Alveolar Fluid Clearance Is Impaired in the Majority of Patients with Acute Lung Injury and the Acute Respiratory Distress Syndrome

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Because experimental studies have shown that intact alveolar epithelial fluid transport function is critical for resolution of pulmonary edema and acute lung injury, we measured net alveolar fluid clearance in 79 patients with acute lung injury or the acute respiratory distress syndrome. Pulmonary edema fluid and plasma were sampled serially in the first 4 hours after intubation. Net alveolar fluid clearance was calculated from sequential edema fluid protein measurements. Mean alveolar fluid clearance was 6%/h. Of the patients, 56% had impaired alveolar fluid clearance (< 3%/h), 32% had submaximal clearance (⩾ 3%/h, < 14%/h), and 13% had maximal clearance (⩾ 14%/h). These findings are contrasted to our recent report of 65 patients with hydrostatic pulmonary edema, in whom mean alveolar fluid clearance was 13%/h; only 25% had impaired clearance whereas 75% had submaximal or maximal clearance (*J Appl Physiol* 1999;87:1301–1312). Acute lung injury with maximal alveolar fluid clearance were more likely to be female (p = 0.03), and less likely to have sepsis (p = 0.01). Endogenous and exogenous catecholamines did not correlate with alveolar fluid clearance. Patients with maximal alveolar fluid clearance had significantly lower mortality and a shorter duration of mechanical ventilation. In summary, in contrast to hydrostatic pulmonary edema, alveolar fluid clearance in patients with acute lung injury and the acute respiratory distress syndrome is impaired in the majority of patients, and maximal alveolar fluid clearance is associated with better clinical outcomes.

Acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) are common causes of acute respiratory failure. Although much has been learned about the pathophysiology of ALI/ARDS, the resolution phase of ALI/ARDS is still poorly understood (1). Early ALI/ARDS is characterized by alveolar epithelial and lung endothelial injury leading to increased permeability pulmonary edema, alveolar filling, and respiratory failure. The reabsorption of pulmonary edema fluid from the alveolar space is necessary for the resolution of ALI/ARDS. A number of experimental studies have demonstrated that intact alveolar epithelial fluid transport function is critical for the resolution of experimental pulmonary edema and acute lung injury. However, little is known about the capacity of the injured alveolar epithelium to resolve pulmonary edema in patients with ALI/ARDS.

Alveolar fluid clearance has been measured in only a few clinical studies (2–4). The maximal capacity of the uninjured alveolar epithelium to clear pulmonary edema fluid has been characterized in a large study of patients with hydrostatic pulmonary edema (3). In that study, 75% of patients with severe hydrostatic pulmonary edema had intact alveolar fluid clearance (⩾ 3%/h). Furthermore, 38% of patients had alveolar fluid clearance rates more than twice the maximally stimulated rate measured in the *ex vivo* human lung (⩾ 14%/h), underscoring the importance of *in vivo* measurements. Previously, alveolar fluid clearance has been measured only in a small number of patients with ALI/ARDS. In contrast to patients with hydrostatic edema, 7 of 16 patients with ARDS were found to have no measurable alveolar fluid clearance, a finding that was associated with poorer oxygenation and increased mortality (2). However, alveolar fluid clearance has never been measured systematically in a large number of patients with ALI/ARDS.

This study was designed to examine alveolar fluid clearance in the setting of alveolar epithelial injury due to ALI/ARDS. The first objective was to measure systematically the rate of net alveolar fluid clearance in a large number of patients with ALI/ARDS. Alveolar fluid clearance in this patient population was then compared with previously reported rates of alveolar fluid clearance in patients with hydrostatic pulmonary edema and no alveolar epithelial injury. The second objective was to study potential mechanisms that regulate alveolar fluid clearance in the setting of acute lung injury, including both catecholamine-dependent and -independent mechanisms. The third objective was to assess whether rapid alveolar fluid clearance is associated with a better prognosis in patients with ALI/ARDS.

METHODS

Patient Selection

Patients with ALI or ARDS as defined by the North American European Consensus Conference definitions (5) were identified from the adult intensive care units of Moffitt-Long Hospital, University of California (San Francisco, CA), and San Francisco General Hospital between 1985 and 1998. Additional inclusion criteria included acute respiratory failure requiring mechanical ventilation and aspirable pulmonary edema fluid within 1 h of tracheal intubation and repeated within 4 h. The initial edema fluid-to-plasma protein ratio was > 0.65, consistent with increased permeability pulmonary edema. The Committee for Human Research (University of California, San Francisco) approved the study.

Sampling of Pulmonary Edema Fluid

Undiluted pulmonary edema fluid and plasma were collected simultaneously as previously described (2). All samples were centrifuged at $3{,}000 \times g$ for 10 min and supernatants were stored at −70° C.

Protein Concentration Measurements

The total protein concentration in edema fluid and plasma was measured by the biuret method (2). If the sample volume was insufficient (< 1% of samples), then refractometry was used.

