Evidence for a Hydrostatic Mechanism in Human Neurogenic Pulmonary Edema*

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Study objectives: To identify the relative contribution of hydrostatic and permeability mechanisms to the development of human neurogenic pulmonary edema.

Design: Retrospective review of patients with neurogenic pulmonary edema who had pulmonary edema fluid analysis.

Setting: University hospital ICU.

Patients: Twelve patients with neurogenic pulmonary edema in whom the associated neurologic condition was subarachnoid hemorrhage (n=8, 67%), postcraniotomy (n=2), and stroke (n=2). Measurements: Protein concentration was measured from pulmonary edema fluid and plasma samples obtained shortly after the onset of clinical pulmonary edema.

Results: The mechanism of pulmonary edema was classified according to the initial alveolar edema fluid to plasma protein concentration ratio. A hydrostatic mechanism (ratio ≥0.65) was observed in seven patients, none of whom had cardiac failure or intravascular volume overload. Five patients had evidence for increased permeability (ratio >0.70). Patients with a hydrostatic mechanism had better initial oxygenation (mean±SD PaO₂/FIO₂ [fraction of inspired oxygen]=233±132) compared with patients with increased permeability (PaO₂/FIO₂=80±42), and oxygenation improved more rapidly in the hydrostatic patients. Overall mortality (58%) was high, but it was related to unresolved neurologic deficits, not to respiratory failure.

Conclusion: Many of our patients had a hydrostatic mechanism for neurogenic pulmonary edema. This is a novel observation in humans since prior clinical case reports have emphasized increased permeability as the usual mechanism for neurogenic pulmonary edema. These findings are consistent with pulmonary venoconstriction or transient elevation in left-sided cardiovascular pressures as contributing causes to the development of human neurogenic pulmonary edema.

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Key words: acute lung injury; pulmonary edema; pulmonary venoconstriction; respiratory failure; subarachnoid hemorrhage

Abbreviations: FIO₂=fraction of inspired oxygen

Florid pulmonary edema can develop acutely in patients who have sustained sudden neurologic injury, including subarachnoid hemorrhage,1–5 intracranial hemorrhage,6,7 head injury,8–10 stroke,11,12 acute hydrocephalus,13,14 and seizure.2,5,15–27 The development of pulmonary edema in the setting of a sudden neurologic event is termed neurogenic pulmonary edema (see Simon28 for review.) Despite many experimental studies in animals, the mechanisms responsible for the development of neurogenic pulmonary edema remain uncertain. In animal models of neurogenic pulmonary edema, evidence for a change in pulmonary vascular permeability has been reported,29,30 suggesting that central mechanisms can alter the barrier function of lung endothelium. Direct damage by high intravascular pressures has been proposed to explain this change in lung vascular permeability.31 However, in some animal models of neurogenic pulmonary edema, increased permeability is not the predominant mechanism.32

Little published data exist on the type of edema found in humans with neurogenic pulmonary edema. To our knowledge, we report the largest human series in which alveolar edema fluid was obtained shortly after the onset of clinical pulmonary edema in patients with sudden neurologic events. Considerable effort was taken to exclude other causes of pulmonary edema, such as cardiac failure and aspi-

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ration of gastric contents. Analysis of the data indicates that humans with neurogenic pulmonary edema commonly have a hydrostatic mechanism for pulmonary edema in the setting of an acute neurologic insult. These data suggest that injury to the pulmonary capillary endothelium is not necessarily a consistent feature of human neurogenic pulmonary edema and lend support to the theory that pulmonary venoconstriction or transiently elevated cardiovascular pressures may have a major role in the development of neurogenic pulmonary edema.

MATERIALS AND METHODS

The hospital charts of all patients who developed potential neurogenic pulmonary edema (see below) and had pulmonary edema fluid analysis between October 1982 and May 1994 at Moffitt-Long Hospital at the University of California, San Francisco were reviewed retrospectively.

Patients were classified as having potential neurogenic pulmonary edema if marked pulmonary edema occurred in the setting of a sudden change in their neurologic condition. Sixteen patients were identified who satisfied these conditions. Two patients were excluded because of a history of cardiac disease (coronary artery disease and previous myocardial infarction); both patients developed clinically apparent cardiac failure following stroke. One patient was excluded for observed aspiration of gastric contents, and another patient with intracranial hemorrhage was excluded because pulmonary edema occurred in the setting of reexpansion of an iatrogenic pneumothorax. The remaining 12 patients were classified as having neurogenic pulmonary edema and constituted the study population. All were free of known cardiac disease prior to their neurologic event.

