Experimental neurogenic pulmonary edema in cats

JULIAN T. HOFF, M.D., AND MERRY NISHIMURA, A.B.

Department of Neurological Surgery, San Francisco General Hospital, University of California School of Medicine, San Francisco, California

Hemorrhagic pulmonary edema was produced consistently in 19 of 20 anesthetized, paralyzed, ventilated cats when intracranial pressure (ICP) was raised for 30 minutes by intraventricular infusion of mock CSF to 150 mm Hg in 14, or 200 mm Hg in six. However, under identical conditions, except that ICP was raised to only 100 mm Hg, three of seven animals did not develop hemorrhagic edema of the lungs and the remaining four had spotty hemorrhage. Thirteen control animals with normal ICP had normal lungs. Gravimetric lung water analysis by Pearce's method confirmed gross and microscopic appearance of hemorrhagic pulmonary edema. Extravascular lung water (p < 0.05) and lung blood (p < 0.05) were significantly greater than control values when ICP was raised to or exceeded 150 mm Hg. Despite hemorrhagic edema, pulmonary gas exchange (O₂, CO₂) remained unaffected.

This animal model allows quantitative measurement of neurogenically-mediated hemorrhagic edema of the lungs before gas exchange is impaired. The model may facilitate clarification of the pathogenesis of neurogenic pulmonary edema and, consequently, refine evaluation of therapy.

KEY WORDS • pulmonary edema • lung water • intracranial pressure

Hemorrhagic pulmonary edema occurs clinically in patients with fatal head injury, and similar pulmonary changes have been observed after brain injury in experimental animals. Presumably the brain insult initiates a neurogenically-mediated hemodynamic "storm." Several authors have examined the various changes of pulmonary and cardiac events that may occur before the onset of neurogenic pulmonary edema. However, efforts to clarify the mechanism of neurogenic pulmonary edema have been frustrated by sparse data in humans and inconsistent observations in experimental animals.

We have developed a feline model system in which hemorrhagic pulmonary edema is produced consistently by raising intracranial pressure (ICP), permitting quantitative as well as qualitative measurements. With this model we will be able to clarify the pathogenesis of neurogenic pulmonary edema.

Materials and Methods

Adult cats weighing 2 to 4 kg were anesthetized with intraperitoneal infusion of sodium pentobarbital, 30 mg/kg, paralyzed with gallamine triethiodide, 20 mg intra-
venously, and ventilated with air by a Harvard small animal respirator through a Sierra valve (deadspace, 4 cc)* attached to a tracheostomy. The animals were fixed in a Kopf stereotaxic frame with the head elevated 30° from horizontal to keep the chest free. Anesthesia was supplemented half-hourly with pentobarbital, 1 cc, 5 mg/cc intravenously.

A Statham P23Db pressure transducer† recorded systemic arterial pressure (SAP) through a polyethylene (PE 90) femoral artery cannula. A Statham P23BB venous transducer measured central venous pressure (CVP) through a femoral vein cannula advanced into the thorax. An infrared gas analyzer‡ determined end tidal CO₂ pressure \( P_{ET-CO_2} \) from the tracheal cannula. A Statham P23Db pressure transducer recorded intracranial pressure (ICP) from a multiperforated polyethylene (PE 50) cannula, filled with saline and placed subdurally through a left parietal burr hole, which was sealed with dental acrylic cement. The SAP, ICP, \( P_{ET-CO_2} \), and CVP measurements were displayed continuously on a Gilson ICT-5 ink pen recorder. Rectal or esophageal temperature was measured continuously§ and maintained between 36° and 38° C by a heating pad. Arterial \( pCO_2 \), \( pO_2 \), pH,|| and hematocrit were determined periodically during a control period, at 10-minute intervals during raised ICP, and at the conclusion of a recovery period.