Rate of Net Alveolar Fluid Clearance

On the basis of the observation that the rate of clearance of edema fluid from the alveolar space is much faster than the rate of protein removal (6), the net alveolar fluid clearance rate was calculated: Percent alveolar fluid clearance = 100 × [1 − (initial edema protein/final

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edema protein)]. This method has been validated in prior clinical and experimental studies (2–4, 6–8). Patients were further categorized into three groups of alveolar fluid clearance on the basis of extrapolations from studies in the *ex vivo* human lung (3, 9): maximal = 14%/h; submaximal, ⩾ 3%/h and < 14%/h; or impaired, < 3%/h. For some analyses the submaximal and maximal clearance groups were combined into an intact clearance group.

Epinephrine Assays

Plasma epinephrine was measured by high-performance liquid chromatography (10). Because the effect of epinephrine on alveolar fluid clearance is short-lived (11), plasma epinephrine values determined at the beginning and the end of the interval over which alveolar fluid clearance was measured were averaged to estimate the mean plasma epinephrine level (3).

Clinical Data

The primary etiology of ALI/ARDS was assessed on the basis of the clinical history. Sepsis was defined by standard criteria (12). Pneumonia was defined as new radiographic infiltrates and positive sputum cultures. Aspiration of gastric contents was defined as a witnessed aspiration event. Clinical data were recorded for the first 24 h after intubation and included hemodynamic parameters, respiratory and ventilatory parameters, multiorgan system function, demographic data, and medications administered. The Simplified Acute Physiology Score II (SAPS II) and the Lung Injury Score (LIS) were calculated (13, 14). Outcome variables included death before hospital discharge, change in alveolar–arterial oxygen difference at 4 and 24 h after enrollment, and days of unassisted ventilation during a 28-d period (15).

Data Analysis

Continuous variables were compared by Students t test or by analysis of variance with the Student–Newman–Keuls test for multiple comparisons. Categorical variables were compared by using χ^2 analysis. Nonparametric data were analyzed by using the Mann–Whitney U test or the Kruskal–Wallis test. Stepwise logistic regression was used to ascertain the independent predictors of (*1*) death and (*2*) greater than 21 d of unassisted ventilation. Statistical significance was defined as $p \leqslant 0.05$. All data are reported as means ± SD unless otherwise noted.

TABLE 1. CLINICAL CHARACTERISTICS OF 79 PATIENTS WITH ACUTE LUNG INJURY OR THE ACUTE RESPIRATORY DISTRESS SYNDROME

Variable	Value*
Age, yr	45 ± 18
Male sex	59%
Race	
White	58%
Asian/Pacific Islander	20%
African American	12%
Hispanic	10%
Present smoker	29%
Etiology of acute lung injury	
Sepsis	53%
Drug overdose/drug reaction	14%
Pneumonia	8%
Aspiration of gastric contents	8%
Multiple transfusion	6%
Other	11%
SAPS II	51 ± 19
Lung Injury Score	2.9 ± 0.7
Hospital mortality	57%

Definition of abbreviation: SAPS II = Simplified Acute Physiology Score II.
* Values represent either means ± SD or percentage of patients.

RESULTS

Patient Characteristics

Over the study period, 116 patients with ALI or ARDS were identified and had two or more samples of pulmonary edema fluid aspirated. Thirty-seven of these patients were excluded from the analysis; 19 patients were excluded because either the first pulmonary edema fluid sample was not obtained within 1 h of endotracheal intubation, or the second sample was not obtained within 4 h of the first sample, and 18 patients were excluded because review of the medical record suggested a hydrostatic cause of pulmonary edema. The remaining 79 patients with ALI or ARDS were studied in the first 4 h after endotracheal intubation and mechanical ventilation. Demographic and clinical data are summarized in Table 1. The most common cause of ALI/ARDS was sepsis, including sepsis of both pulmonary and nonpulmonary origin. The mean initial edema fluid-to-plasma protein ratio was 0.98 ± 0.26, consistent with pulmonary edema due to increased permeability of the alveolar capillary barrier. Of note, the overall severity of illness was exceedingly high, as evidenced by the high SAPS II and the hospital mortality rate of 57%. The degree of pulmonary physiological impairment was also high, with a mean LIS of 2.9. Of the 79 patients, 7 patients met the definition of ALI; the remaining 72 met the definition of ARDS.

Alveolar Fluid Clearance

Net alveolar fluid clearance was measured as the change in protein concentration between the first and last edema fluid samples obtained during the first 4 h after intubation and mechanical ventilation. The rate of alveolar fluid clearance ranged from a minimum of 0%/h (no net alveolar fluid clearance) to a maximum of 49%/h, with a mean of 6%/h. One additional patient had a rate of alveolar fluid clearance of 53% over 30 min, after which no further edema fluid samples could be aspirated. This patient was classified as having maximal alveolar fluid clearance.

