Lung Edema Clearance: 20 Years of Progress
Selected Contribution: Mechanisms that may stimulate the resolution of alveolar edema in the transplanted human lung

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Ware, Lorraine B., Xiohui Fang, Yibing Wang, Tsutomu Sakuma, Timothy S. Hall, and Michael A. Matthay. Selected Contribution: Mechanisms that may stimulate the resolution of alveolar edema in the transplanted human lung. J Appl Physiol 93: 1869–1874, 2002. First published August 2, 2002; 10.1152/japplphysiol.00252.2002.—Pulmonary edema is common in organ donors and lung transplant recipients. Therefore, we assessed the responsiveness of human donor lungs to pharmacological agents that stimulate clearance of alveolar edema. Organ donors whose lungs were rejected for transplantation were studied. After resection, transport (4°C), and rewarming (37°C) of lungs, alveolar fluid clearance was measured with (n = 8 donors) or without (n = 23 donors) β-adrenergic stimulation. Terbutaline-stimulated clearance (10−4 M) was higher than unstimulated clearance (7.1 ± 1.3 vs. 4.8 ± 2.4%/h, P < 0.01). Second, we determined whether medications given to the organ donor were associated with the extent of pulmonary edema or the rate of alveolar fluid clearance in the harvested lung. Preharvest administration of dopamine in low to moderate doses was associated with faster alveolar fluid clearance (r = 0.62, P < 0.01). Preharvest administration of diuretics was associated with lower extravascular lung water-to-dry weight ratios. This study provides the first evidence that a β2-adrenergic agonist stimulates alveolar fluid clearance in the human donor lung. Aerosolized β2-adrenergic agonists may have therapeutic value for hastening the resolution of alveolar edema during the management of donors before resection of lungs for transplantation or in the posttransplant setting. pulmonary edema; β-agonist; alveolar epithelial fluid transport; alveolar epithelium; lung preservation

PULMONARY EDEMA IS A COMMON problem in both organ donors and lung transplant recipients. In organ donors, pulmonary edema contributes substantially to poor donor lung function, the primary reason for rejection of lungs for transplantation (23). In lung transplant recipients, pulmonary edema as a result of reperfusion injury occurs in 15–35% of lung recipients and is associated with poor outcome (39). In patients with reperfusion pulmonary edema, the ability of the alveolar epithelium to remove pulmonary edema from the alveolar space is critical to the resolution of reperfusion pulmonary edema (41). Intact alveolar epithelial transport function is also important in the resolution of pulmonary edema in patients with acute lung injury (42) and hydrostatic pulmonary edema (40). Many experimental studies have reported that β2- and dopaminergic agonists can stimulate alveolar epithelial fluid transport in the experimental setting (reviewed in Ref. 22). Despite these findings, neither β2- nor dopaminergic agonists have been studied in clinical pulmonary edema. A recent National Institutes of Health workshop emphasized the need for more studies of the potential therapeutic value of β2-adrenergic therapy for accelerating the resolution of alveolar edema (9). Other investigators have also recommended a more complete evaluation of treatments that could hasten the resolution of alveolar edema (38).

Evaluation of lung preservation regimens for lung transplantation has traditionally focused on lung endothelial function as a marker of adequate lung preservation (26). New evidence, however, indicates that alveolar epithelial function may be equally important (25). Despite the critical importance of alveolar epithelium...
lial transport function to postoperative lung graft function, the preservation of alveolar epithelial fluid transport has not been measured in studies of regimens for lung preservation. Furthermore, the alveolar epithelial fluid transport function in the lungs of critically ill organ donors has never been assessed. In the only studies to date to assess alveolar epithelial fluid transport in the excised human lung, lungs from healthy patients undergoing elective lung resections for malignancy were studied (30–32).

The overall goal of this study was to assess the responsiveness of the human donor lung to drugs that stimulate alveolar epithelial fluid transport. The first objective was to determine whether alveolar epithelial fluid transport can be stimulated by terbutaline in human lungs from brain-dead organ donors after lung harvest, cooling, and rewarming to 37°C. The second objective was to determine whether medications given to the organ donor before lung harvest have any impact on the extent of pulmonary edema or on the rate of basal or stimulated alveolar fluid clearance in the harvested lung. Finally, because pulmonary edema is common in both lung donors and lung recipients, the third objective was to determine whether there is a relationship between the rate of alveolar fluid transport and extravascular lung water.