After a 2-hour control period, ICP was raised at a rate of 1 mm Hg/sec by hand-controlled infusion of mock CSF (Elliot’s solution, pH 7.22 to 7.25) into the right lateral ventricle through a stereotaxically-placed No. 22 spinal needle. The burr hole was sealed with dental acrylic cement. In seven animals ICP was raised to 100 mm Hg, in 14 animals to 150 mm Hg, and in six animals to 200 mm Hg; this level was maintained for 30 minutes or until cerebral perfusion pressure (CPP) was zero (CPP = SAP – ICP). Mock CSF infusion was then stopped, and ICP allowed to return to baseline. Figure 1 is a recording from one experiment. Infused CSF volumes were determined for each group of animals with raised ICP. At 100 mm Hg, CSF was \( 27 ± 15 \) cc/kg; at 150 mm Hg, CSF was \( 44 ± 14 \) cc/kg; and at 200 mm Hg, CSF was \( 42 ± 11 \) cc/kg. After a 30-minute recovery period, heparin sodium (2500 to 3000 units) was administered intravenously to the animals, and they were killed by an overdose of barbiturate (Repose, 1 cc). Elapsed anesthesia time for each experiment was 3 hours.

The brains were removed and examined grossly after 0.1 cc of Evans blue dye had been injected into the ventricular needle. Proper needle placement was verified by the presence of dye in the ventricles and basal cisterns. A 10-cc sample of heart blood was taken and the inflated lungs were removed. Blood was drained for about 1 minute, and the lungs were then weighed. Representative sections from the lungs of three animals with gross hemorrhagic pulmonary edema were fixed in 10% buffered formalin, embedded in paraffin, sectioned, mounted, and stained with hematoxylin and eosin. The specimens were examined microscopically.

Gravimetric analysis of lung water was calculated by Holcroft and Trunkey’s modification of the method described by Pearce, et al.18 The lungs were weighed, then homogenized with distilled water in a Waring blender,* weighed again to determine the amount of added \( H_2O \), and centrifuged† at 12,000 rpm for 30 minutes at 4° C. Wet and dry weights of whole blood, lung homogenate, and lung supernatant were determined by weighing aliquots of the samples before and after they had been oven-dried at 75° C for 24 hours. The following formulas were used in calculating the results:14,18

*Blender made by Waring Products Division, New Hartford, Connecticut.
†Ultra centrifuge manufactured by Ivan Sorvall, Inc., Newtown, Connecticut.
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FIG. 1. Polygraph tracing of an experiment showing the effect of raised intracranial pressure (ICP) (150 mm Hg) on systemic arterial pressure (SAP), determined end tidal CO₂ (PetCO₂), and central venous pressure (CVP). Note the early and persistent rise of PetCO₂ as ICP remains elevated. Arterial pO₂ falls slightly as ICP remains elevated, rising again during the recovery period. A rise in SAP occurs when ICP approaches baseline mean SAP (the Cushing response).

Blood weight (BW) =
\[
\frac{\text{Hb (supernatant)} \times \%\text{H}_2\text{O (homogenate)}}{\text{Hb (whole blood)}} \times \frac{\%\text{H}_2\text{O (supernatant)}}{\%\text{H}_2\text{O (homogenate)} \times \text{homogenate weight}} \times \text{added H}_2\text{O}.
\]

Blood H₂O = %H₂O (blood) × BW.

Total lung H₂O (TLW) = (%H₂O [homogenate] × homogenate weight) − added H₂O.

Extravascular lung water (EVLW) = TLW − blood H₂O.

Extravascular dry weight (EVDW) = lung weight (LW) − BW − EVLW.

Seven control animals without CSF infusion and six control animals with mock CSF infused intravenously (49 ± 4 cc/kg in 30 minutes) were studied after similar anesthesia time and operative procedures. The data from control and experimental animals were compared by Student’s unpaired t-test (Mann-Whitney).

Results

Of the 20 animals in which ICP was steadily raised to or beyond 150 mm Hg and sustained for 30 minutes, 19 developed hemorrhagic edema. Gross hemorrhage was more severe in all six animals with ICP raised to 200 mm Hg than in those with ICP increased to 150 mm Hg (13 of 14). Hemorrhage was distributed uniformly throughout the lungs, although microscopically it was most obvious within interstitial tissue (Fig. 2). Alveoli, bronchioles, and bronchi commonly contained edema fluid. Gravimetric analysis of the lungs showed them to be heavy (lung weight), congested (blood weight), and edematous (extravascular lung water = EVLW). Table 1 compares values of experimental and control samples. Four of seven animals with ICP increased to 100 mm Hg had focal hemorrhage. Although blood weight in the lungs of animals with ICP elevated to 100 mm Hg exceeded that in control animals, other gravimetric indices of hemorrhagic pulmonary edema (LW, TLW, and EVLW) did not differ from controls.