Edema fluid was obtained in most patients by one of the authors (M.A.M.) and clinical data were recorded at the time of fluid collection. The hospital charts of all 12 patients were reviewed carefully for clinical history, diagnosis, time of onset of neurologic event, arterial blood gases, and fractional partial pressure of inspired oxygen (FIO₂). In addition, the following data were obtained from the hospital chart when available: ECG, QT interval (expressed as QTC=QT/[R-R]1/2 where R-R is the preceding R to R interval to the QT measurement), serial cardiac enzymes (creatine kinase with isoenzymes and lactate dehydrogenase), and measurements of hemodynamic parameters, including central venous pressure. Pulmonary arterial pressures were measured in only one patient (described in “Results” section).

After endotracheal intubation, 1 to 2 mL of pulmonary edema fluid was suctioned by an in-line trap with no prior irrigation of the catheter or endotracheal tube with saline solution, as we have done before.33 The specimens were centrifuged and the supernatant was frozen at −70°C until the total protein concentration was measured. A paired plasma sample was obtained for measurement of total protein in the plasma.

The total protein concentration of the pulmonary edema fluid and simultaneous plasma samples were expressed as a ratio (edema fluid to plasma protein ratio) because of its proven utility in distinguishing hydrostatic from increased permeability as a mechanism for pulmonary edema.7,25–27 Ratios ≤0.65 were classified as representing hydrostatic pulmonary edema. Ratios >0.70 were considered to be consistent with an increase in lung endothelial and epithelial permeability.

The time between the neurologic ictus and edema fluid sampling was recorded. For patients whose ictus was not observed, the time of ictus was marked halfway between the last time the patient was seen healthy and the time of being found. The ability to oxygenate patients was expressed as an index of the partial pressure of arterial oxygen (PaO₂, mm Hg) to the delivered FIO₂ (PaO₂/FIO₂); high indexes represent lower alveolar-to-arterial oxygen differences while low values represent larger differences.

Test of statistical significance for differences in the initial oxygenation and QT intervals utilized the Student’s pooled t test for difference of means in groups of different sample size.

RESULTS

Patient Diagnoses and Demographics

Sixteen patients over a 12-year period developed sudden onset of pulmonary edema following a change in neurologic condition; all had pulmonary edema fluid obtained for analysis. Patients with concomitant cardiac disease, gastric aspiration, or another potential cause (reexpansion pulmonary edema) were excluded (four patients, see “Materials and Methods” section) to focus on patients with no cause for pulmonary edema other than a sudden change in neurologic status. These 12 patients constitute the group classified as having neurogenic pulmonary edema (Table 1).

Eight patients suffered subarachnoid hemorrhage; in seven of these eight patients, the source of bleeding was from an intracranial saccular aneurysm. Two patients suffered a stroke: one had a complete middle cerebral artery stroke and the other had a cerebellar hemorrhage. Two other patients developed pulmonary edema postoperatively after resection of cerebral arteriovenous malformations. Five patients sustained their neurologic event in the hospital and the other seven were endotracheally intubated at home or in the emergency department.

Pulmonary Edema Fluid Analysis

The pulmonary edema fluid protein to plasma protein ratio was calculated from the first available specimen from each patient (Fig 1). Seven patients had edema fluid protein to plasma protein ratios under 0.65 (range, 0.43 to 0.64) while five exceeded 0.70 (range, 0.71 to 1.3) (Table 1). Average edema to plasma protein ratios (±SD) were 0.54±0.09 and 0.99±0.26 for the hydrostatic and the increased permeability groups, respectively. The edema fluid protein to plasma protein ratios tended to be higher when sampled with greater latency from the neurologic ictus (Fig 1). However, this was not a consistent finding since two of the five patient samples obtained 10 or more hours after the neurologic event had a ratio ≤0.65 (Fig 1). Since some of these samples may have been obtained during the resolution of alveolar edema, edema fluid protein to plasma protein ratios may have been increased in some patients owing to

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active sodium and fluid transport across the alveolar epithelium33,36 (see “Discussion” section).

**Radiologic Data**

Review of chest radiography revealed no distinguishing feature that could separate patients with a hydrostatic mechanism from patients with an increased permeability mechanism for their neurogenic pulmonary edema (Fig 2).

