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Cardiopulmonary Response to an Induced Pulse in Intracranial Pressure (42316)

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Abstract. Increased intracranial pressure may result in the Cushing response. We applied a short pulse of pressure to the cranial cavity of anesthetized cats which were intubated, curarized, ventilated, and the cranium exposed to an 80- to 100-msec pulse of pressure at 5.3 atm. The following significant increases developed: Intracranial pressure rose from 7.4 ± 1.5 to 150.6 ± 19.4 mm Hg, systolic arterial peak pressure from 130.7 ± 8.1 to 299.0 ± 11.4, pulmonary peak pressure from 18.9 ± 1.9 to 42.9 ± 4.9. Alveolar lavage protein in controls was 6.7 ± 0.4 mg/g lung compared to 11.9 ± 2.0 in the experimental group. Extravascular lung water/dry weight ratios increased from 3.36 ± 0.04 in controls to 3.51 ± 0.09 but varied inversely with pulmonary systolic peak pressures ($r = -0.59$). These results showed that a pulse of pressure applied to the cranium of cats produced lung edema which was inversely related to pulmonary artery pressures.

Clinical studies have shown that head injuries may result in pulmonary complications including the development of edema (1). This response has been termed "neurogenic" or "neurohemodynamic" pulmonary edema. Similarly, animal studies have demonstrated the development of pulmonary edema during or following cerebral trauma (2–4). The frequency of occurrence following severe head injury is approximately 11 to 28% in clinical studies (3). The incidence of edema associated with elevated intracranial pressure ranges from nearly 100% with sustained large pressure increases to less than 10% when intracranial pressure changes are small or very transient.

Sarnoff and Sarnoff (5) showed that sympathetic pathways are of major importance in the neurohemodynamic response to injection of intercisternal fibrin. The development of pulmonary edema was attributed to the subsequent systemic and pulmonary blood pressure increases. In contrast, Cameron and De (6) contended that the sympathetic discharge associated with intercisternal fibrin injection had a direct neural influence on the pulmonary capillaries acting to increase their permeability. Theodore and Robin (7) emphasized the importance of a shift of blood from the systemic to the pulmonary vascular system which according to their theory not only in itself caused fluid movement out of the pulmonary vessels but also damaged the capillary walls so that the development of edema persisted. The importance of a distinct α- and β-adrenergic stimulus and the need for an intact sympathetic system for the pressor response to occur was emphasized by Brashear and Ross (8). Several recent studies suggest that a systemic hypertension need not precede the development of neurogenic pulmonary edema (9). Pulmonary volume loading may play a major role in the development of edema (10). Some recent evidence indicates that a direct influence on pulmonary capillary permeability may exist (11), but other studies indicate that permeability changes are secondary to damage from an initial pressure surge or to an expanded cross-sectional area (12). Venular spasm may also play a role (13). Millen and Glauser (14) showed that pulmonary edema can develop in cats exposed to a short pulse of intracranial pressure even when the pulmonary arterial pressure does not exceed normal values. From this it would appear that there might be some direct neural or humoral edemagenic factors involved.

In the present study we induced an abrupt pulse of intracranial pressure in anesthetized cats and measured the response of the cardiovascular and pulmonary systems. In particular we were interested in the relationship of hemodynamic factors to the development of lung edema induced by a brief pulse of intracranial pressure.