The lungs of control animals were grossly normal except for segmental atelectasis in three animals without CSF infusion and in two with mock CSF infused intravenously. The brains of all animals were grossly normal. Evans blue was distributed evenly within the ventricular system and throughout the basal cisterns.
During each raised ICP experiment, arterial oxygenation remained adequate (>70 mm Hg), despite the development of hemorrhagic pulmonary edema (Table 2). Usually PaO₂ fell modestly, while PaCO₂ rose, during the period of raised ICP, then returned toward baseline in the recovery period (Fig. 1). Similarly, CVP rose during ICP elevation (14 cm H₂O, maximum) but fell toward normal during recovery; CVP changed little in control animals with or without an intravenous infusion of mock CSF. Hematocrit usually fell during CSF infusion, whether fluid was given intraventricularly or intravenously, then rose toward baseline values during the recovery period (Table 2).

In two of seven animals, SAP rose 16% from control levels when ICP was raised to 100 mm Hg, but CPP remained 25 mm Hg or above. In 11 of 14 animals, SAP increased an average of 33% during an ICP level of 150 mm Hg, and in five of six animals, the average increase was 52% when ICP was 200 mm Hg. Cerebral perfusion pressure never rose above 30 mm Hg in either the 150 mm Hg or 200 mm Hg group. When CPP fell to zero or below in three of six animals with ICP at 200 mm Hg, the elevation was terminated (at 20, 10, and 20 minutes).

**Discussion**

We have demonstrated in this study that hemorrhagic edema can be produced with consistency (95% reproducibility when ICP is maintained at 150 mm Hg or 200 mm Hg) by increasing intracranial pressure. However,
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Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>PaCO₂ (mm Hg)</th>
<th>Arterial pH</th>
<th>PaO₂ (mm Hg)</th>
<th>Hematocrit</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>37.6 ± 1.4</td>
<td>7.34 ± 0.03</td>
<td>92 ± 8</td>
<td>41 ± 4</td>
</tr>
<tr>
<td>ICP = 100 mm Hg</td>
<td>39.4 ± 2.9</td>
<td>7.34 ± 0.06</td>
<td>90 ± 7</td>
<td>33 ± 5</td>
</tr>
<tr>
<td>recovery</td>
<td>38.2 ± 2.6</td>
<td>7.35 ± 0.04</td>
<td>91 ± 7</td>
<td>35 ± 8</td>
</tr>
<tr>
<td>control</td>
<td>37.7 ± 3.0</td>
<td>7.31 ± 0.06</td>
<td>91 ± 12</td>
<td>35 ± 7</td>
</tr>
<tr>
<td>ICP = 150 mm Hg</td>
<td>41.3 ± 2.4</td>
<td>7.29 ± 0.04</td>
<td>88 ± 8</td>
<td>37 ± 8</td>
</tr>
<tr>
<td>recovery</td>
<td>37.8 ± 2.1</td>
<td>7.32 ± 0.03</td>
<td>94 ± 6</td>
<td>31 ± 8</td>
</tr>
<tr>
<td>control</td>
<td>36.3 ± 3.9</td>
<td>7.33 ± 0.07</td>
<td>104 ± 5</td>
<td>41 ± 4</td>
</tr>
<tr>
<td>ICP = 200 mm Hg</td>
<td>42.3 ± 2.1</td>
<td>7.24 ± 0.04</td>
<td>91 ± 12</td>
<td>37 ± 7</td>
</tr>
<tr>
<td>recovery</td>
<td>41.4 ± 4.9</td>
<td>7.23 ± 0.08</td>
<td>99 ± 17</td>
<td>37 ± 6</td>
</tr>
</tbody>
</table>

the feline model does have specific limitations. First, the cat develops hemorrhagic lungs with greater predictability than do other species, including dogs and primates. Therefore, conclusions derived from this model may not be satisfactorily analogous to man. Second, a moderate amount of fluid must be infused before fixed levels of ICP are reached and maintained. Findings in the control animals indicate that this fluid volume is of little consequence, although the hematocrit does fall transiently during infusion and CVP does rise slightly, suggesting a possible fluid volume excess. Third, the cat is subject to frequent upper respiratory infections, particularly in winter, thus necessitating numerous control experiments. And fourth, increased ICP may be only one of various neural stimuli that cause hemorrhagic pulmonary edema in man and animals.