A total of 44 patients (56%) had impaired alveolar fluid clearance (< 3%/h) whereas 35 patients (44%) had intact alveolar fluid clearance (⩾ 3%/h) (Figure 1). For some analyses, the group with intact alveolar fluid clearance was broken down into those with submaximal clearance (⩾ 3%/h, < 14%/h) and those with maximal clearance (⩾ 14%/h). The submaximal group included 32% of the patients (n = 25), with a mean

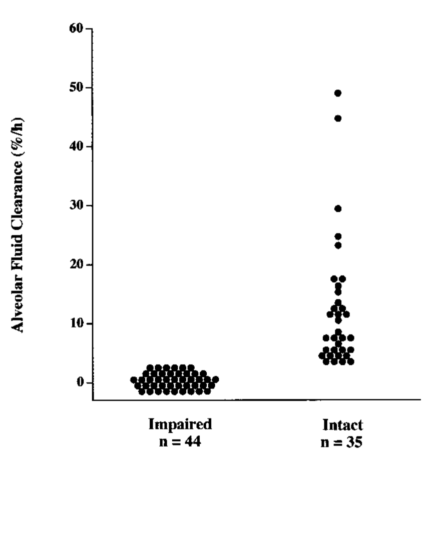

Figure 1. Plot of rate of alveolar fluid clearance in 79 patients with acute lung injury or the acute respiratory distress syndrome, showing that the majority of patients had impaired alveolar fluid clearance. Alveolar fluid clearance was measured from serial protein concentrations in the pulmonary edema fluid samples obtained from 79 patients. Intact clearance was defined as ⩾ 3%/h and impaired clearance as < 3%/h. Each symbol (*solid circle*) represents the rate of alveolar fluid clearance in a single patient. n = number of subjects.

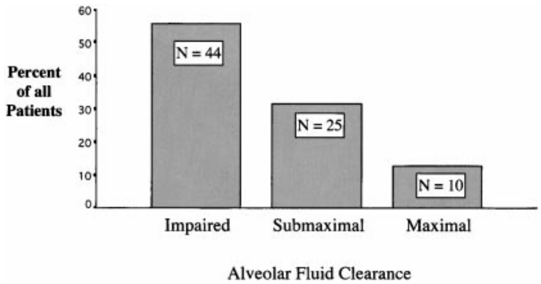

Figure 2. Percentage of patients with three categories of alveolar fluid clearance: impaired (< 3%/h), submaximal (⩾ 3%/h, < 14%/h), or maximal (⩾ 14%/h). Alveolar fluid clearance was measured during the first 4 h after intubation and mechanical ventilation in 79 patients with acute lung injury or the acute respiratory distress syndrome. *Solid columns* show the percentage of 79 patients in each group. N = number of subjects.

rate of alveolar fluid clearance of 8 ± 3%/h (Figure 2). The maximal group included 13% of the patients (n = 10), with a mean rate of alveolar fluid clearance of 34 ± 28%/h.

To exclude a rise in plasma protein as a cause of net alveolar fluid clearance, plasma protein concentrations were compared at the beginning and end of each time interval over which alveolar fluid clearance was measured. Among the patients with impaired alveolar fluid clearance, plasma protein was 4.8 ± 0.8 g/dl at the first time point and 4.6 ± 1.0 g/dl at the second time point. Among the patients with submaximal alveolar fluid clearance, plasma protein was 5.1 ± 0.9 g/dl at the first time point and 5.0 ± 1.1 g/dl at the second time point. Among the patients with maximal alveolar fluid clearance, plasma protein was 5.6 ± 0.8 g/dl at the first time point and 5.6 ± 0.5 g/dl at the second time point. None of these differences were significant. Thus, changes in the intravascular protein osmotic pressure did not appear to influence the rate of net alveolar fluid clearance.

Relationship Between Baseline Clinical Characteristics and Alveolar Fluid Clearance

The association between selected clinical and demographic variables and the three categories of alveolar fluid clearance was evaluated by univariate analysis (Table 2). There was no significant association between demographic factors such as age or race and rate of alveolar fluid clearance. Interestingly, 8 of the 10 patients with maximal alveolar fluid clearance were female. By contrast, the majority of patients with submaximal or impaired alveolar fluid clearance were male, a significant difference ($p = 0.03$). Overall, mean alveolar fluid clearance was 9 ± 13%/h in females compared with 4 ± 6%/h in males ($p < 0.01$).

Although the number of current smokers was low, only one patient with maximal clearance was a smoker compared with 24% of the patients with submaximal or impaired clearance ($p = 0.12$). In addition, smokers had a higher initial edema fluid-to-plasma protein ratio, an index of alveolar capillary barrier permeability (median 1.03 versus 0.88 for nonsmokers, $p < 0.05$) and a trend toward more white blood cells in the pulmonary edema fluid (median $5.3 \times 10^6/\mu l$ versus $1.5 = 10^6/\mu l$ in nonsmokers, $p = 0.16$). There was no association between body temperature or Lung Injury Score and rate of alveolar fluid clearance (Table 2).