METHODS

Identification of rejected lungs. Between September 1, 1998 and September 30, 2000, the California Transplant Donor Network identified donors whose lungs were not used for transplantation because of failure to meet the standard selection criteria (14) and whose next-of-kin had given informed consent for research. The study protocol was approved by the California Transplant Donor Network medical committee.

Protocol for lung resection. The lungs were resected en bloc by standard techniques without the use of a pulmonary preservation solution. The lungs were transported to our laboratory at 4°C after inflation to the donor’s standard tidal volume. The average time from lung resection to rewarming in the laboratory was 6–8 h. For measurement of hemoglobin for the calculation of the water-to-dry weight ratio, a blood sample was obtained from the donor at the time of lung harvest. After transport, tissue samples were obtained from the right lower lobe for gravimetric measure of the water-to-dry weight ratio. Additional lobes were used for other studies (43). Overall, lungs were studied from 31 donors. Because only one or two lobes were routinely available for measurements of alveolar fluid clearance, only one condition was studied per donor, either terbutaline-stimulated alveolar fluid clearance (8 donors) or, for comparison, unstimulated alveolar fluid clearance (23 donors). The rates of unstimulated clearance have been previously reported (43).

Measurement of the rate of alveolar fluid clearance. Net alveolar fluid clearance was measured by using our usual method but with minor modifications (28, 31, 32). After the excised lungs were placed in plastic bags with the mainstem bronchi accessible, a segmental bronchus was occluded by a 3-mm balloon tracheal tubing and inflated to 10 cmH2O with 100% O2. After lungs were rewarmed for 2 h in a 37°C water bath (31), 40–100 ml of a 37°C isosmolar solution of 5% bovine serum albumin in Ringer lactate with 8 μCi of 125I-labeled albumin were instilled into the occluded segment. The lung was reinfated to 10 cmH2O. After 1 h at 37°C, alveolar fluid was aspirated from the occluded segment. In a subgroup of lungs, a second sample of alveolar fluid was aspirated after 2 h. 125I-albumin activity was measured in the supernatants of the aspirates after centrifugation at 3,000 rpm × 10 min. The unstimulated rate of alveolar fluid clearance was measured by comparing the 125I-albumin activity of the aspirate at the end of the 1- or 2-h time period with the 125I-albumin activity of a baseline aspirate obtained 2 min after instillation (13, 28, 31, 32). In a subset of lungs (8 pairs), stimulated alveolar fluid clearance was measured by adding 10−4 M terbutaline to the instillate.

Donor clinical characteristics. The medical record of each donor was reviewed and demographic characteristics, reason(s) for lung rejection, medical history, cause of brain death, radiographic findings, hemodynamic and ventilatory parameters, culture results, and medications were recorded from the medical record. Medications known to affect the extent of pulmonary edema (diuretics) and the rate of alveolar fluid clearance [β-adrenergic agonists (Refs. 5, 30), dopamine (Refs. 2, 3), glucocorticoids (Ref. 11), and β-receptor antagonists] were analyzed. Because the infusion rate for dopamine varied and because dopamine may affect the rate of alveolar fluid transport capacity at the transcriptional level (2, 16), the cumulative dose over 24 h was calculated and classified as low (average rate of < 3 μg·kg−1·min−1), moderate (3–6 μg·kg−1·min−1), or high (>6 μg·kg−1·min−1). Low to moderate doses have dopaminergic effects and have been shown to increase alveolar fluid clearance experimentally (3, 4, 34). Therefore, the primary analysis of dopamine was done on lungs that had been exposed to low to moderate doses of dopamine.

Measurement of extravascular water-to-dry weight ratio. A segment of the right lower lobe was excised and homogenized for gravimetric measurement of the extravascular water-to-dry weight ratio by standard methods (5, 20) in lungs from 21 of the 23 donors in whom unstimulated rates of alveolar fluid clearance were measured. The extravascular water-to-dry weight ratio of normal lung is 3.2–4.2 (37).

Statistical analysis. Continuous variables are described as means with standard deviations and were compared with an unpaired Student’s t-test or ANOVA with post hoc analysis by Student-Newman-Keuls. Categorical variables were compared with χ2. For bivariate correlations, the Pearson correlation coefficient was calculated. Differences with a P value of <0.05 were considered statistically significant.