Hemorrhagic, edematous lungs with raised ICP seen in this study may have resulted from sympathetically-mediated stress on the entire vascular system. The earliest response to raised ICP is an increase in the SAP (Cushing response). Earlier experiments have documented sequential systemic and pulmonary vascular changes, suggesting that neurogenic pulmonary edema is induced by hemodynamic overload. Eighty-four percent of our animals with hemorrhagic edematous lung (ICP = 150 or 200 mm Hg) developed systemic hypertension. The remaining 16% did not have significant rises in SAP. Similar variability of the Cushing response in cats has been observed before.

Recent work substantiates that lung lesions are induced by changes in vascular pressure; that work demonstrated the appearance of pulmonary artery hypertension and hemorrhagic edema of the lungs when systemic arterial pressure is raised, either by cerebral compression with an intracranial balloon or by infusion of catecholamines intravenously. Conversely, interference with sympathetic effectors, either by spinal cord transection or by ganglionic blocking agents, has prevented hemorrhagic pulmonary edema in experimental animals further implicating the essential role of a vasomotor crisis triggered by severe stress.

Central to the argument for a generalized vasomotor storm as the precursor of neurogenic pulmonary edema is the development of pulmonary venous hypertension. However, few investigators have documented elevated pressure either in the pulmonary veins or the left atrium of experimental animals. Those who have, moreover, have done so inconsistently. The alveolar-capillary membrane is vulnerable to pressure stress, according to Szidon, et al. When that barrier is disrupted by elevated capillary pressure, pulmonary edema may develop. But elevation of pulmonary artery wedge pressure suggesting left atrial hypertension has been recorded only rarely in man despite clinical evidence of neurogenic pulmonary edema. Thus, proponents of the vasomotor crisis hypothesis are frustrated by abundant but inconsistent data.

Moss, et al., offer an alternative explanation for the pulmonary hemorrhages that
follow a cerebral insult. Without significant left atrial pressure elevation, “neurogenic” pulmonary edema has been found in a variety of laboratory animals, reportedly due to pulmonary capillary stasis resulting from constriction of autonomically-controlled postcapillary venules. In those animals, pulmonary vascular resistance was thought to rise, producing pulmonary arterial hypertension and extravasation from arterioles and capillaries. Some clinical evidence also suggests that in man left atrial pressure may remain normal, despite neurogenic pulmonary edema. Yet other investigators have shown that pulmonary vascular resistance falls when sympathetic nerves to the lungs of animals are stimulated, implying dilatation of capillaries and postcapillary venules. All that can be stated at this point is that the evidence for a direct effect of a brain insult upon pulmonary vessels, resulting in lung hemorrhage, is inconsistent and remains inconclusive.

Most previous studies have concentrated on pressure changes in the systemic and pulmonary vasculature. Hemorrhagic edema, the actual pathological entity, has not been described in detail, nor has it been quantified. Our model will allow quantification of the lesion and correlation of its severity with other variables, including pressure changes.

Although hemorrhagic pulmonary edema is an uncommon clinical problem in patients with nervous system disease, the pathological entity is commonly seen at autopsy in patients for whom the disease proves fatal. We believe neurogenic pulmonary edema may be one end of a broad spectrum of pulmonary lesions common to patients with brain injury. Other parts of the same spectrum may include arteriovenous shunting, ventilation-perfusion maldistribution, subclinical edema with vascular congestion, and increased susceptibility to pulmonary infections. Further work with our model may define factors common to the diverse entities of the spectrum and indicate better means of controlling the pulmonary sequelae of brain injury.

References

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*Address reprint requests to:* Julian T. Hoff, M.D., Department of Neurological Surgery, University of California School of Medicine, San Francisco, California 94143.

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