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Hydrostatic mechanisms may contribute to the pathogenesis of human re-expansion pulmonary edema

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Abstract *Objective:* The primary objective was to test the hypothesis that clinical re-expansion pulmonary edema is predominantly due to increased permeability of the alveolar-capillary barrier. A secondary objective was to determine if the alveolar epithelium was functionally intact in patients with re-expansion pulmonary edema by measuring net alveolar epithelial fluid transport in a subset of patients. *Design:* Retrospective study of mechanically ventilated patients with re-expansion pulmonary edema. *Setting:* Two academic tertiary care hospitals. *Patients:* Seven patients with acute onset of re-expansion pulmonary edema after tube thoracostomy or thoracentesis. *Interventions:* Pulmonary edema fluid and plasma were collected at the time of onset of re-expansion edema. *Measurements and results:* Contrary to our hypothesis, the mean initial edema fluid to plasma protein ratio was 0.58±0.21, supporting a hydrostatic mechanism of edema formation. Four of the patients had an initial edema fluid to plasma protein ratio of less than 0.65, consistent with pure hydrostatic pulmonary edema, while the others had a slight increase in permeability (edema fluid to plasma ratios of 0.67, 0.71 and 0.77), perhaps due to capillary stress failure from hydrostatic stress. Alveolar fluid clearance (mean 9.8±8.0%/h) was intact in the subset of three patients in whom it was measured. *Conclusions:* This study provides the first direct evidence that hydrostatic forces may contribute to the development of re-expansion pulmonary edema.

Keywords Alveolar epithelium ·
Alveolar epithelial fluid transport ·
Pleural effusion · Pneumothorax ·
Thoracentesis · Thoracostomy

Introduction

Re-expansion pulmonary edema is a rare condition associated with the re-expansion of a collapsed lung after the drainage of fluid or air from the pleural space [1, 2, 3, 4, 5]. Re-expansion edema usually develops within 24 h of the drainage procedure and is characterized by acute arterial hypoxemia, decreased pulmonary compliance and patchy or diffuse alveolar infiltrates in the re-expanded lung with histologic evidence of pulmonary edema [6, 7].

Although most patients recover, re-expansion pulmonary edema can be fatal [8].

The mechanisms underlying re-expansion pulmonary edema have been investigated experimentally [9, 10, 11, 12] and indicate a possible role for neutrophils and increased capillary permeability. However, the pathogenesis of clinical re-expansion pulmonary edema has been studied in very few patients [6, 12, 13, 14] and the mechanisms in the clinical setting remain unclear. Furthermore, the capacity of the alveolar and distal airway

epithelium to remove edema fluid in the setting of re-expansion pulmonary edema has never been studied.

We therefore collected undiluted pulmonary edema fluid and plasma from seven patients with acute re-expansion pulmonary edema. The primary objective was to test the hypothesis that re-expansion edema is predominantly due to increased permeability of the alveolar-capillary barrier. By sampling undiluted pulmonary edema fluid and plasma near the onset of re-expansion edema, it was possible to measure the edema fluid to plasma protein ratio, a direct measure of permeability of the alveolar capillary barrier [15, 16, 17]. In addition, in three patients we were able to determine if the alveolar epithelium was functionally intact by measuring changes in the protein concentration in serial pulmonary edema fluid samples; a rise in edema fluid protein concentration indicates net alveolar epithelial fluid transport [16, 18].

Methods

Patient selection and clinical data collection

Between 1984 and 2001, seven patients were identified with acute clinical re-expansion pulmonary edema within 24 h of thoracentesis or tube thoracostomy. Clinical criteria for the diagnosis of re-expansion pulmonary edema included the development of hypoxemia and new infiltrates in the re-expanded lung within 24 h of thoracentesis or tube thoracostomy. Medical records were comprehensively reviewed. All chest radiographs for each patient were reviewed by two of the investigators in conjunction with a radiologist. This study was approved by the Committee for Human Research at the University of California, San Francisco and the Institutional Review Board at the University of California, Los Angeles with a waiver of informed consent.