A striking finding was that only 20% of patients with maximal alveolar fluid clearance had sepsis as the cause of ALI/ARDS compared with 76% of the patients with submaximal alveolar fluid clearance and 50% of those with impaired clearance ($p = 0.01$). Overall, mean alveolar fluid clearance was twice as high in patients without sepsis, 8 ± 13%/h versus 4 ± 5%/h in patients with sepsis ($p < 0.05$). SAPS II also tended to be lower in the patients with maximal clearance, with a mean of 39 ± 10 compared with 55 ± 21 in the patients with submaximal clearance and 51 ± 19 in the patients with impaired clearance ($p = 0.10$).

TABLE 2. COMPARISON OF BASELINE CLINICAL CHARACTERISTICS IN PATIENTS WITH IMPAIRED, SUBMAXIMAL, AND MAXIMAL ALVEOLAR FLUID CLEARANCE

	Alveolar Fluid Clearance			
Variable	Impaired (n = 44)	Submaximal (n = 25)	Maximal (n = 10)	p Value
	N/Total (%)			
Male sex	28/44 (64)	16/25 (64)	2/10 (20)	0.03
Race, white/total	22/41 (54)	14/23 (61)	7/10 (70)	0.61
Present smoker	9/38 (24)	6/25 (24)	1/9 (11)	0.12
Sepsis	22/44 (50)	19/25 (76)	2/10 (20)	0.01
	Mean ± SD			
Age, yr	46 ± 18	45 ± 20	43 ± 12	0.10
Lung Injury Score	2.9 ± 0.7	2.9 ± 0.	2.7 ± 0.7	0.66
A–a oxygen difference	481 ± 138	495 ± 133	411 ± 157	0.33
Pa_{O_2}/FI_{O_2} ratio	114 ± 62	110 ± 67	131 ± 48	0.70
Tmax, degrees Celsius	38.3 ± 0.9	38.2 ± 1.4	38.1 ± 0.7	0.82

Definition of abbreviations: A–a oxygen difference = alveolar–arterial oxygen difference; FI_{O_2} = fraction of inspired oxygen; N = no. of subjects; Pa_{O_2} = arterial partial pressure of oxygen; Tmax = maximum temperature in the first 24 h.

Relationship Between Alveolar Fluid Clearance and Clinical Outcomes

A univariate analysis was done to test for an association between the rate of net alveolar fluid clearance and clinical outcomes including mortality, days of mechanical ventilation, and improvement in oxygenation. Overall, the group of patients with maximal alveolar fluid clearance had better clinical outcomes than patients with submaximal or impaired alveolar fluid clearance. Hospital mortality was 20% in patients with maximal clearance compared with 62% in patients with submaximal or impaired alveolar fluid clearance, a significant difference (Figure 3). In addition, the mean rate of alveolar fluid clearance was much higher in patients who survived compared with patients who died, 9 ± 13%/h in survivors versus 4 ± 4%/h in nonsurvivors, an almost 3-fold difference ($p = 0.01$). The

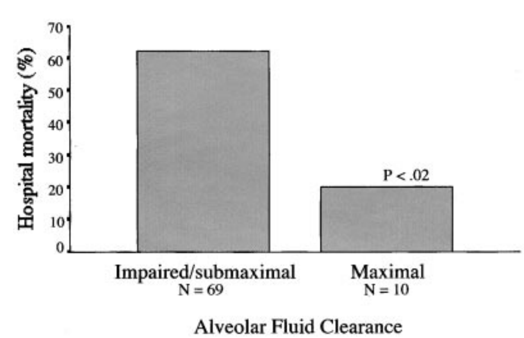

Figure 3. Plot of hospital mortality of two groups of patients with acute lung injury or the acute respiratory distress syndrome: those with maximal alveolar fluid clearance (⩾ 14%/h) and those with impaired or submaximal alveolar fluid clearance (< 14%/h). Columns represent percent hospital mortality in each group. Hospital mortlality of patients with maximal alveolar fluid clearance was significantly less ($p < 0.02$). N = number of patients.

median duration of unassisted ventilation in a 28-d period was significantly longer in patients with maximal alveolar fluid clearance, 23 versus 0 d in patients with submaximal or impaired alveolar fluid clearance (Figure 4). In addition, those patients who had a shorter duration of mechanical ventilation (⩾ 21 d of unassisted ventilation) had a mean alveolar fluid clearance of 11 ± 13%/h compared with 4 ± 8%/h in patients with a longer duration of mechanical ventilation (< 21 d of unassisted ventilation, $p = 0.005$). Finally, 100% of the patients with maximal alveolar fluid clearance had improved oxygenation at 24 h after study enrollment versus only 69% of patients with submaximal or impaired alveolar fluid clearance ($p = 0.09$). When just the first 4 h after enrollment were considered, patients with improved oxygenation had a mean alveolar fluid clearance rate of 7 ± 8%/h compared with patients with the same or worse oxygenation, who had a mean alveolar fluid clearance rate of 5 ± 10%/h ($p = 0.04$). In addition, the change in oxygenation over the first 4 h had a modest correlation with the rate of alveolar fluid clearance ($r = 0.39$, $p = 0.001$).

