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Neurogenic Pulmonary Edema in a Pulmonary Normotensive Model (42598)

DAVID L. BECKMAN, DAVID D. GINTY, AND A. CLARK GAITHER

Department of Physiology, School of Medicine, East Carolina University, Greenville, North Carolina 27834

Abstract. In the present study our aim was to determine whether or not neurogenic pulmonary edema would develop from a brief pulse of intracranial pressure (ICP) in the absence of any obvious pulmonary hypertension. There were three groups of cats: sham-operated controls, ICP only, and ICP plus variable occlusion of the pulmonary artery. Partial occlusion of the pulmonary artery was carried out by placing a ligature around the pulmonary trunk and mechanically constricting the artery to maintain pulmonary arterial pressure (PAP) and left atrial pressure (LAP) at pre-ICP levels. In sham-operated animals the extravascular lung water/blood free dry weight ratio (EVLW/BFDW) was 3.26 ± 0.07 and broncho-alveolar lavage (BAL) protein, 6.49 ± 0.62 mg/g lung. ICP-only caused a rise in PAP, left atrial pressure, and EVLW/BFDW to 3.67 ± 0.08 ($P < 0.05$). ICP with partial occlusion of the pulmonary artery prevented any rise in PAP or LAP while EVLW/BFDW rose to 3.67 ± 0.10 ($P < 0.05$) and BAL protein was 8.37 ± 1.27 mg/g lung. Our results show that EVLW/BFDW can increase with neurogenic pulmonary edema in cats in the absence of an obvious increase in pulmonary arterial or left atrial pressure.

Pulmonary edema is found to develop in response to exposure of the central nervous system to increased pressure (1–3) and to traumatic impact or cerebral compression in an animal model (4) or in humans (5). Centrally mediated pulmonary edema has been termed neurogenic pulmonary edema. The edema could be caused by pulmonary microvascular hypertension, an increase in pulmonary capillary permeability, or an accumulation of lung lymph volume due to surface area recruitment.

Neurogenic pulmonary edema (NPE) is usually associated with systemic and pulmonary hypertension (2, 6). Sarnoff and Sarnoff (6) have used the term "neurohemodynamic pulmonary edema" concluding that the edema in dogs is a result of increased hydrostatic pressure on the lung microvasculature. Chen *et al.* (7) found that cerebral compression results in pulmonary hypertension in rats secondary to systemic arterial constriction and left ventricular strain. It was concluded that pulmonary hypertension was the cause of the NPE. However, Garcia-Uria *et al.* (8) and Millen and Glauser (9) showed that pulmonary hypertension is not always a prerequisite for the resultant edema in cats. NPE developing from a pulse of pressure applied to the crania of cats were found to be inversely related to pulmonary arterial pressures (3). Sheep responded to increased intracranial pressure (ICP) with pulmonary microvascular recruitment (10–11) and increases in protein-rich lymph flow. Species differences may account for the variations in reported results.

In the present study we set out to observe the effects of a brief pulse of pressure applied to the cranial cavity on the development of edema in the lungs. We were interested in seeing if pulmonary edema would develop in cats in the absence of mean pulmonary arterial or left atrial hypertension. Pulmonary arterial pressure (PAP), left atrial pressure (LAP), systemic arterial pressure (SAP), and arterial blood gas values were monitored. In one group of animals we attempted to hold PAP and LAP at control pressures by partially occluding the pulmonary artery.

Materials and Methods. Experiments were carried out on 19 cats (body weights between 1.81 and 3.70 kg) surgically anesthesized with ketamine (Vetalar HCl, 35 mg/kg plus 10% acepromazine) with maintenance doses of 20 mg/kg given every 30 min. Three groups of cats were studied: group 1, sham-operated; group 2, subjected to a brief pulse of ICP; and group 3, subjected to ICP while the PAP and LAP were maintained at baseline pressures. Surgical procedures were identical in all three groups.