Materials and Methods. Fifteen surgically anesthetized cats of mixed sex, body weight

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1–3 kg, were exposed to a brief pulse of high intracranial pressure. A group of 10 normal controls was similarly treated without exposure. The cats were anesthetized with ketamine (35 mg/kg, Ketalar HCl) with maintenance doses given every 30 min or as needed. The cranial surgical preparation consisted of removing the temporalis muscle from the midline of the skull, placing a 9-mm burr hole through the central saggital sinus while leaving the dura intact, and attaching to the skull a formed brass plate with a Silastic gasket. The plate contained a port fitted with an 8 mm i.d. polyethylene tube 30 mm in length filled with buffered saline which led to a fluid reservoir. A valved connection from a standard pressure cylinder containing nitrogen led into the saline reservoir; from this a pulse of pressure was released, its characteristics dependent on the regulated source of pressure from the tank and the duration that the valve was opened. The pressure was preset at 80 psi (5 atm) and the valve opened for 80–100 msec. The pressure curve was sensed via a high pressure solid state transducer (Microswitch, 0–100 psi) connected to a polygraph (Grass Instruments Model 7D), and concomitantly observed on the screen of an oscilloscope (Tektronix Model 7633). The high pressure transducer was attached to the fluid column 20 mm from the cerebral entry point via a 13 mm i.d. tube.

Under local lidocaine anesthesia, a polyethylene catheter was threaded into the descending aorta via the left femoral artery. A Silastic catheter was placed into the pulmonary artery via the left jugular vein while observing the pressure pulse on the oscilloscope. A lumbar puncture using a 20-gauge needle was performed which allowed for constant monitoring of spinal pressures for the duration of the experiment. These pressures were recorded on the polygraph using standard transducers (Statham, Model P23). The cat was then intubated and curare (0–5 mg/kg body wt) administered im, with regular maintenance doses given. The cat was ventilated with a small animal respirator (Model 676, Harvard Apparatus, Millis, Mass.) which was adjusted to give standard control blood gas values for oxygen (99.8 mm Hg), carbon dioxide (30.8 mm Hg), and pH (7-33) (Radiometer BMS 3MK2 Blood Microsystem Radiometer, Copenhagen). Blood samples were taken from a cannula placed in the right femoral artery for determination of blood gases, catecholamines, angiotensin-converting enzyme (ACE), and the hematocrit. When control samples had been taken and the respirator adjusted to give normal blood gas values, the cranium was exposed to the pulse while recording the pressure variables. Samples for catecholamines and ACE determinations were taken 30 sec after application of the pulse. Subsequent blood samples were taken every 15 min; pressures were recorded continuously. The blood samples to be used for the catecholamine measurements were collected in tubes containing EDTA, then cooled and centrifuged; later the serum was collected and frozen at −5°C until analyzed. Catecholamine levels were determined using the radioenzymatic assay kit (Cat-A-Kit, Upjohn Diagnostics). Blood samples for determination of ACE were collected in heparinized tubes, the plasma from which was frozen at −5°C until analyzed using the method of Cushman and Cheung (15). Blood samples for the determination of hemoglobin were collected in heparinized tubes and analyzed by the cyanmethemoglobin method (Dry Drabkin's Reagent and a stable, human hemoglobin standard, Sigma). The percentage water in blood was determined by weighing the blood sample and placing it in an oven at 80°C until no change was noted on subsequent weighings.

The cat was maintained on a ventilator for 120 min; it was then disconnected and the lungs were excised for examination. A series of 10 normal control cats were treated in the same manner as experimental animals which included partial drilling of the hole in the cranium, attachment to the respirator, recording pressures, and holding for the same 120-min period. Upon termination of these procedures analyses were performed on the blood and lung samples of both control and experimental animals. The lungs were excised within 2 min after the respirator was disconnected, the chest was opened, the trachea clamped off and the lung and heart removed together. With the tracheal clamp removed, the heart and lung were separated and fatty tissue removed. The whole lungs were then weighed, examined for gross damage, and assigned a relative value according to the degree of injury, and then photographed. Lung gross damage estimates