When a multivariate analysis was done, only sepsis and a SAPS II ⩾ 50 predicted hospital mortality. Sepsis had an odds ratio of 7.7 (2.2–26.4) and SAPS II ⩾ 50 had an odds ratio of 3.6 (1.0–12.8). Similarly, only the absence of sepsis (odds ratio 0.47, 95% CI 0.24–0.94) or a SAPS II < 50 (odds ratio 0.35, 95% CI 0.15–0.81) predicted 21 or more days of unassisted ventilation.

Plasma Epinephrine Levels

To investigate a possible association between endogenous catecholamines and rate of alveolar fluid clearance, mean interval plasma epinephrine and norepinephrine levels were measured in a subset of 29 patients. Average interval epinephrine concentrations ranged from 0 to 75,674 pg/ml with a median of 124 pg/ml. Average interval norepinephrine concentrations ranged from 0 to 118,546 pg/ml with a median of 689 pg/ml. Reported maximum plasma epinephrine concentrations in unstressed, supine, normotensive control human subjects are ~ 100–150 pg/ml (16, 17). Reported maximum plasma norepinephrine concentrations in unstressed, supine, normotensive control human subjects are ~ 250–400 pg/ml (16). There were no significant differences in the plasma epinephrine levels (Figure 5) or norepinephrine levels (data not shown) when compared with rates of alveolar fluid clearance. When epinephrine and norepinephrine levels were combined, or the administration of exogenous catecholamines (dobutamine or inhaled β-agonists) was considered along with endogenous epinephrine or norepinephrine levels, there was still no correlation with alveolar fluid clearance (data not shown). Furthermore, when individual patients were considered, it was clear that maximal alveolar fluid clearance could occur despite low levels of endogenous catecholamines, and conversely, that alveolar fluid clearance could be impaired despite high levels of endogenous catecholamines. For example, three patients with high plasma epinephrine levels (mean, 26,509 pg/ml) had no net alveolar fluid clearance, whereas two patients with maximal alveolar fluid clearance (mean, 36.2%/h) had no measurable plasma epinephrine. Pulmonary edema fluid levels of epinephrine and norepinephrine were measured in a small subset of patients and did not correlate with rate of alveolar fluid clearance (data not shown).

Pharmacological Agents

Medications with potential effects on alveolar epithelial ion transport including diuretics (furosemide), exogenous glucocorticoids (methylprednisolone, hydrocortisone), inhaled β-agonists, (alupent, albuterol), and vasoactive agents (dobutamine, dopamine, epinephrine, norepinephrine, neosynephrine) were studied. There was no significant association between treatment with any of these agents and rate of alveolar fluid clearance.

Hemodynamic Indexes

Central venous pressure (Pcv) was measured in a total of 43 patients. There was no association between baseline Pcv, or decline in Pcv and the rate of alveolar fluid clearance. The number of patients with measurements of pulmonary arterial wedge pressure was too few for analysis. Patients with maximal alveolar fluid clearance were less likely to have shock in the first 24 h after study enrollment, although this difference did not reach significance ($p = 0.20$). Objective measurement of cardiac function by echocardiography within 48 h of pulmonary edema fluid sampling was obtained in 43 of the 79 patients. The mean ejection fraction was 56 ± 14%. The rate of alveolar fluid clearance was not significantly associated with ejection fraction.

Ventilatory Parameters

Baseline indices of oxygenation in patients with different rates of alveolar fluid clearance are summarized in Table 2. The baseline alveolar–arterial oxygen difference, and the ratio of arterial partial pressure of oxygen to inspired oxygen fraction

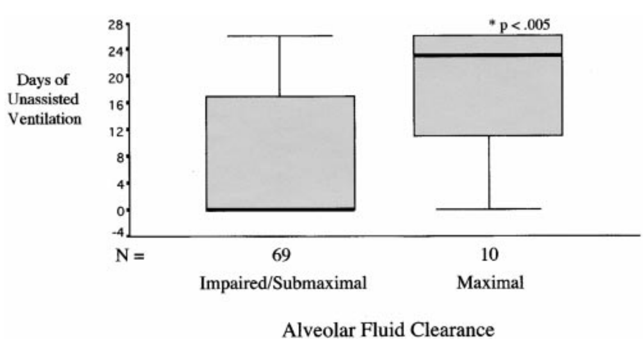

Figure 4. Box plot summary of days of unassisted ventilation in a 28-d period in two patient groups: those with maximal alveolar fluid clearance (⩾ 14%/h) and those with impaired or submaximal alveolar fluid clearance (< 14%/h). Each box encompasses 50% of the data (25th to 75th percentiles). Error bars encompass 80% of the data (10th to 90th percentiles). The *thick horizontal lines* represent median values. N = number of patients. Note that the duration of unassisted ventilation was significantly longer (*p < 0.005) in the patients with maximal alveolar fluid clearance, a better clinical outcome.