RESULTS

Donors. Donor clinical characteristics for the lungs used for measurement of control and terbutaline-stimulated alveolar fluid clearance are summarized in Table 1. The two groups of donors were well matched demographically, although the terbutaline group had significantly lower oxygenation. The reasons for rejection of the lungs for transplantation were multiple and similar in both groups. The most common reasons were poor oxygenation (48%), cigarette smoking (26%), chest radiograph abnormality (26%), underlying pulmonary disease (16%), and suspected infection or aspiration (16%).

Alveolar fluid clearance measurements. In the terbutaline group, mean alveolar fluid clearance was 7.1 ± 1.3%/h in the first hour, a significant increase compared with the mean alveolar fluid clearance of
Table 1. Comparison of the clinical characteristics of organ donors whose lungs were harvested for measurement of unstimulated (control) or stimulated (terbutaline) alveolar fluid clearance

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Unstimulated (n = 23)</th>
<th>Terbutaline (n = 8)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>41 ± 13</td>
<td>41 ± 19</td>
<td>0.97</td>
</tr>
<tr>
<td>Caucasian</td>
<td>65%</td>
<td>75%</td>
<td>0.61</td>
</tr>
<tr>
<td>Men</td>
<td>52%</td>
<td>25%</td>
<td>0.24</td>
</tr>
<tr>
<td>Current smoker</td>
<td>52%</td>
<td>50%</td>
<td>0.62</td>
</tr>
<tr>
<td>Head trauma</td>
<td>70%</td>
<td>40%</td>
<td>0.34</td>
</tr>
<tr>
<td>PaO₂ (FiO₂ = 1.0), Torr</td>
<td>385 ± 123</td>
<td>266 ± 131</td>
<td>0.045</td>
</tr>
<tr>
<td>Cumulative 24-h dopamine dose, mg</td>
<td>405 ± 369</td>
<td>483 ± 127</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Values are means ± SD or percent of patients; n = no. of donors. PaO₂, arterial PO₂; FiO₂, inspired O₂ fraction.

4.8 ± 2.4% in the unstimulated group (43) (P < 0.05; Fig. 1).

Effect of preharvest medications on the rate of alveolar fluid clearance. The rate of unstimulated alveolar fluid clearance was compared with preharvest doses of medications known to enhance or impair alveolar fluid clearance, including dopamine, β-adrenergic agonists, glucocorticoids, and β-adrenergic receptor antagonists. All but one donor received intravenous dopamine during the 24 h before harvest. There was no difference in the mean cumulative dose of dopamine received between the control alveolar fluid clearance group and the terbutaline-stimulated alveolar fluid clearance group (Table 1). There was a linear association between the unstimulated rate of alveolar fluid clearance and cumulative dose of preharvest dopamine when doses in the low to moderate range (dopaminergic) were considered (r = 0.62, P < 0.01) (Fig. 2). The four patients who received a very high dose of dopamine (≥650 mg) had very low rates of alveolar fluid clearance (mean of 2.1 ± 1.0). There were too few donors who had received preharvest β-adrenergic agonists for analysis.

Fig. 1. Terbutaline stimulates alveolar fluid clearance in the ex vivo human donor lung. Lungs were harvested from brain-dead organ donors, cooled to 4°C, and transported. After lungs were rewarmed to 37°C, alveolar fluid clearance was measured with or without the addition of 10⁻⁴ M terbutaline. Values are means ± SD; N = no. of donors. *P < 0.01.

Fig. 2. Low to moderate doses of preharvest dopamine are associated with increased alveolar fluid clearance rates in the harvested ex vivo human lung. For each donor, the cumulative dose of dopamine in the 24 h before lung harvest was calculated and compared with the measured rate of unstimulated alveolar fluid clearance. The cumulative dose was further classified as low to moderate (<600 mg) or high (>600 mg). There was a linear association between increasing doses of preharvest dopamine in the low to moderate range (r = 0.62, P < 0.01).

