Pulmonary edema is an uncommon but potentially fatal complication of epilepsy and status epilepticus. Its pathogenesis remains uncertain. Such postictal pulmonary edema has been suggested as the cause of sudden, unexplained death in epileptics.1

Our previous and current studies of the pulmonary vascular sequelae of status epilepticus are performed in adult sheep in which pulmonary lymphatic flow is used to quantify transcapillary fluid flux in lung.2 In earlier work, we found that seizures produced a marked, but brief, elevation in pulmonary vascular pressures and a subsequent prolonged increase in pulmonary lymph flow.3 We subsequently demonstrated that the lymph flow elevation is caused by the pulmonary vascular hypertension, as such lung fluid flux alterations can be duplicated by mechanical pulmonary vascular pressure elevations in the absence of nervous system manipulation.4 Because pulmonary transcapillary fluid flux increases steeply with high pulmonary vascular pressures,5 and the magnitude of the pulmonary vascular pressure changes predict pulmonary edema in some models,6,7 we studied the effect of seizures on pulmonary vascular pressures and resultant lung lymph flow in animals with baseline elevations of pulmonary vascular pressures and compared these findings with those in animals previously studied that were subjected to status epilepticus alone.

METHODS

Five fasted well-hydrated female Suffolk sheep weighing 35 to 40 kg were studied. Anesthesia was induced with thiopental sodium and maintained with 1 percent halothane delivered in a mixture of 60 percent oxygen and 40 percent nitrous oxide. Catheters were placed in the femoral artery (Ao) and vein and through a left thoracotomy into the pulmonary artery (PA) and left atrium (LA). A 30-ml balloon (Foley) catheter also was placed in the LA. Through a right thoracotomy, the caudal mediastinal node was identified, its caudal tip resected and efferent duct cannulated; diaphragmatic lymphatics were cauterized. Both sides of the chest were left open and the animals ventilated with 5 cm water positive end-expiratory pressure. Arterial blood gases were monitored every 30 min and partial pressure of carbon dioxide (Pco2) maintained between 35 and 45 mm Hg by ventilatory adjustment. Vascular pressures were continually displayed on a polygraph recorder and lymph and plasma samples collected at 15-min intervals. Cardiac output was measured by thermal dilution technique each 15 min.

Animals were maintained until one hour of stable vascular pressures and lymph flow had occurred. Saline solution was then gradually infused into the left atrial balloon until a LA pressure of approximately 25 mm Hg was reached. Care was taken to avoid systemic hypotension during balloon inflation. Vascular pressures and lymph flow then were permitted to stabilize. When two hours of new stable vascular pressures and pulmonary lymphatic flow (Ql) were obtained, the animals were paralyzed with gallamine triethiodide (5 mg/kg), halothane anesthesia was discontinued and status epilepticus was induced by intravenous administration of bicuculline (2 mg/kg), a gamma amino butyric acid inhibitor that produces status epilepticus but has no direct effect on lung lymph flow or protein flux.8,9 Continual seizure activity was confirmed by electroencephalographic monitoring.

The total protein concentration of each lymph and simultaneously collected plasma sample was ascertained by a modified Biuret method and the albumin determined by a BCG dye-binding method using a Technicon auto analyzer. The statistical significance was ascertained using repeated mea-

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sures analysis of variance with a Newman-Keuls' and Duncan's multiple-range post hoc test. These data were then compared with those from nine animals previously reported that were identically prepared except that status epilepticus was induced without prior elevation of LA pressure. Although not previously published, the five animals reported here were studied during the same year as the nine animals in the previously published work.

RESULTS

Following a one-hour stable baseline level, LA pressure was increased to 25 mm Hg (16 to 22 mm Hg > baseline) over approximately 15 min. With the increase in LA, the mean PA rose from 19.6 to 30.4 mm Hg. There was no change in central venous pressure.

The new steady state lymph flow was 24.2 ± 16.3 ml/h, a doubling from the pre-balloon inflation baseline value of 11.7 ± 7 ml/h. During the same period of time, the lymph-to-plasma protein ratio fell 26 percent from 0.68 to 0.50.

Following two hours of stable vascular pressures and lymph flow, status epilepticus was induced, which continued for the duration of the experiment. Within 15 s of the onset of seizure activity, mean aortic pressure rose from 84 to 220 mm Hg, and then slowly returned to baseline over 45 min. Cardiac output increased slightly (from 2.1 to 2.6 L/min) during the first half hour only. Pulmonary vascular pressures were elevated for the first 15 min (LA, from 25 to 57 mm Hg and PA, from 30 to 65 mm Hg). The lymph flow elevation following the seizure reached a mean of 31 ± 15 ml/h at the end of the first hour of seizure activity (26 percent greater than the post-balloon inflation value and 173 percent greater than the pre-balloon inflation baseline). Lymph flow remained elevated at a mean of 30 to 32 ml/h for the duration of the experiment (2.5 h following seizure onset). During the seizure-induced elevation in Qv, the mean lymph-to-plasma protein (L/P) ratio dropped from 0.50 to 0.44, but this decrease was not significant (Fig 1, Table 1).