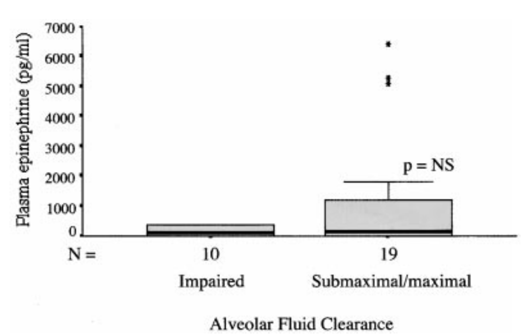

Figure 5. Box plot summary of mean plasma epinephrine level in two groups of patients: those with impaired alveolar fluid clearance (< 3%/h) and those with submaximal or maximal alveolar fluid clearance (⩾ 3%/h). Each box encompasses 50% of the data (25th to 75th percentiles). Error bars encompass 80% of the data (10th to 90th percentiles). The *thick horizontal lines* represent median values. * Represents outliers. There was no significant difference between groups. N = number of patients; NS = not significant.

(Pa_{O_2}/FI_{O_2}) were not different between the groups. The group of patients with maximal alveolar fluid clearance tended to have lower peak airway pressures by 6–7 cm H_2O compared with the other groups, but this difference was not significant. There was also no significant difference in tidal volume or positive end-expiratory pressure (PEEP) among the three groups, although overall, the maximal clearance group had a lower mean PEEP and tidal volume per kilogram. Of the 10 patients with maximal alveolar fluid clearance, only 2 (20%) had a tidal volume greater than 12 ml/kg. By contrast, of the 65 patients with submaximal or impaired alveolar fluid clearance, 30 of 65 (46%) had a tidal volume greater than 12 ml/kg ($p = 0.17$).

DISCUSSION

Alveolar fluid clearance, an important function of the alveolar epithelium, has never been systematically characterized in a large group of patients with ALI or ARDS. The major findings of this study can be summarized as follows. First, net alveolar fluid clearance was impaired (< 3%/h) in the majority (56%) of patients. Maximal clearance (⩾ 14%/h) occurred in only 13% of patients, indicating that in the setting of clinical acute lung injury, only a minority of patients are able to upregulate alveolar fluid clearance. Second, females, nonsmokers, and patients without sepsis were more likely to have maximal alveolar fluid clearance. Furthermore, in this retrospective analysis, the rate of alveolar fluid clearance was not clearly associated with levels of endogenous or exogenous catecholamines. Third, the group of patients with maximal alveolar fluid clearance had better clinical outcomes, including lower hospital mortality, a shorter duration of mechanical ventilation, and a trend toward improved oxygenation at 24 h after endotracheal intubation.

The first objective was to characterize alveolar fluid clearance in a large number of patients with ALI or ARDS. The method used to quantify net alveolar fluid clearance was to measure serial protein concentrations in the pulmonary edema fluid, a modification of our validated experimental method used routinely by many investigators to quantify alveolar fluid clearance (6–8, 10, 11, 18–24). Are there other possible explanations for the increase in protein concentration in serial edema fluid samples? One possible explanation would be an increase in permeability of the alveolar capillary barrier causing an influx of edema fluid with a higher protein concentration. While it is conceivable that this occurred in some patients, even an increase to maximal permeability with alveolar flooding with pure plasma would fail to explain the rise in edema fluid protein to greater than simultaneous plasma protein in 25 of the 35 patients who had intact alveolar fluid clearance. A second possible explanation would be a rise in plasma protein over the sampling period leading to an influx of more protein-rich fluid into the alveoli, even with no change in alveolar capillary barrier permeability. However, we carefully quantified the changes in plasma protein over the period of edema fluid sampling and there was no rise in plasma protein over time (*see* RESULTS). A third possible explanation would be the production of protein by cells in the airway or alveolar space, including inflammatory cells or epithelial cells. However, airway secretions have a low protein concentration (~ 0.5 g/dl) (2) and thus tend to dilute rather than increase the total protein concentration. For these reasons, and because this and other clinical studies have shown correlations between alveolar fluid clearance and meaningful clinical indices of improvement in pulmonary edema such as improvement in chest radiograph and oxygenation (2–4), we believe that our method correctly estimates net alveolar fluid clearance in the majority of patients.

The most striking finding of our study was that alveolar fluid clearance was impaired (< 3%/h) in the majority of patients (56%). Only a minority of patients had maximal alveolar fluid clearance (⩾ 14%/h). Previously, alveolar fluid clearance has been measured only in a small group of 16 patients with ARDS (2). In that study, nearly half (7 of 16) of the patients had no net alveolar fluid clearance, a finding that was associated with poorer oxygenation and increased mortality. The current study has several advantages. First, the larger number of patients allows a rigorous analysis of factors associated with impaired or intact alveolar fluid clearance. Second, the current study quantifies the percent alveolar fluid clearance per hour, allowing differentiation of those patients with the most upregulated, maximal alveolar fluid clearance from those with slower, submaximal, or impaired alveolar fluid clearance. Third, clinical factors that might be associated with the rate of alveolar fluid clearance were more thoroughly analyzed.