Collection of pulmonary edema fluid

The first pulmonary edema fluid sample was collected in all seven patients at the onset of clinically evident re-expansion pulmonary edema. Serial edema fluid samples at sequential time points up to 12 h after the initial sample were collected in three of the seven patients. Pulmonary edema fluid was collected by the authors or trained respiratory therapists as previously reported [16]. Briefly, a soft 14-Fr-gauge suction catheter was advanced into a wedged position in a distal bronchus via the endotracheal tube. Pulmonary edema fluid was collected in a suction trap by gentle suction. Simultaneous plasma samples were obtained. Pulmonary edema fluid was centrifuged at 14,000 g for 20 min and plasma samples were centrifuged at 3,000 g for 10 min. The supernatants were aspirated and stored at -70°C.

Protein determination and cell counts

Protein concentrations were measured in duplicate in thawed edema fluid supernatants and plasma by the Biuret method, as previously described [16]. Edema fluid cell and differential counting were carried out using standard methods in the hospital laboratory.

Calculation of edema fluid to plasma protein ratios and alveolar fluid clearance

The ratio of the protein concentration in pulmonary edema fluid to simultaneous plasma protein was calculated as previously described [16]. A ratio equal to or less than 0.65 is diagnostic of a hydrostatic mechanism of pulmonary edema, as we and other investigators have reported [16, 17, 19]. The net rate of alveolar fluid clearance was calculated by comparing the final and initial pulmonary edema fluid protein concentrations in patients with sequential samples. This rate was expressed as a percent clearance per hour to estimate the net clearance of fluid across the distal airway and alveolar epithelium [20]. These methods have been previously validated in dog and sheep lungs [21, 22, 23], as well as in clinical studies of human pulmonary edema [16, 17, 24, 25, 26].

Results

A summary of patient clinical characteristics is presented in Table 1. All patients had the acute onset of radiographically confirmed pulmonary edema after thoracentesis or tube thoracostomy that was clinically severe and required intubation and mechanical ventilation. Prior to the drainage procedure there was no evidence of pulmonary edema in any patient. No patient had evidence of any

Table 1 Characteristics of seven patients with re-expansion pulmonary edema

Patient	Age/Gender	Diagnosis	Procedure	Volume drained (l)	Initial-PaO$_2$/FIO$_2$[a]	4 h PaO$_2$/FIO$_2$[a]	Edema fluid protein (g/dl)	Plasma protein (g/dl)	Edema-plasma protein ratio	Alveolar fluid clearance (%/h)	Days ventilated/outcome
1	66/F	Post coronary artery bypass graft with pneumothorax	CT	Air	224	314	0.6	4.9	0.12	NA	2/Died
2	41/F	Post pericardotomy	CT	2.0	120	79	3.9	6.8	0.58	NA	3/Survived
3	24/M	Lymphoma	T	1.6	61	Expired	2.9	4.8	0.59	NA	1/Died
4	31/M	Lymphoma	T	2.4	61	71	3.9	6.0	0.65	4	1/Died
5	39/M	Hepato-hydrothorax	T	2.5	76	147	3.4	5.1	0.67	7	17/Survived
6	58/F	Post pericardotomy	O	1.5	310	375	3.8	5.3	0.71	NA	1/Survived
7	32/F	Iatrogenic pneumothorax	CT	Air	225	350	4.0	5.2	0.77	19	5/Survived

CT chest tube drainage, *T* thoracentesis, *O* operative drainage
[a] Initial PaO$_2$/FIO$_2$ ratio at time of edema fluid sampling and 4 h after edema fluid sampling

Table 2 Relationship of sampling interval to initial edema fluid to plasma protein ratio

Patient	Time from drainage procedure to intubation (h)	Time from drainage procedure to edema sampling (h)	Edema fluid to plasma protein ratio
1	6	6	0.12
2	3	4	0.58
3	2	2	0.59
4	4.5	4.75	0.65
5	Intubated prior to drainage	2.25	0.67
6	1.25	1.75	0.71
7	1	1	0.77

other underlying cause of pulmonary edema, such as acute lung injury or heart failure, that would alter the protein concentrations present in the airspace fluid or the fluid-absorbing capability of the alveolar epithelium. Three patients ultimately died. Patient 1 died from the consequences of a cardiac arrest. Patient 3 died from widespread lymphoma; at autopsy there was evidence of pulmonary edema, but no histologic evidence of diffuse alveolar damage. Patient 4 died from pericardial tamponade due to lymphomatous involvement of the pericardium.