A recent report of an association between high-dose glucocorticoid treatment and improved donor lung function (12) has led to the routine administration of high-dose glucocorticoids to organ donors in our region. All but one of the 31 total donors received high-dose glucocorticoid therapy during the 24–48 h before lung harvest (mean total dose of 1,350 ± 610 mg of methylprednisolone), and there was no association between the total dose and the rate of alveolar fluid clearance. Only four donors in the control group received β-adrenergic receptor antagonists. Three of these four (75%) had impaired alveolar fluid clearance, whereas only 16% of patients who did not receive β-adrenergic blocking agents had impaired alveolar fluid clearance (P < 0.04).

The extent of pulmonary edema as measured by the extravascular lung water-to-dry weight ratio was compared between donors who did and those who did not receive preharvest doses of diuretics. Donors who had received 40 mg or more of furosemide or 25 g of mannitol in the 48 h before procurement had lower water-to-dry weight ratios than those who had not (4.1 ± 0.5 vs. 4.7 ± 0.5, P < 0.05). Among donors who received any dose of furosemide after brain death (n = 16), there was a modest inverse correlation between furosemide dose and the extravascular water-to-dry weight ratio (r = −0.56, P < 0.05).

Association between extravascular lung water and the rate of alveolar fluid clearance. Lungs with more pulmonary edema, as evidenced by a higher water-to-dry weight ratio, had lower rates of unstimulated alveolar fluid clearance (Fig. 3) (r = −0.58, P < 0.01).

DISCUSSION

The primary goal of this study was to assess the responsiveness of the human donor lung to drugs that stimulate alveolar epithelial fluid transport. The major findings can be summarized as follows. First, alveolar...
epithelial fluid transport can be stimulated by a β-agonist, terbutaline, in the harvested and rewarmed human lung. Second, in a retrospective analysis, administration of dopamine before lung harvest in low to moderate dopaminergic doses seems to be associated with more rapid rates of alveolar epithelial fluid transport in the harvested lung. Third, in a retrospective analysis, administration of diuretics to the donor before lung harvest is associated with a lesser degree of pulmonary edema in the harvested lung. Fourth, there is an inverse relationship between the rate of unstimulated alveolar fluid clearance and the extravascular lung water.

The findings of this study can be compared with prior studies of stimulated alveolar fluid clearance in the ex vivo human lung. Sakuma et al. (30, 32) reported that the β-agonists terbutaline and salmeterol could stimulate alveolar fluid clearance in the excised human lung. In one study, the terbutaline (10^{-4} M)-stimulated rate of alveolar fluid clearance was ~12.5% over 2 h, or 6.25%/h (32). This can be compared with the mean rate of terbutaline-stimulated alveolar fluid clearance in the present study of 7.1 ± 1.3%/h in the first hour, a comparable result. In a later study (30), a lower concentration of terbutaline (10^{-6} M) was less effective at stimulating alveolar fluid clearance, with a rate of ~13% over 4 h or 3.3%/h. By contrast, salmeterol at relatively low concentrations (10^{-6} M) had a strong stimulatory effect on alveolar fluid clearance. There were too few donor lungs available in the present study to evaluate different concentrations of terbutaline or to study other β-agonists. This is an important area for future research.

The finding that a β-adrenergic agonist can stimulate alveolar fluid clearance in the human donor lung may ultimately have clinical significance for the management of pulmonary edema in the lung donor and the lung recipient. Pulmonary edema is a common problem in lung donors that contributes to poor lung function, the most common reason for rejection of lungs for transplantation (23). In the lung recipient, pulmonary edema due to reperfusion lung injury occurs in 15–35% of recipients and is a major cause of primary graft failure, morbidity, and mortality in the lung transplant population (39). β-Adrenergic agonists have been shown to enhance the resolution of pulmonary edema experimentally (6, 8, 33) and have a good safety profile in critically ill patients (10, 19). Furthermore, the clinical utility of β-adrenergic agonists for one type of pulmonary edema has now been demonstrated: inhalation of the β-agonist salmeterol was recently shown to reduce the incidence of high-altitude pulmonary edema in those at risk (35). Our laboratory (1) has recently reported that conventional doses of nebulized albuterol administered through the mechanical ventilator circuit in critically ill patients with pulmonary edema achieve therapeutic concentrations in the alveolar compartment. Thus the administration of inhaled β-agonists might ultimately have a role as a therapeutic intervention to enhance the resolution of alveolar edema in both lung donors and lung transplant recipients with acute pulmonary edema.