were made by the same person and were based on an arbitrary scale from 0 to +5, zero representing the normal lung, and +1 to +5 representing increasing degrees of atelectasis, consolidation, enlargement, and hemorrhagic discoloration. The right lung was rinsed three times with 0.9% saline (10 ml/g lung tissue) according to the procedure of Oyarzun and Clements (16). Each rinse was adjusted for the amount of retained fluid to avoid overdistension. The pooled lung wash was mixed well and stored at −20°C until analyzed. Total phospholipids (TPL) were extracted and purified in chloroform–methanol (17), evaporated to dryness under nitrogen, the residues reacted with osmium tetroxide in carbon tetrachloride, and the reaction product chromatographed over neutral alumina columns to isolate disaturated phosphatidylcholine (DSPC) (18). Lung lavage cholesterol and protein were measured as indices of capillary endothelial and alveolar epithelial permeability changes. Cholesterol (CHOL) was measured by the Lieberman-Burchard color reaction (19), and protein by the Bio-Rad method. All values were divided by 0.65 to compensate for mean recovery rates and expressed as milligram per gram wet lung weight. The middle lobe of the left lung was removed, weighed, placed in a drying oven at 80°C until the weight no longer changed and the wet weight/dry weight ratios were determined. The rest of the left lung was used to determine blood weight and the extravascular water/extravascular dry weight ratio using the method of Pearce (20). The brains of cats exposed to pressure were examined for evidence of injury.

All data were recorded casewise into 64 variables, stored on disks, and analyzed using the Apple IIe computer and Abstat statistical package (Anderson-Bell). The data are expressed as means ± standard errors. The significant changes from baseline values were determined by the paired or unpaired *t* test. Correlation and regression analyses were used to compare the relationships between peak hemodynamic values and the pulmonary parameters. A probability value (*P*) of less than 0.05 is considered significant.

Results. The results from the present study showed that an 80- to 100-msec pulse of pressure at 80 psi applied to the cranial cavity of anesthetized cats resulted in large increases in intracranial, systemic, and pulmonary blood pressures. These changes were associated with increased levels of circulating catecholamines, lung lavage protein, cholesterol, ACE, gross lung injury, and extravascular lung water. There was, however, a significant negative correlation between pulmonary arterial pressures and evidence of edema formation (Fig. 1). Cats with higher peak intracranial and pulmonary arterial pressures had lower extravascular and total lung weights.

Intracranial pressure as estimated from a lumbar spinal cannula rose to a peak at 38

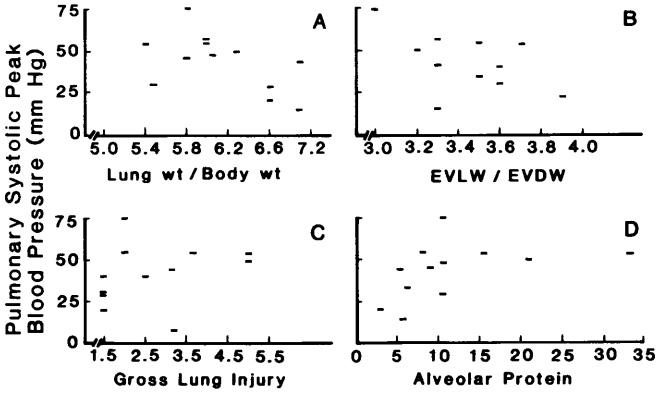

FIG. 1. Values of (A) lung weight/body weight ratios, (B) extravascular lung water/extravascular dry weight ratios, (C) gross lung injury indices, and (D) alveolar protein concentrations versus pulmonary systolic peak pressures.