Pulmonary edema fluid analysis

The mean initial edema fluid to plasma protein ratio, a measure of alveolar-capillary barrier permeability was 0.58±0.21, suggesting that hydrostatic forces contributed to the formation of pulmonary edema in these patients. Four of the seven patients had an initial edema fluid to plasma protein ratio less than 0.65 (Table 1), consistent with pure hydrostatic pulmonary edema. Three patients had edema fluid to plasma protein ratios greater than 0.65 (mean value of 0.72), a finding that is consistent with a modest increase in protein permeability [16, 17, 19]. There was no correlation between the time interval from drainage to edema fluid sampling and the initial edema fluid to plasma protein ratios (Table 2).

In five patients, sufficient pulmonary edema fluid was obtained to analyze cell counts. The edema fluid white blood cell counts were 0.013–207 cells/μl (mean 42.0 cells/μl) with 41–94% neutrophils. The edema fluid red blood cell counts were 0.28–315 cells/μl (mean 64.4 cells/μl).

Resolution of alveolar edema

Serial sampling of pulmonary edema fluid allowed calculation of the net rate of alveolar fluid clearance in three patients. All of these patients had intact alveolar fluid clearance (Table 1), ranging from 4–19%/h with a mean of 9.8±8.0%/h. Over the time frame studied, the presence of intact clearance was not associated with any change in ventilator parameters, such as tidal volume or the level of

positive end-expiratory pressure (PEEP). All patients were ventilated in an intermittent mandatory ventilation mode with tidal volumes averaging 10 ml/kg (range 5.9–14.9 ml/kg). PEEP levels ranged from 5 to 12 cmH$_2$0 and the level of PEEP was not changed during the time of sequential edema fluid sampling. There was no correlation between higher tidal volumes or PEEP and higher protein concentrations in the edema fluid.

Cardiac and hemodynamic data

Normal left ventricular systolic function was documented in four of the seven patients by echocardiography. Hemodynamic monitoring (two patients with a central venous catheter, one with pulmonary artery catheter) was performed on the day of the drainage procedure in three patients. Patient 4 had a pulmonary arterial wedge pressure of 16 mmHg at the time of edema fluid sampling. Patients 1 and 6 had central venous pressures of 5–9 and 8–12 mmHg, respectively, on the day of edema fluid sampling.

Radiographic data

All seven patients had patchy or diffuse infiltrates in the re-expanded lung consistent with re-expansion edema. Review of serial radiographs demonstrated that the infiltrates developed after the re-expansion of the lung in all patients. There was no radiographic evidence of pulmonary edema prior to the drainage procedures.

Discussion

The primary objective of this observational study was to test the hypothesis that re-expansion pulmonary edema is due to increased protein permeability of the alveolar-capillary barrier. This was accomplished by measuring the ratio of pulmonary edema fluid to plasma protein concentration at the onset of re-expansion edema. The second objective was to study the alveolar fluid transport capacity of the re-expanded lung by measuring the protein concentration in serial pulmonary edema fluid samples in

a subset of the patients in whom serial samples were available.

Unexpectedly, the mean edema fluid to plasma protein ratio was 0.58±0.21 and the initial edema fluid to plasma protein ratio was less than or equal to 0.65 in four of the seven patients, suggestive of a contribution of hydrostatic mechanisms to the edema formation. There was no evidence that elevated intravascular pressures contributed to edema formation. Analysis of the hemodynamic parameters and echocardiography did not reveal any evidence of left ventricular systolic dysfunction or volume overload in this group of patients. This finding is consistent with prior reports in which re-expansion pulmonary edema has been noted to occur in patients with documented hypovolemia [27, 28].

The pathogenesis of re-expansion pulmonary edema is unknown. A number of mechanisms have been suggested, including increased permeability of pulmonary capillaries, a decrease in perivascular pressure, ischemia reperfusion injury, free radical injury, the effects of a high negative pressure, decreased functional surfactant, atelectasis, hypoperfusion, tissue injury secondary to stretching, airway obstruction, hypoxia and decreased lymph flow [8, 29]. During the re-expansion, heterogeneous areas of hypoxic vasoconstriction may lead to areas of under-perfusion and over-perfusion [30]. Higher perfusion in areas of high negative pressure or decreased lymph flow as well as pulmonary venous constriction may lead to hydrostatic edema.