**Cardiopulmonary Data**

Initial systemic BPs at the time of the acute neurologic event were not different between the hydrostatic and increased permeability groups (Table 1). Initial blood gas samples revealed a range of oxygenation abnormalities (Fig 3). The mean PaO2/FIO2 index for the hydrostatic group was significantly higher than the permeability group (p<0.033), but the small sample size makes this conclusion tentative. When all arterial blood gas values were plotted (Fig 4), the hydrostatic group had better oxygenation than patients with increased permeability edema over the first 24 h. The patient’s respiratory status, however, did not influence mortality since six of the seven deaths were in the hydrostatic group; death was from a neurologic cause in all patients and none died from respiratory failure. Pulmonary artery pressures were available in only one patient. He developed subarachnoid hemorrhage after attempted endovascular embolization of an intracranial aneurysm. Immediately following subarachnoid hemorrhage, he was endotracheally intubated and then he developed ventricular tachycardia. Florid pulmonary edema developed and he was resuscitated with cardioversion, epinephrine, and atropine. A pulmonary artery catheter, which was inserted 2 h after the onset of pulmonary edema, revealed a pulmonary artery wedge pressure of 14 mm Hg, cardiac output of 4.4 L/min, and systemic vascular resistance of 1,354 mm
Figure 2. Anteroposterior chest radiographs showing bilateral pulmonary densities consistent with pulmonary edema from (top) a patient with edema to plasma protein ratio of 0.62 (hydrostatic group), and (bottom) edema to plasma protein ratio of 0.99 (increased permeability group).

Edema fluid was sampled at 88 min after subarachnoid hemorrhage revealing an edema protein to plasma protein ratio of 0.71, classifying the patient in the increased permeability group.

ECGs were available in nine patients. Four of these nine patients had prolonged QT intervals using QTc>0.44 s for men and QTc>0.45 s for women (Table 1). Serial cardiac enzyme levels were measured in four patients (Table 1), including two of the four with prolonged QT interval; none had evidence of increased MB fraction of creatine kinase. QT intervals became normal within 1 to 2 days in all patients except one whose interval was initially normal and later developed QT prolongation (QTc=0.49 s) before her death. QTc intervals did not differ between hydrostatic (0.447±0.04 s) and increased permeability groups (0.453±0.03 s).

DISCUSSION

Neurogenic pulmonary edema is characterized by an increase in extravascular lung water in patients who have sustained a sudden change in neurologic condition.\textsuperscript{28,37} The mechanism by which neurogenic pulmonary edema occurs is not clear, and two divergent theories have been proposed to explain its development: increased lung capillary permeability or increased pulmonary vascular hydrostatic pressures.

Figure 3. Initial blood oxygenation in patients with neurogenic pulmonary edema expressed as the ratio of measured \( P_{O_2} \) (mm Hg) divided by the \( FIO_2 \); lower ratios indicate a more severe oxygenation deficit. Data shown as mean ±SD.

Figure 4. Time course of oxygenation, expressed as \( P_{O_2}/FIO_2 \), for patients with hydrostatic and increased permeability pulmonary edema. Shading indicates 95% confidence intervals of linear regression for each group.
Increased permeability as a mechanism for neurogenic pulmonary edema is supported by some animal studies that have reported high interstitial (lung lymphatic) or alveolar protein concentrations in the cat,\textsuperscript{35} rat,\textsuperscript{39} rabbit\textsuperscript{29,40} and sheep.\textsuperscript{11} Increased permeability may be caused by damage to the capillary endothelium or by direct neural influences on capillary permeability. Theodore and Robin\textsuperscript{31} advanced the "blast theory" which proposes that a neurally induced transient rise in intravascular pressure may damage the endothelium causing protein-rich plasma to escape into the interstitial and alveolar spaces. In support of this theory, high intravascular pressures have been shown to damage pulmonary capillaries,\textsuperscript{42,43} and such high pressures can develop in animals during experimental neurogenic pulmonary edema.\textsuperscript{32,44} In humans, elevated pulmonary artery wedge pressures have been observed in a few cases.\textsuperscript{7,45} However, pulmonary edema can develop with normal pulmonary artery wedge pressures (Table 2), suggesting a neural-mediated, pressure-independent influence on capillary permeability.\textsuperscript{1,14}