We previously reported measurements of alveolar fluid clearance from 65 mechanically ventilated patients with severe hydrostatic pulmonary edema recruited over the same time period from the same intensive care units as in the current study (3). In that study, mean alveolar fluid clearance was 13%/h as compared with a mean alveolar fluid clearance of 6%/h in the current study of ALI/ARDS. Using the same classifications as in the current study, only a small minority of patients with hydrostatic pulmonary edema (25%) had impaired alveolar fluid clearance (< 3%/h) and more than one-third (38%) had maximal alveolar fluid clearance (⩾ 14%/h) (Figure 6). The patients with hydrostatic edema had a similar degree of pulmonary physiologic impairment and overall severity of illness as the patients with ALI/ARDS, with a comparable LIS (2.9 ± 0.6) and a high severity of illness as measured by SAPS II (45 ± 16). Thus, the rate of net alveolar fluid clearance is independent of the amount of pulmonary edema as measured by the LIS, and the cause of pulmonary edema is an important determinant of the rate of resolution. Patients with hydrostatic pulmonary edema are far more likely to have preserved or upregulated alveolar fluid clearance than those with ALI/ARDS. This difference is probably due to preservation of an intact and functional alveolar epithelial barrier in the majority of patients with hydrostatic edema.

Eighty percent of the patients with maximal alveolar fluid clearance were female as opposed to only 35% of the patients

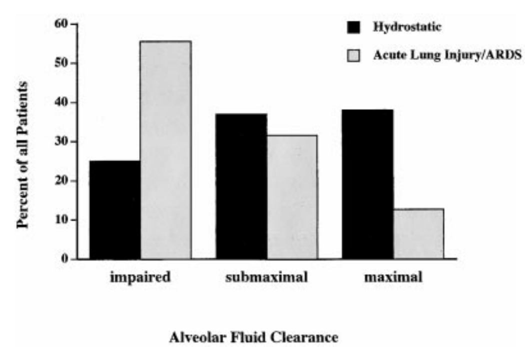

Figure 6. Comparison of rates of alveolar fluid clearance in two groups of patients: 65 mechanically ventilated patients with severe hydrostatic pulmonary edema and 79 mechanically ventilated patients with acute lung injury or the acute respiratory distress syndrome. Columns represent the percentage of patients in each group with three categories of alveolar fluid clearance: impaired (< 3%/h), submaximal (⩾ 3%/h, < 14%/h), or maximal (⩾ 14%/h). Data on patients with hydrostatic pulmonary edema reproduced with permission from Verghese GM, Ware LB, Matthay BA, Matthay MA. *J Appl Physiol* 1999;87:1301–1312.

with impaired or submaximal clearance (p = 0.03). Furthermore, the majority (seven of eight) of the female patients with maximal alveolar fluid clearance were less than 55 yr old, suggesting that they were premenopausal. This is an intriguing observation because experimental data indicate that in rats, exposure to estrogen and progesterone increases both the expression and function of the epithelial sodium channel (25). Cigarette smoking has never been associated with adverse outcomes in ALI/ARDS (12, 26). Although the number of smokers in our study was small (n = 20), there was a trend toward fewer smokers in the maximal alveolar fluid clearance group (p = 0.10), suggesting that cigarette smoking may have had an adverse effect on alveolar fluid clearance. In addition, smokers had a higher initial edema fluid-to-plasma protein ratio, an index of alveolar capillary barrier permeability, and tended to have more white blood cells in the pulmonary edema fluid. Although the effects of smoking on alveolar epithelial fluid transport have not been investigated experimentally, cigarette smoking has been shown to cause increased alveolar epithelial permeability (27), intraalveolar accumulation of neutrophils, and intraalveolar oxidant stress (28, 29).

In addition to sex and smoking status, the cause of ALI/ARDS was an important determinant of alveolar fluid clearance. As shown in Figure 7, patients with sepsis were significantly less likely to have maximal alveolar fluid clearance. The most likely explanation is that sepsis was associated with more severe and lasting injury to the alveolar capillary barrier than other causes of lung injury, such as aspiration of gastric contents or primary pneumonia. In classic ultrastructural studies by Bachofen and Weibel (30), sepsis-associated lung injury was characterized by necrosis and sloughing of the alveolar epithelial barrier. This hypothesis is also supported by our experimental study of sheep (31), in which intravenous infusion of *Pseudomonas aeruginosa* for 8 h led to severe alveolar epithelial injury and abolished alveolar epithelial fluid transport function in 30% of the sheep. However, not all experimental models of sepsis are associated with impaired alveolar fluid clearance. In a short-term, 4-h rat model of bacteremia, alveolar fluid clearance was increased because of increased levels of endogenous catecholamines (10).

Catecholamines upregulate alveolar fluid clearance in both the normal and the injured lung in a variety of species, including the human lung. Endogenous epinephrine has been shown to upregulate alveolar fluid clearance under several experimental conditions including hypovolemic and septic shock in rats (10, 32), and neurogenic pulmonary edema in dogs (21). A variety of exogenous β_2-agonists, including terbutaline, salmeterol, epinephrine, and dobutamine, can also stimulate alveolar fluid clearance (6, 20, 33–37). Although β_2-agonists were the first to be characterized, isoproterenol, a β_1- and β_2-agonist, has been shown to upregulate alveolar fluid clearance by a β_1-dependent mechanism (22). Therefore, we carefully quantified both endogenous and exogenous catecholamines including both β_1- and β_2-agonists.