DISCUSSION

We compared the pulmonary vascular response to seizures in five sheep prepared with preseizure elevation in pulmonary vascular pressure, to that of nine animals studied during seizures alone. We examined variables in three areas: vascular pressures, pulmonary lymph flow, and the L/P ratio.

The systemic vascular response to seizures was identical in the two groups (ie, seizures alone vs seizures with elevated pulmonary vascular pressures) both in the amount of the increase and in the length of time the systemic pressure (Ao) was elevated (Table 1). Although the elevation in pulmonary vascular pressures induced by the seizure also was identical in the two groups, a notable difference was that the animals with LA balloon inflation started the pulmonary vascular seizure-induced rise from a much higher baseline of 25 mm Hg LA pressure. In fact, the actual maximum pulmonary vascular pressure obtained in these animals was almost 20 mm Hg higher than in animals experiencing seizures alone (Fig 2). In both groups, the cardiac output also briefly rose −0.5 L/min during the first half hour following the onset of the seizure, and then returned to a steady baseline level. Thus, the baseline pulmonary vascular pressures do not alter the magnitude of the systemic or pulmonary vascular response (ie, the pressure change from baseline) to a seizure (Fig 2).

The lung lymph flow in sheep increases following the spike of pulmonary microvascular pressure, peaking at twice the baseline value by 45 min, and remaining significantly elevated as long as four hours after the onset of seizures. Similar changes occur following the transient brief pulmonary vascular pressure elevations following norepinephrine infusion and transient pressure elevation induced by balloon inflation or intravascular saline infusions. In animals

**Table 1—Vascular Pressures and Lung Fluid Flux during Seizures**

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>After LA Balloon</th>
<th>Peak</th>
<th>15 min</th>
<th>30 min</th>
<th>60 min</th>
<th>120 min</th>
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<tbody>
<tr>
<td>Aa</td>
<td>99 ± 15</td>
<td>238 ± 19†</td>
<td>179 ± 20†</td>
<td>124 ± 22†</td>
<td>93 ± 19</td>
<td>86 ± 15</td>
<td></td>
</tr>
<tr>
<td>PVH + sz</td>
<td>94 ± 15</td>
<td>84 ± 13</td>
<td>220 ± 19†</td>
<td>163 ± 21†</td>
<td>132 ± 24†</td>
<td>87 ± 28</td>
<td>68 ± 22</td>
</tr>
<tr>
<td>PA</td>
<td>19 ± 4</td>
<td>43 ± 23†</td>
<td>19 ± 7</td>
<td>19 ± 6</td>
<td>18 ± 6</td>
<td>17 ± 6</td>
<td></td>
</tr>
<tr>
<td>PVH + sz</td>
<td>19 ± 6</td>
<td>30 ± 4</td>
<td>65 ± 17†</td>
<td>36 ± 10</td>
<td>31 ± 2</td>
<td>30 ± 4</td>
<td>28 ± 4</td>
</tr>
<tr>
<td>LA</td>
<td>6 ± 2</td>
<td>40 ± 18†</td>
<td>9 ± 3</td>
<td>6 ± 5</td>
<td>4 ± 3</td>
<td>4 ± 2</td>
<td></td>
</tr>
<tr>
<td>PVH + sz</td>
<td>5 ± 3†</td>
<td>25 ± 1</td>
<td>57 ± 15†</td>
<td>26 ± 12</td>
<td>25 ± 4</td>
<td>24 ± 4</td>
<td>23 ± 4</td>
</tr>
<tr>
<td>Qv</td>
<td>11.0 ± 3.4</td>
<td>...</td>
<td>14.8 ± 2.1</td>
<td>20.2 ± 10†</td>
<td>21.7 ± 12.5†</td>
<td>16 ± 5.9†</td>
<td></td>
</tr>
<tr>
<td>PVH + sz</td>
<td>11.7 ± 7†</td>
<td>24.2 ± 16.3</td>
<td>26.6 ± 15.5</td>
<td>28.6 ± 14.6†</td>
<td>30.6 ± 15.4†</td>
<td>31.9 ± 19†</td>
<td></td>
</tr>
<tr>
<td>L/P</td>
<td>0.72 ± 0.7</td>
<td>0.05 ± 0.08</td>
<td>0.46 ± 0.06</td>
<td>0.47 ± 0.07</td>
<td>0.43 ± 0.07</td>
<td>0.44 ± 0.1</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: systemic (Ao), pulmonary artery (PA), left atrial (LA) pressures, pulmonary lymphatic flow (Qv), and the lymph to plasma protein ratio (L/P) during baseline (BL), following LA pressure elevation to 25 mm Hg (after LA balloon inflation) and during status epilepticus. Peak pressures (peak) and at 15, 30, 60 and 120 min of status. Pulmonary vascular hypertension (PVH) refers to animals (n = 5) in which status was induced following LA pressure elevation. Seizure (Sz) refers to animals (n = 9) with status epilepticus without prior elevation of LA. (Data from Simon et al.) Statistical analysis in the PVH animals compared all values to those obtained following elevation of LA pressure (after LA Balloon).