The finding of a low edema fluid to plasma protein ratio in the majority of our patients suggests that hydrostatic forces probably play an important role in the development of re-expansion edema. Also, the edema fluid to plasma protein ratio in three of the seven patients in whom the level was greater than 0.65 was only very modestly elevated with a mean value of 0.72. In our prior studies of patients with clinical acute lung injury and the acute respiratory distress syndrome, the alveolar capillary barrier permeability was much higher, with mean initial edema fluid to plasma protein ratios typically greater than 0.90. For example, in three recent studies of a total of 108 patients with acute lung injury and the acute respiratory distress syndrome, the mean edema fluid/plasma protein ratio was 0.92 [31], 0.94 [17] and 0.98 [25], indicating that the level of 0.72 in three of the seven patients in this study reflects only a modest increase in alveolar-capillary permeability to protein.

Our findings stand in contrast to two previous reports of increased protein concentrations in the pulmonary edema fluid of some patients with re-expansion pulmonary edema [6, 32]. However, only three patients were included in these studies. Furthermore, the time interval between the collection of pulmonary edema after the onset of pulmonary edema was not reported. If there was a delay in collecting the edema fluid, then re-absorption of salt and water would result in an increased protein concentration in the edema fluid, a finding that would then be misinterpreted as indicative of increased permeability edema as the primary mechanism for edema formation. In our study, the initial samples were collected as soon as clinically feasible after the onset of re-expansion edema, and all were collected within 6 h of the inciting drainage procedure (mean 3.1±1.8 h). There was no correlation between the time of sampling and edema fluid to plasma protein ratio (Table 2).

Based on the new data in this study, hydrostatic mechanisms appear to contribute to the development of acute lung edema in re-expansion pulmonary edema. In some patients there is a small increase in protein permeability. One potential unifying explanation for the findings in this study is that hydrostatic forces initiate edema formation after acute re-expansion of the lung; but in some patients there is an associated stress capillary failure that results in a transient increase in protein permeability, as others have described [33, 34]. In fact, West and colleagues have proposed that alveolar capillary stress failure can occur in the setting of heterogeneous re-expansion of atelectatic lung, leading to a mixed picture of protein-poor (hydrostatic) and increased permeability edema [34]. This concept of high pressure-induced traumatic breaks in the basement membranes of the alveolar capillary barrier has been demonstrated in animal models, cardiogenic pulmonary edema, neurogenic pulmonary edema and high altitude pulmonary edema [34]. Thus, hydrostatic forces in patients with clinical re-expansion pulmonary edema may occur in some subjects without injury to the alveolar capillary barrier, while leading to injury in others.

This interpretation is also consistent with several previous experimental reports that have found that re-expansion pulmonary edema is characterized by the recruitment of neutrophils, the release of neutrophil granular contents in the air spaces and increased vascular permeability that are correlated with increased interleukin-8 and monocyte chemotactic protein concentrations in the bronchoalveolar lavage fluid [6, 10, 11, 35]. A number of clinical studies have reported the presence of inflammatory biologic markers in patients with hydrostatic pulmonary edema [36, 37]. In addition, patients with hydrostatic edema have elevated levels of platelet activating factor in their bronchoalveolar lavage fluid and significantly negative transpulmonary gradients of E-selectin and L-selectin in their serum [38, 39]. Finally, in experimental studies, a pure hydrostatic pressure elevation in lung capillaries increases the endothelial expression of P-selectin, suggesting that a hydrostatic stress alone may induce white cell adhesion and inflammation [40, 41]. In keeping with this hypothesis, patients with hydrostatic pulmonary edema may have significant neutrophilia in their pulmonary edema fluid [24].

Alveolar fluid clearance, an important function of the alveolar epithelium, was intact in the three patients in

whom it was measured. Net alveolar fluid clearance was quantified by measuring serial protein concentrations in the pulmonary edema fluid, a method that has been validated and used by many investigators to quantify alveolar fluid clearance [16, 17, 24, 25, 42]. Although the sample size was small, the presence of intact alveolar fluid clearance is consistent with previous measurements of alveolar fluid clearance in patients with hydrostatic pulmonary edema [24].

In conclusion, the results of this study provide some evidence that hydrostatic forces in the lung microcirculation generated by rapid re-expansion of the collapsed lung may contribute to clinical re-expansion pulmonary edema.

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