Prior to this report, measurement of pulmonary edema fluid protein has been reported in only 12 patients in five different studies (Table 2). In most patients, the edema fluid protein to plasma protein ratios exceed 0.70, suggesting increased permeability as the mechanism for neurogenic pulmonary edema. In one study,\textsuperscript{11} the authors reported that the edema fluid protein to plasma protein ratio "reached" 0.90 in five patients, but they did not report the time of sampling relative to the time of onset of pulmonary edema. In another study of four patients, half of the patients did have a ratio \( \leq 0.65.\textsuperscript{34}"

Our data suggest that hydrostatic edema forms in patients with neurogenic pulmonary edema not infrequently, contrary to the conclusions of several prior clinical reports. In most of these clinical reports, the interval from the onset of pulmonary edema to sampling of edema fluid was not reported. Edema fluid protein concentration rises as salt and water are actively transported from the alveoli.\textsuperscript{33} Also, alveolar fluid clearance is accelerated by high plasma epinephrine levels,\textsuperscript{36} which may be present in patients with sudden changes in neurologic condition.\textsuperscript{35,46} Therefore, the time from onset of clinical edema to time of fluid sampling is critical for interpreting edema fluid protein to plasma protein ratios. Since the latency period was not reported in previous case reports, some cases of apparent increased permeability pulmonary edema may actually represent hydrostatic edema sampled during the resolution phase. In fact, in our study, two patients also had edema fluid sampled at later time intervals (840 and 845 min) with relatively high ratios (1.1 and 1.3) consistent with resorption of alveolar fluid. Thus, it is possible then that even more of our patients had a hydrostatic mechanism for their edema. Taken together with four other patients described previously from our institution,\textsuperscript{34} 9 of 16 total patients (56\%) had unequivocal evidence for a hydrostatic mechanism for their pulmonary edema. Two patients who had edema fluid sampled within 2 h did have ratios exceeding 0.65 (Fig 1), suggesting that fluid absorption alone does not explain all cases of high edema fluid protein concentration in neurogenic pulmonary edema.

Interestingly, our data are in agreement with

<p>| Table 2—Previous Reports of Neurogenic Pulmonary Edema With Edema Fluid Analysis or Hemodynamic Monitoring* |
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<table>
<thead>
<tr>
<th>N</th>
<th>Edema/Plasma Protein Ratio</th>
<th>PCWP</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>&quot;Reached&quot; 0.90</td>
<td>5.3 + 1.1 mm Hg</td>
<td>Brainstem stroke; postoperative resection of brainstem tumor</td>
</tr>
<tr>
<td>1</td>
<td>0.76+0.06</td>
<td>40 mm Hg</td>
<td>Intracranial hemorrhage</td>
</tr>
<tr>
<td>1</td>
<td>0.86</td>
<td>4 mm Hg</td>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>4</td>
<td>1.25</td>
<td>12 mm Hg</td>
<td>Status epilepticus</td>
</tr>
<tr>
<td>1</td>
<td>0.92</td>
<td>5 mm Hg</td>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>1</td>
<td>0.64</td>
<td>5 mm Hg</td>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>1</td>
<td>0.61</td>
<td>5 mm Hg</td>
<td>Epidural hematoma</td>
</tr>
<tr>
<td>1</td>
<td>0.85</td>
<td>4 mm Hg</td>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>15</td>
<td>Not done</td>
<td>7.8 + 2.1 mm Hg</td>
<td>Intracranial hemorrhage; subarachnoid hemorrhage</td>
</tr>
<tr>
<td>1</td>
<td>Not done</td>
<td>CVP &quot;normal&quot;</td>
<td>Closed head injury</td>
</tr>
<tr>
<td>1</td>
<td>Not done</td>
<td>5 mm Hg</td>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>1</td>
<td>Not done</td>
<td>4, 48, 20 mm Hg</td>
<td>Intracranial hemorrhage, known congestive heart failure; three episodes of pulmonary edema</td>
</tr>
<tr>
<td>1</td>
<td>Not done</td>
<td>CVP=3 cm H2O</td>
<td>Status epilepticus</td>
</tr>
<tr>
<td>1</td>
<td>Not done</td>
<td>CVP=6 cm H2O</td>
<td>Acute hydrocephalus; colloid cyst of the third ventricle</td>
</tr>
</tbody>
</table>

* CVP=central venous pressure; PCWP=pulmonary capillary wedge pressure.