± 11.8 sec following application of the pressure pulse from 7.4 ± 1.5 to 150.6 ± 19.4 mm Hg (Table 1). Systemic systolic peak artery pressures more then doubled from 130.7 ± 8.1 mm Hg to a peak of 299.0 ± 11.4 mm Hg at 31 ± 6.7 sec after the pulse. Pulmonary arterial systolic peak pressure also rose from 18.9 ± 1.9 to 42.9 ± 4.9 mm Hg at 119 ± 25.8 sec after the pulse. Circulating norepinephrine levels rose dramatically from 2689 pg/ml in our surgical preparations just prior to the pressure pulse to 23,373 at 30 sec following the pulse; these values returned toward normal after 15 min. Circulating epinephrine levels developed a similar trend rising from 1467 pg/ml to 22,930. The lungs were examined within 5 min following sacrifice. The lung gross appearance index, in which a 0 was assigned to normal lungs and +5 for severe grossly hemorrhagic lungs, indicated a moderate injury level with an experimental value of 2.5 ± 0.3. Protein levels in lung lavage fluid increased from a mean control value of 6.7 ± 0.4 mg/g lung tissue to 11.9 ± 2.0 ($P < 0.05$) in experimental group (Table II). ACE activity increased from a mean control value of 0.27 ± 0.04 to 0.46 ± 0.03 nmole/ml, $P < 0.05$, at 30 sec after the pulse in the experimental group. Blood gas values remained essentially unchanged throughout the 120 min. Three out of 15 cats exposed to the pulse of intracranial pressure died before the 120-min duration of postinjury evaluation; the data from these animals were included because they did not differ in any significant manner from those of the survivors. Examination of brain tissue revealed subarachnoid hemorrhages and macroscopic hemorrhages throughout the brainstem. Cortical contusions and lacerations were minimal.

There was clear evidence of some edema development. Lung weight/body weight ratios increased from 5.3 ± 0.2 in controls to 6.4 ± 0.2 ($P < 0.05$) in the experimental group. Extravascular lung water/dry weight ratios increased from 3.36 ± 0.04 to 3.51 ± 0.09 ($P < 0.05$). Lung wet weight/dry weight ratios increased from 4.52 ± 0.04 to 4.73 ± 0.07 ($P < 0.05$). Blood weight/body lung weight ratios were unchanged. Lung lavage cholesterol increased from 0.18 ± 0.01 mg/g lung to 0.24 ± 0.02. DSPC levels were unchanged.

The lung weight/body weight ratios, extravascular lung water/dry weight ratios and arterial blood oxygen levels all were inversely related to the pulmonary arterial systolic peak pressures ($r = -0.66, -0.59, -0.57$, respectively; $N = 10$–12, $P < 0.05$; Figs. 1A, B). In contrast, the gross lung injury index and alveolar protein varied directly with the pulmonary arterial peak pressures ($r = 0.35$; Figs. 1C, D).

Discussion. The results from the present study showed that transient pressure applied to the cranial cavity resulted in marked increases in intracranial, systemic, and pulmonary arterial pressures. Circulating catecholamines increased approximately tenfold just after the pulse but returned to near control levels after 15 min. Lung edema developed with increased lavage protein content indicative of increased capillary and alveolar permeability. Increased extravascular lung water varied inversely with the pulmonary arterial peak pressures.

The reciprocal relationships between pulmonary arterial peak pressures and extravascular lung water as well as lung weight/body weight ratios suggest that the edemagenic mechanisms are not directly dependent on hydrostatic pressure. Millen and Glauser (14) showed that a pulse of pressure applied to the cranium of anesthetized cats resulted in the development of pulmonary edema in the absence of a rise in aortic, pulmonary arterial, or wedge pressures. Our results, however, showed marked rises in pulmonary arterial pressures but they were inversely related to the development of edema. While selective reabsorption of edema fluid could conceivably account for this negative correlation, it probably did not occur. The cats with the greatest peak pulmonary arterial pressures also sustained the most prolonged pressure elevations which would oppose fluid reabsorption. Furthermore, of the 15 cats exposed, 3 died within 20 min of the pulse, with little chance for fluid reabsorption but the results from these did not differ in any appreciable way from the 2-hr survivors including the amount of water present in the lungs.