The left femoral artery was cannulated to measure SAP and to take blood samples for measurement of hemoglobin, pH, PO_2, and

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PCO_2. The chest was opened through a midline incision and the cats were intubated and given positive pressure ventilation. The PO_2, PCO_2, and pH were monitored and the ventilator was adjusted to obtain normal levels (PO_2, 80–110 mm Hg; PCO_2, 28–35 mm Hg). Catheters were placed in the pulmonary artery through the wall of the right ventricle and into the left atrium through the left atrial appendage. All pressures were recorded on a Grass Model 7D polygraph. In order to partially occlude the pulmonary artery, a ligature was placed around it with both ends passed through a polyethylene tube. Pulling the line partially constricted the artery against the tube and the blood pressure downstream dropped. Upon completion of the surgery, the catheters were secured and the cat was placed in a prone position. Baseline recordings of all pressures and heart rate were made and one final blood gas sample was taken before the ICP.

After briefly occluding the pulmonary artery in order to partially control for this variable and test for catheter location, pressures were monitored in the sham control cats for 30 min and the animals were sacrificed. Groups 2 and 3 were subjected to ICP by means of a brief pressure pulse applied for 800 msec. (3). A saline-filled catheter was inserted into a burr hole through the saggital sinus and sealed. Pressure from a standard gas cylinder at 80 psi was applied to a saline reservoir through a valved connection. The pulse duration and pressure were selected to produce NPE with minimal saline entry. The pressure was sensed via a high-pressure solid-state transducer (Microswitch 0–100 psi) connected to a polygraph. In group 3 the PAP was maintained at the prestressed control level for that animal by the device described earlier. Pressure downstream from the occluding line was monitored and recorded. All cats were sacrificed by severing the aortas.

After 30 min of ICP the trachea was clamped in all three groups to prevent blood from entering the lungs which were quickly removed, weighed, and examined for gross hemorrhagic damage. The left lung was homogenized within 10 min of excision and used to determine the extravascular lung water/blood free dry weight ratio (EVLW/BFDW). This method developed by Pearce (12) entailed measuring dry weights of lung homogenate and supernatant to obtain the percentage of water in the lungs. Subtracting the blood weight as measured by hemoglobin content gave the extravascular lung water. Bronchoalveolar lavage (BAL) protein content of the right lung was determined. Within 20 min of excision the lung was rinsed three times with 0.9% NACl (10 ml/g lung tissue) (13) and the wash fluid was stored at −20°C until analysis. The lung wash protein was assayed by the Bio-Rad method (14). The data are expressed as mean values ± standard errors. All values were compared using analysis of variance and the paired or unpaired t test.

Results. Experiments were performed in three groups of animals. In all three groups combined, the mean baseline values for SAP, PAP, and LAP were 78.7 ± 1.4, 11.1 ± 0.1, and 3.0 ± 0.1 mm Hg. PO_2 and PCO_2 were 105.4 ± 0.3 and 30.0 ± 0.1 mm Hg, respectively. In the sham control group these values remained essentially unchanged (Table I). The EVLW/BFDW for the sham control group was 3.26 ± 0.07 and the BAL protein content in the lung wash was 6.5 ± 0.6 mg/g lung. The gross appearance was completely normal.

In group 2 cats subjected to the ICP (Table I), pulmonary edema developed as seen by a significant increase in EVLW/BFDW values by 13%. In these cats, SAP, PAP, and LAP rose substantially. The lungs were assigned a number from 0 (normal) to +5 indicating a severe gross hemorrhagic appearance of the lungs. The gross appearance indicated moderate hemorrhage with an average assigned value of 1.6.

In group 3 cats where the pulmonary artery was partially constricted to hold the blood pressures in the lungs fairly constant, PAP was held to within 3 mm Hg of its pre-ICP control value and mean LAP did not rise more than 2 mm Hg. SAP rose by 48 mm Hg. Although PAP and LAP were nearly unchanged in these animals there was a significant increase in EVLW/BFDW ratio over sham control cats. Blood gas values and BAL protein remained unchanged. The gross appearance indicated moderate hemorrhage with an average value of 1.4.