An important finding of this study was that some of the medications administered to the donor were associated with enhanced alveolar epithelial fluid transport capacity. Although these observations were made in a retrospective analysis, they may help to guide future prospective trials of donor management. Low to moderate doses of dopamine were associated with faster rates of alveolar fluid clearance. This finding confirms several recent reports that dopamine upregulates the rate of alveolar fluid clearance in both the normal (3) and the injured (34) rat lung, an effect that is mediated by binding to the dopamine-1 receptor, not the β-adrenergic receptors (4). By contrast, the four donors who received high doses of dopamine, out of the dopaminergic range, had very low rates of alveolar fluid clearance. In this group, the high doses of dopamine may have been a marker of circulatory shock, a condition that has been associated with impaired alveolar fluid clearance in both animal models (24, 27) and humans (40). Although the overall severity of pulmonary edema was low in the donor lungs, the degree of edema was lowest in donors who had received higher doses of diuretics. This finding supports the longstanding hypothesis that lowering pulmonary vascular pressure can reduce the magnitude of pulmonary edema (21, 29, 37).

The inverse correlation of alveolar fluid clearance with the extent of pulmonary edema suggests that the presence of interstitial edema may limit the ability to clear alveolar fluid in the absence of circulation, an observation that is supported by similar findings in a noncirculating mouse model (15, 17) but one that has never been made in the human lung. Once reimplanted and reperfused, the extent of interstitial pulmonary edema might not limit the rate of alveolar fluid clearance unless persistent interstitial edema developed from an increase in lung endothelial permeability. Be-
cause reimplanted lungs presumably do not have normally functioning lung lymphatic drainage, the rate of resolution of interstitial edema might be slower than in the normal lung.

A major impediment to lung transplantation is adequate graft preservation. Prolonged graft ischemia results in unacceptable rates of primary graft failure and limits the optimal utilization of donor lungs (36). Despite years of study, the optimal regimen for lung preservation has not yet been developed (7, 18). Most researchers have focused on maintenance of lung endothelial integrity as a goal of lung preservation (26). However, there is recent evidence for a critical role for preserved alveolar epithelial fluid transport capacity to hasten the resolution of reperfusion pulmonary edema (41). Other alveolar epithelial functions such as surfactant production may also be critical to graft preservation (25). Our study suggests that alveolar epithelial fluid transport capacity can be reliably measured in the ex vivo human donor lung and might be used as one functional endpoint to assess different preservation strategies.

There are some limitations of this study. First, measurements of ex vivo alveolar fluid clearance do not necessarily predict alveolar epithelial fluid transport capacity in the reperfused in vivo lung. Second, lungs were preserved only by cooling and rewarming in this study. Future studies are needed to evaluate the effect of different preservative flushes on the preservation of alveolar epithelial fluid transport capacity. The time between harvest and rewarming for measurement of alveolar fluid clearance was 6–8 h, which may have had an adverse impact on alveolar epithelial fluid transport function. However, our laboratory’s prior study (32) in the ex vivo human lung indicated that the rate of alveolar fluid clearance was the same after cooling for 6–8 h and rewarming compared with lungs studied immediately after resection. Third, the donor lungs used in this study were all rejected for transplantation and thus may not accurately reflect alveolar epithelial transport function in donor lungs that are used for transplantation. Despite this, the rates of basal and stimulated alveolar fluid clearance were surprisingly similar in the donor lungs and correlated well with prior studies in lungs rejected for malignancy (32). Finally, the analysis of donor medications that were associated with the rate of alveolar fluid clearance and the extent of pulmonary edema was retrospective and cannot definitively establish a cause-and-effect relationship.

In conclusion, this study provides the first evidence that a β2-adrenergic agonist can stimulate alveolar epithelial fluid transport in the harvested, cooled, and rewarmed human donor lung. This result suggests the possible therapeutic value of aerosolized β2-adrenergic agonists for hastening the resolution of alveolar edema during the clinical management of brain-dead donors prior to resection of lungs for transplantation and in the posttransplant setting. Furthermore, medications administered to the donor, such as dopamine or diuretics, might have positive effects on donor lung fluid balance and deserve further study. Finally, future studies of lung preservation techniques should consider incorporating measurements of alveolar epithelial fluid transport function into the assessment of the value of new methods of preservation.

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