Increased vascular surface area cannot be ruled out as the cause of this weight change. If it occurred, however, it could not have been dependent on pulmonary arterial pressures

TABLE I. CARDIOPULMONARY RESPONSE TO AN INDUCED PULSE OF INTRACRANIAL PRESSURE IN CATS

		Control	Experimental
Systemic arterial peak pressure systolic/diastolic (mm Hg)	N	15	15
	$\bar{X}$	130.7/89.3	299.0*/255.0*
	SE±	8.1/8.4	11.4/6.3
Pulmonary arterial peak pressure (mm Hg)	N	12	12
	$\bar{X}$	18.9/13.4	42.9*/31.5*
	SE±	1.9/1.6	4.9/5.0
Intracranial peak pressure (mm Hg)	N	12	12
	$\bar{X}$	7.4	150.6*
	SE±	1.5	19.4
Norepinephrine (pg/ml)	N	12	9
	$\bar{X}$	2689	23373*
	SE±	809	8560
Epinephrine (pg/ml)	N	12	7
	$\bar{X}$	1467	22930*
	SE±	232	2858
Lung gross appearance (scale 0 to +5)	N	9	15
	$\bar{X}$	0.0	2.5*
	SE±	0.0	0.3
Angiotensin-converting enzyme (nmole/ml)	N	12	12
	$\bar{X}$	0.27	0.46*
	SE±	0.04	0.03

Note. N indicates sample size; N exceeds 10 (number of control animals) when animals served as their own controls and paired differences were used for statistical analyses.

* $P < 0.05$.

TABLE II. PULMONARY RESPONSE TO AN INDUCED PULSE IN INTRACRANIAL PRESSURE

		Control	Experimental
Protein (mg/g)	N	9	15
	$\bar{X}$	6.7	11.9*
	SE±	0.4	2.0
Lung weight/body wt × 1000	N	10	15
	$\bar{X}$	5.3	6.4*
	SE±	0.2	0.2
Extravascular lung water/dry wt	N	9	14
	$\bar{X}$	3.36	3.51*
	SE±	0.04	0.09
Lung wet wt/dry wt	N	10	15
	$\bar{X}$	4.52	4.73*
	SE±	0.04	0.07
Cholesterol (mg/g lung)	N	9	15
	$\bar{X}$	0.18	0.24*
	SE±	0.01	0.02
DSPC (mg/g lung)	N	9	15
	X	2.00	1.73
	SE±	0.22	0.16

* $P < 0.05$

because it too would be inversely related to extravascular lung water. Bowers *et al.* (11) showed that extreme pulmonary hypertension was not a prerequisite to neurogenic pulmonary edema, and Hoff *et al.* (9) showed that increased systemic arterial pressure was not essential. However in a related study Garcia-Uria *et al.* (21) concluded that increased pulmonary arterial pressure, rather than systemic, was the single most important precursor of edema.

Blood oxygen levels at 60 min after the pulse were inversely related to lung gross injury ($r = -0.84$), pulmonary artery pressure ($r = -0.569$), and lung lavage protein ($r = -0.809$) but as expected varied directly with extravascular lung water ($r = 0.340$) and lung weight/body weight ratios ($r = 0.416$). It would appear that the small amount of extravascular fluid did not interfere with oxygen transfer but that the presence of protein or related changes did reduce gas diffusion.

The ratio of bronchoalveolar lavage cholesterol to DSPC has been shown to be important to the normal function of the surface active layer lining the alveoli (22). The increase found in the present study might be expected to raise the minimum surface tension, alter the lung mechanics, and promote the development of edema. While sympathetic stimulation alone decreases the cholesterol/DSPC ratio (23), it is increased by mechanical head injury (24) and the pulse of intracranial pressure given in the present study.

The results from the present study tend to confirm previous reports of hemodynamic events and the development of lung edema associated with a rise in intracranial pressure. Increases in lavage protein and cholesterol were found as well as a large rise in circulating catecholamines. A short pulse of pressure to the cranium resulted in the development of minimal lung edema which was not dependent on a pulmonary hypertension, but which was negatively correlated with the pulmonary arterial pressure response. The edemagenic mechanisms probably involve both hemodynamic and permeability factors.

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