungs are extrapolated to the in vivo situation.

Interpretation of the Results

In noninjured isolated rabbit lungs, partial liquid ventilation had no effects on capillary filtration,15 but we found significant effects in acid-injured lungs. In the injured lungs, filtration coefficients were reduced markedly after 30 min of partial liquid ventilation without, however, returning to baseline filtration values before induction of injury. In addition, we found immediate effects on ongoing filtration measured during a sustained increase in capillary pressure. The amount of filtered...
Hydrochloric acid injury was induced following baseline determinations (time 0 min). Partial liquid ventilation was instituted 30 min after induction of hydrochloric acid injury (time 30 min). There were no significant changes over time within the groups or significant differences between the three groups at corresponding times. Thus, neither hydrochloric acid instillation nor subsequent perfluorocarbon instillation affected mean pulmonary arterial or capillary pressures.

Fluid decreased by approximately 50% after instillation of 5 ml perfluorocarbon/kg body weight. This volume represents approximately one third of the residual capacity of New Zealand white rabbits (about 15 ml/kg body weight). Further increments of perfluorocarbon had no relevant additional effect on immediate fluid filtration.

The underlying mechanisms for our observations may be explained by different effects. In general, capillary filtration depends on the balance of hydrostatic and oncotic forces across the microvascular barrier and its reflection coefficient and hydraulic conductivity, as well as its surface area. Instillation of fluids, especially of those with a high density, such as perfluorocarbons, might affect interstitial pressures and alter the balance of hydrostatic forces across the capillary membrane. However, neither mean pulmonary artery nor mean capillary pressures of the acid-injured lungs were changed with partial liquid ventilation, similar to the results obtained from noninjured isolated rabbits lungs. Also, plasma oncotic pressure of the perfusate was not changed during our experiments. We did not measure the oncotic pressure of the interstitial space; however, we are not aware of any reason why interstitial oncotic pressure should have decreased during partial liquid ventilation and thus could be responsible for the observed reduction in fluid filtration in the injured lungs. Therefore, changes in hydrostatic or oncotic pressure gradients are unlikely to explain the observed effects alone. Changes in reflection coefficients and hydraulic conductivity are likely but limited to the alveolar membrane. Probably, a thin film of perfluorocarbon at the alveolar membrane acts as a water-rejecting coat throughout the lung and prevents or diminishes the occurrence of alveolar edema because water is immiscible with perfluorocarbons. However, such a potential fluid barrier at the alveolar membrane does not prevent filtration into the interstitial space until its capacity is reached.

An alternative explanation may relate to effects on intrapulmonary blood flow distribution after bronchial instillation of perfluorocarbons. We have shown recently that filling the residual functional capacity of isolated rabbit lungs redistributed blood flow from dependent to nondependent lung regions. If the injury primarily affects dependent lung regions, the vascular surface area with increased permeability might be reduced by redistribution. That is, partial liquid ventilation possibly shifts blood perfusion away from regions with increased permeability. However, this hypothesis must be proved by further studies. In this context, it must be considered that many other factors also may influence intrapulmonary blood flow distribution, such as alveolar oxygen tension, positioning, or ventilation with positive end-expiratory pressure.

### Table 1. Pulmonary Arterial and Capillary Pressures

<table>
<thead>
<tr>
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<th>Group 1: Gas Ventilation (n = 6)</th>
<th>Group 2: Gas Ventilation (n = 6)</th>
<th>Group 3: Partial Liquid Ventilation (n = 6)</th>
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<tbody>
<tr>
<td>Time</td>
<td>Pulmonary arterial pressure (cm H₂O)</td>
<td>Capillary pressure (cm H₂O)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 min 30 min 60 min</td>
<td>0 min 30 min 60 min</td>
<td>0 min 30 min 60 min</td>
</tr>
<tr>
<td>Pulmonary arterial</td>
<td>17.7 ± 3.1 17.5 ± 3.1 17.8 ± 2.9</td>
<td>17.8 ± 2.7 18.3 ± 3.0 18.7 ± 3.9</td>
<td>17.3 ± 2.6 18.0 ± 2.7 18.8 ± 3.1</td>
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<tr>
<td>Capillary pressure</td>
<td>7.2 ± 1.2 7.0 ± 1.4 7.5 ± 1.5</td>
<td>6.8 ± 1.5 7.0 ± 1.3 7.3 ± 1.4</td>
<td>7.3 ± 1.4 7.2 ± 1.2 7.1 ± 1.5</td>
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Mean ± SD. Data from 18 isolated blood-perfused rabbit lungs; pulmonary arterial pressure at a flow rate of 100 ml/min and a pulmonary venous pressure of 4 cm H₂O; capillary pressure determined by simultaneous occlusion of inflow and outflow of the pulmonary vasculature (double occlusion technique). Hydrochloric acid injury was induced following baseline determinations (time 0 min). Partial liquid ventilation was instituted 30 min after induction of hydrochloric acid injury (time 30 min). There were no significant changes over time within the groups or significant differences between the three groups at corresponding times. Thus, neither hydrochloric acid instillation nor subsequent perfluorocarbon instillation affected mean pulmonary arterial or capillary pressures.

![Image](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931230/)

**Fig. 2.** Effects of partial liquid ventilation on the amount of filtered fluid during a continuous hydrostatic challenge (increase in capillary pressure by 20 cm H₂O). Five minutes after the beginning of the hydrostatic challenge, increasing amounts of perfluorocarbon were instilled into the bronchial system. The amount of filtered fluid was reduced immediately to approximately 50%, with 5 ml perfluorocarbon/kg body weight. Data from 6 isolated blood perfused rabbit lungs are presented as mean ± SD. P value refers to Wilcoxon rank sum test. HCl = hydrochloric acid.
In addition, partial liquid ventilation might exert a “lavage-like” activity on hydrochloric acid or edema fluid and reduce the vicious circle associated with ongoing lung injury. Because perfluorocarbons have a higher density and do not mix with hydrochloric acid, the acid may be removed from the alveolar membrane of dependent lung regions and may be transferred to less dependent parts of the airways from which they might be removed more easily so that the physicochemical injury is limited. Such beneficial effects associated with “lavage-like” activities of perfluorocarbons have been observed in acute pulmonary edema resulting from sucrose instillation or meconium aspiration.16,17

Beneficial effects of partial liquid ventilation on pulmonary fluid filtration also have been observed in other chemical or physical injuries, such as pulmonary arterial injection of oleic acid,18 cobra venom factor,19 or mechanical alveolar overinflation.20 However, results were not consistent. In a recent study in dogs with oleic acid–induced lung injury,21 partial liquid ventilation significantly reduced pulmonary neutrophil activity, without any effects on lung water concentration or pulmonary transcapillary escape rate 5 and 21 h after the injury. Therefore, it is possible that effects of partial liquid ventilation on filtration are limited to the early phase of capillary injury (first hour), such as in our experiments, and that later effects primarily involve inflammatory responses, for example, less recruitment of activated neutrophils from extrapulmonary sites to the lung22 by chemotactic cytokines, such as interleukin 8.23

In conclusion, partial liquid ventilation with perfluorocarbons reduced filtration coefficients in hydrochloric acid–injured lungs. These effects started immediately after bronchial instillation and were not associated with changes in pulmonary artery, capillary, or airway pressures. We suggest that in the early phase of acid injury, reduction of fluid filtration contributes to the beneficial effects of partial liquid ventilation on pulmonary function.

References


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