Interestingly, levels of endogenous catecholamines did not correlate with alveolar fluid clearance (Figure 5). The administration of exogenous catecholamines also did not correlate with alveolar fluid clearance. Furthermore, when the combination of either high levels of endogenous catecholamines or the administration of exogenous catecholamines was considered, there was still no association with rate of alveolar fluid clearance. Why did endogenous and exogenous catecholamines fail to increase alveolar fluid clearance? There are several possible explanations. First, the analysis of catecholamine levels was done retrospectively and thus was not designed to test the hypothesis in a prospective, randomized fashion. Second, in some patients, injury to the alveolar epithelium may have rendered it unable to respond to catecholamine stimulation (38, 39). Third, the presence of high levels of endogenous or exogenous catecholamines over a prolonged period may have led to β-agonist receptor downregulation. Fourth, the majority of patients may not have received a sufficient or sustained exposure to alveolar β-agonists; only 30% of the patients received an inhaled β-agonist, and many of these received only one dose. Randomized trials of inhaled β-agonists are needed to definitively answer the question of whether patients with ALI/ARDS can increase alveolar fluid clearance in response to an adequate intraalveolar concentration of β-agonist.

In addition to catecholamines, several other pharmacological agents can increase alveolar fluid clearance. Dopamine increases alveolar fluid clearance by stimulation of the dopamine 1 receptor (23, 24, 40). However, we found no association between administration of dopamine and rate of alveolar fluid clearance. Glucocorticoids also enhance alveolar fluid clearance experimentally (41), but there was no association between administration of glucocorticoids and alveolar fluid clearance. An additional catecholamine-independent mechanism that might be important in determining the rate of alveolar fluid clearance is alveolar epithelial Type II cell hyperplasia (42, 43).

This study establishes that rapid alveolar fluid clearance is associated with improved clinical outcomes in patients with ALI/ARDS. Maximal alveolar fluid clearance was associated with decreased mortality, shorter duration of mechanical ventilation, and a trend toward improved oxygenation at 24 h after study enrollment. These findings lend support to the hypothesis that the resolution phase of ALI/ARDS is an important determinant of outcome. However, when a multivariate analysis was done, only sepsis and SAPS II were independent predictors of death or prolonged mechanical ventilation. One explanation is that sepsis is such a strong predictor of poor outcome in this and other studies (12, 26, 44). When only patients without sepsis were further analyzed by logistic regression, SAPS II continued to predict mortality and alveolar fluid clearance entered the regression with a p value of 0.12. A second explanation is that impaired alveolar fluid clearance and sepsis are closely associated variables. In fact, the association of sepsis with an inability to upregulate alveolar fluid clearance may, in part, explain why sepsis is associated with increased mortality from ALI/ARDS.

A limitation of our study is that because it was confined to those patients that could have serial samples of pulmonary

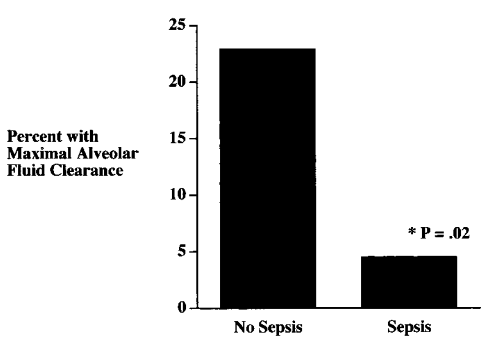

Figure 7. Plot of percentage of patients with maximal alveolar fluid clearance (⩾ 14%/h) in two groups of patients with acute lung injury or the acute respiratory distress syndrome: those with no evidence of sepsis, and those with sepsis. The percentage of septic patients with maximal alveolar fluid clearance was significantly less (p = 0.02) than that of nonseptic patients.

edema fluid aspirated, the results are generalizable only to this population. However, we believe that our study population represented ALI/ARDS patients from our institution remarkably well. Comparing our patient population with a prospective study of 123 consecutive patients with ALI/ARDS admitted to our institution (12), mortality was similar (58 versus 57% in the current study, with a mean age of 52 (versus 45 in current study) and a similar incidence of sepsis (41 versus 53% in the current study).

In conclusion, this study has several important new findings. Alveolar fluid clearance was impaired in the majority of patients with clinical acute lung injury, in contrast to our previous findings in patients with pulmonary edema from hydrostatic causes. Because maximal alveolar fluid clearance was associated with improved clinical outcomes including lower mortality and a shorter duration of mechanical ventilation, future investigations should focus on the mechanisms for impaired alveolar fluid clearance in ALI/ARDS. As emphasized in editorials and reviews (45–47), new therapies targeted at enhancing alveolar fluid clearance may hasten the resolution of ALI/ARDS and improve survival.

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