Discussion. Our results are in agreement with previous studies that have indicated that neurogenic pulmonary edema, as evidenced by increased EVLW/BFDW ratios, can de-

TABLE I. HEMODYNAMIC AND PULMONARY RESPONSES TO A SHORT PULSE OF RAISED INTRACRANIAL PRESSURE

	Group 1 sham controls ($N = 6$)	Group 2 ICP controls ($N = 6$)		Group 3 ICP with PAP controlled ($N = 7$)	
		Before ICP	After	Before ICP	After
SAP	80.5 ± 5.9	83.0 ± 2.9	161.7 ± 16.9*	71.9 ± 4.8	119.9 ± 12.6*
PAP	10.9 ± 0.6	10.6 ± 1.0	27.0 ± 2.8*	11.7 ± 0.9	14.7 ± 1.50
LAP	2.9 ± 0.3	2.8 ± 0.6	5.6 ± 2.0	3.3 ± 0.5	5.0 ± 0.7
pH	7.30	7.34	7.31	7.31	7.26
PO_2	106.1 ± 6.3	104.8 ± 2.4	97.3 ± 4.5	105.3 ± 4.2	102.2 ± 7.2
PCO_2	29.5 ± 2.5	28.4 ± 1.0	30.7 ± 1.8	32.2 ± 2.8	35.0 ± 4.8
EVLW/BFDW	3.26 ± 0.07	—	3.67 ± 0.08**	—	3.67 ± 0.10**
BAL Protein	6.49 ± 0.62	—	9.00 ± 3.4	—	8.37 ± 1.27

Note. All values are expressed as means ± SE. All pressures are given in mm Hg and protein as mg/g lung. Pressure values after ICP are given as peak pressures.

* Significantly different ($P < 0.05$) using paired t test.

** Significantly different ($P < 0.05$) from sham control groups using analysis of variance.

velop in cats in the absence of obvious pulmonary hypertension (8, 9). The 11–13% increase in lung water from NPE reported here is of magnitude comparable to that reported in other studies (15) using the Pearce method (12) for determining EVLW/BFDW. The blood gas changes were minor following ICP. The increase in EVLW/BFDW was presumably insufficient to interfere with gas exchange. BAL protein was also unchanged indicating that alveolar edema did not develop. Minor gross lung injury in the form of hemorrhagic discoloration and a patchy atelectasis developed on most lungs from ICP-exposed cats.

Sarnoff and Sarnoff (6) have postulated that during the Cushing response the left ventricle reaches its work-failure threshold and is unable to pump the blood that enters it. Therefore left atrial and pulmonary hypertension develop with resultant pulmonary edema. Guyton and Lindsey (16) showed in dogs that the lung wet wt/body ratio started to increase only when LAP exceeded 25 mm Hg. When plasma protein concentration was decreased to 47% of control levels the edema began to develop at an LAP of 11 mm Hg. In the present study plasma protein levels decreased to only 78% of pre-ICP levels and LAP remained below 6 mm Hg. Rippe *et al.* (17) found similar values using different techniques. The increases in LAP in the present study as well as others (8) were small and thus not likely to be the cause of the edema. LAP peak pressures in group 3 briefly rose to as high as 5 mm Hg. Partial occlusion of the pulmonary artery reduced the rise in SAP presumably due to decreased blood flow. Although SAP still rose significantly above control values, a similar rise in SAP has been shown by Hoff *et al.* (15) not to be a cause of NPE.

Species variations may account for different results from studies with dogs and rats in which hemodynamic influences appear to dominate in the edemagenic response to increased ICP (6, 7); in sheep, microvascular recruitment has been established as the cause of increased protein-rich lymph production during raised ICP (11); in cats, NPE may develop in the absence of pulmonary hemodynamic influences (3, 8, 15) as supported by the present findings. A recent study by Marin (18) showed that intracisternal injection of veratrine in dogs produced NPE due to both hemodynamic and increased permeability mechanisms. The airway fluid-to-plasma protein concentrations for veratrine-induced NPE lay midway between the high values from alloxan-produced edema and low values from hemodynamic pulmonary edema. Jones *et al.* (11) showed that "a change in microvascular surface area (not permeability) is the primary mechanism underlying increases in protein-rich lung lymph flow" in sheep following elevation of ICP. Prerecruitment by raising LAP to 30 mm Hg prevented any additional increase in lymph flow from increased ICP. In the present study in cats, LAP values rose less than 2 mm Hg in the PAP-occluded group. While an increase

in pulmonary blood flow might possibly account for recruitment, use of the occluder would tend to decrease flow.

In this study pulmonary edema, as evidenced by an increase in EVLW/BFDW, developed in cats in the absence of any obvious pulmonary hypertension. Similar results were reported by Garcia-Uria *et al.* (8). This leads us to conclude that, in this feline model, NPE results from causes other than hemodynamic changes.

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