†p < 0.01. Statistical analysis in the PVH animals compared all values to those obtained following elevation of LA pressure (after LA Balloon).

p < 0.05; for the seizure alone animals (Sz), each experimental value was compared to the baseline figure.
reported here with elevation in pulmonary vascular pressure prior to seizure induction, the average volume of efferent lymph increased by only one third, from 24 to 32 ml/h following the seizure. However, during the pulmonary vascular pressure elevation by LA balloon inflation of 25 mm Hg, the QL doubled from 12 to 24 ml/h so that the total rise in lymph flow from the original baseline to the seizure peak was actually somewhat greater in the pulmonary vascular hypertension animal than in the animals subjected to seizures alone (Table 1, Fig 1 and 3). The attenuated rise in QL following the seizure may be explained in part by prior surface area recruitment effected by the elevation in baseline pulmonary vascular pressures, thereby eliminating this component of the lymph flow response to the seizure-induced pressure transient. Alternately, very high pressure transients may produce effects different from those of steady state experiments. Minnear et al noted only a small increase in QL in sheep developing pulmonary edema when subject to pressure transients greater than 50 mm Hg. Pietra et al reported hemoglobin within interendothelial junctions in dog lobes subject to pulmonary perfusion pressures of 50 mm Hg. Data from steady state experiments, in contrast, demonstrate a steepening of the slope of lymph flow response to changes at high pulmonary vascular pressures. Maximum values studied by Parker et al were less than 50 mm Hg. With high pressure transients, pulmonary vascular pressure elevation by mechanical means may have different results from those induced by sympathetic nervous system stimulation. Although Simon et al found no difference in the effect upon pulmonary lymph flow that followed seizure-induced pulmonary vascular pressure transients vs duplication of the pressure transients by LA balloon inflation, Minnear et al reported sustained lymph flow changes following norepinephrine infusion, but transient lymph flow elevations following brief LA balloon inflation producing a similar height and elevation of LA pressures.

The pulmonary vascular hypertension did not alter

% Δ in lymph flow from baseline

Figure 3. Data from Table 1. Effect of bicuculline-induced seizures on lung lymph flow in sheep following pulmonary vascular pressure elevation via LA balloon inflation (↑ LA) compared with values in animals subjected to seizures alone. (Data from Simon et al.)

Pulmonary Vascular Pressure and Lung Lymph Flow (Simon et al)
the consequences of the seizure on the sieving characteristics of the pulmonary capillaries as determined by the L/P ratio. During the prolonged period of increased LA pressure held at 25 mm Hg (20 mm Hg above baseline), the L/P ratio dropped from a baseline of 0.7 to 0.5 along with a rise in lymph flow from 12 to 25 ml/h. These values correspond closely to those obtained by others during similar experimental manipulations.11,12,13 Once the seizure was induced, there was a further drop in L/P but only by 12 percent at 120 min. This drop was identical in amount and time course both to that seen following seizures in our previous experimental animals8 and to that seen in animals in which a transient mechanical increase in the pulmonary vascular pressure was used to duplicate the hydrostatic effect of seizures.4 Although not significantly different, the L/P ratio drop after the seizure-induced elevation in pulmonary vascular pressures was less than that seen during the LA balloon inflation used to increase baseline pulmonary vascular pressures (12 percent as opposed to 26 percent), despite a greater elevation in pulmonary vascular pressure during the seizure (LA pressure changes of 32 mm Hg following the seizure, 20 mm Hg during LA balloon inflation). These results might be explained by dilution of interstitial proteins resulting from the increased fluid volume in the interstitial space occurring during LA balloon inflation. In steady state experiments, the fall in the L/P ratio is attenuated as lung lymph flows increase.5 Although in the steady state experiment of Parker et al8 no change in pulmonary vascular permeability was observed, those studies did not involve left atrial pressures above 50 mm Hg, as seen in these studies. Such vascular pressure transients have been reported to produce pulmonary edema and to be associated with airway fluid to plasma protein concentrations approaching unity.4 Thus, in the studies reported here, some degree of alteration in permeability of the capillary endothelium occasioned by the central nervous system-induced, brief, sharp increase in pulmonary vascular pressure may have occurred, as hypothesized by Theodore and Robin.16

These experiments demonstrate that the magnitude and duration of seizure-induced elevations of pulmonary vascular pressures are not altered by substantial elevations in baseline pulmonary vascular pressure (LA pressure increase of 25 mm Hg) (Fig 2). Thus, patients with pulmonary vascular hypertension may be at greater risk of unbalanced Starling's forces and resultant pulmonary edema during seizures. Whether or not such higher pulmonary vascular pressures transients during seizures (as those reported here in the animals prepared with LA balloon inflation prior to seizure induction) produce a permeability alteration in the pulmonary capillary bed duplicating the syndrome of neurogenic pulmonary edema reported in humans is not resolved by these studies. However, the nervous system manipulations reported by Maron* using veratrine injection into the cisterna magna of dogs produced pulmonary edema. The wet-dry lung weights were highest in the animals with the highest pulmonary vascular pressures and the airway fluid to plasma protein concentration ratio supported a pulmonary capillary permeability barrier breakdown in the animals with the highest pulmonary vascular pressures.

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