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obtained, were pulmonary edema, veratrine intracisternal neurogenic whom hemodynamic onsets. In Serial cardiac problems. In hospital, one protein was 0.65 on the of our patients developed their neurologic event out of the hospital, five of these seven had initial edema fluid protein to plasma protein ratios under 0.65, a finding that is inconsistent with aspiration. Of the five in whom neurogenic pulmonary edema occurred in the hospital, one developed neurogenic pulmonary edema while intubated and the other four were tracheally intubated by a “code blue” team. None of these five patients had clinical aspiration on direct visualization of the upper airway and none had eaten in the preceding 12 h.

In our series, patients included as having neurogenic pulmonary edema had no history of cardiac problems. Serial cardiac enzymes were sampled in four patients and were nondiagnostic for myocardial infarction. In the 10 patients who had more than one ECG, no evolution of ECG changes consistent with acute myocardial infarction was observed. Many of our patients developed QT prolongation, a finding that is often observed in subarachnoid hemorrhage and other sudden neurologic events (see article by Samuels47). The release of catecholamines during the ictus may induce this conduction disturbance and cause cardiac pump failure.1 Since we did not measure pulmonary artery pressures in most patients or do echocardiography, we cannot exclude a transient or persistent rise in vascular pressures causing neurogenic pulmonary edema in our patients. In the one patient in whom pulmonary artery pressures were obtained, the catheter was inserted 2 h after the onset of pulmonary edema which may have missed a significant, transient rise in pulmonary artery pressures. Typically, in the few reported cases in which hemodynamic measurements have been made, pulmonary arterial wedge pressures have been normal (Table 2). These data must be distinguished from patients who develop direct myocardial depression with reduced ejection fraction and congestive heart failure during the neurologic ictus, as reported by Mayer et al.1 In their series, even though they confirmed a depressed ejection fraction echocardiography in five patients with subarachnoid hemorrhage, only one of the four monitored invasively had a pulmonary artery wedge pressure above 12 mm Hg when first measured. These pressures were measured at least 14 h after subarachnoid hemorrhage and therefore may not represent intravascular pressures at the time of ictus. Similarly, in the largest series in which pulmonary arterial pressures have been reported in neurogenic pulmonary edema, Touho et al48 found normal pulmonary artery occlusion pressures in all 15 patients who developed a significant alveolar-to-arterial oxygen gradient and increased lung water. However, the time of measurement of hemodynamic parameters relative to the neurologic ictus was not reported. This underscores the need to record hemodynamic parameters during such a neurologic event to document whether intravascular pressures do rise transiently and substantially. Also, review of the chest radiographs in our patients (Fig 2) did not identify features that could distinguish hydrostatic from increased permeability as the mechanism of pulmonary edema, as we have previously reported.49

Whether hydrostatic pulmonary edema can be produced with normal cardiac filling pressures in neurogenic pulmonary edema is unknown, but hydrostatic pulmonary edema could be caused by active pulmonary venoconstriction. Pulmonary veins contain smooth muscle which, when constricted, can cause hydrostatic edema in the dog with induced intracranial hypertension.50 In an isolated lung model, elevated resistance to pulmonary blood flow has been found during induced intracranial hypertension.50 This increased resistance is produced by venoconstriction, precipitated perhaps by circulating catecholamines, predominantly epinephrine.51 Active pulmonary venoconstriction raises capillary pressures and can produce hydrostatic edema. Even though pulmonary venous pressure would rise, pulmonary artery wedge pressure would be normal or low because blood flow through the measured vascular segment is prevented with the occlusion balloon. Such a mechanism could explain both the observed variance in pulmonary edema protein concentration and the presence of normal “wedge pressure” in humans who develop neurogenic pulmonary edema. In addition, a direct, neurally mediated increase in capillary permeability as discussed above could cause pulmonary edema without a change in the pulmonary artery occlusion pressure. It is likely that a combination of factors produces neurogenic pulmonary edema and the relative balance of each
determines the type and extent of edema for any given patient. For example, the volume status of the patient, the left ventricular compliance, and perhaps degree of autonomic neuropathy in any patient could influence the pressure changes at the pulmonary capillary during a neurologic ictus.

In summary, in the largest single series of patients with neurogenic pulmonary edema in which pulmonary edema fluid has been evaluated, the primary mechanism of neurogenic pulmonary edema was commonly related to hydrostatic mechanisms. These data provide evidence to support transient left heart failure or neurally mediated pulmonary venoconstriction as possible mechanisms for the development of neurogenic pulmonary edema in humans.

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