# Effects of sequential periods of intracranial hypertension on lung fluid balance[1]

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*Summary.* Pulmonary hemodynamics and fluid and protein exchange were examined in dogs subjected to three successive periods of intracranial hypertension. Results indicate that the alteration in lung fluid balance is due to increased microvascular surface area following capillary recruitment. The relationship to the mechanism of neurogenic pulmonary edema is discussed.

Pulmonary edema often follows traumatic brain injury and may be associated with elevated intracranial pressure (ICP)[2-5]. Since the edema is associated with a sudden large increase in sympathetic activity in response to cerebral dysfunction caused by the compression of cerebral blood vessels it is most commonly referred to as neurogenic pulmonary edema (NPE)[6]. It has been suggested that NPE is caused by increased pulmonary microvascular permeability either by a direct, neurally mediated mechanism[7], or through indirect damage caused by cyclic and extremely high pulmonary blood pressures[8]. It has been reported that elevation of ICP in experimental animals results in an increase in the flow of protein-rich lymph from the lung[9,10]. The response has been attributed to increased pulmonary microvascular permeability. Recent data from our laboratory, however, indicate that the increase in the flow of protein-rich lymph which follows increased ICP is caused by a pressure-dependent recruitment process which increases microvascular surface area available for filtration, not by an increase in permeability[11].

The present study was undertaken to provide further evidence in support of the above hypothesis. We examined the effects of sequential periods of increased ICP on the flow and composition of right lymphatic duct (RLD) lymph in dogs, reasoning that if the response to increased ICP were readily reversible over short periods of time it would be unlikely to be due to increased pulmonary microvascular permeability and is more probably explained by recruitment.

*Materials and methods.* We anesthetized 9 mongrel dogs weighing an average of 20.3 kg with sodium pentobarbital (30 mg/kg, i.v.) and ventilated them with a mixture of 50% oxygen in air. Throughout the experiment end tidal $CO_2$ was maintained at approximately 4%. Blood gas values were measured periodically throughout the experiments (radiometer model BMS3MK2). Arterial oxygen tension remained above 200 Torr in each animal ($227 \pm 39$ Torr), while carbon dioxide tension was $37 \pm 5$ Torr. A femoral artery was cannulated for measurement of systemic arterial blood pressure (Psa) and for withdrawal of arterial blood samples and a femoral vein for the administration of drugs. Pulmonary arterial (Ppa) and left atrial (Pla) blood pressures were obtained with a flow directed catheter (Thermodilution Model 93-111-7F, Edwards Laboratories) introduced through the right jugular vein. The same catheter was used with a thermodilution cardiac output computer (Model 9520, Edwards Laboratories) to determine cardiac output. In all animals a silastic catheter was sealed in position within the subdural space over the right parietal cortex and used to monitor as well as elevate ICP. ICP was elevated by raising a steady level reservoir of warmed artificial cerebrospinal fluid.

Lymph was obtained from the right lymphatic duct by the method of Vreim and Okuda[12]. Animals were heparinized systemically following cannulation of the RLD. Lymph (L) and plasma (P) protein concentrations were determined from centrifuged samples drawn at 10-min and 20-min intervals respectively throughout the experiment with a refractometer (Model 10400, American Optical). From these the lymph to plasma protein concentration ratio (L/P) was determined. Vascular pressures and cardiac output were recorded during each 10-min lymph collection period. A 30–75 min control period was conducted in all animals prior to the initial period of ICP elevation. We continued this period for 7 h in one animal as sham-control where there were no further manipulations. After the initial control period, ICP was elevated to match mean Psa during three successive periods which ranged from 30–90 min. At the end of each period of ICP elevation, ICP was lowered to baseline until hemodynamic parameters had stabilized, this ranged from 30–70 min and was 39 min on average. This baseline period thus served as a control period for the succeeding period of ICP elevation. In all instances elevation of ICP to levels at least matching Psa produced a cerebral ischemic response characterized by marked cycling of systemic and pulmonary blood pressures.

Data were analyzed using a paired t-test. A level of $p \leqslant 0.05$ was accepted as indicative of statistical significance.

*Results.* Data from the 8 experimental animals are presented as mean values $\pm$ SD in the table. Baseline hemodynamic values are within the reported range for pentobarbitalized dogs, thus the potential of hyperoxic ventilation to decrease pulmonary vascular resistance (PVR) was apparently offset by anesthesia[13]. Elevation of ICP produced an increase in lymph flow rate ($\dot{Q}L$) during each period of intracranial hypertension. This was manifest as an average increase of 68.7% across all animals for all periods of intracranial hypertension. The largest increase occurred in response to the initial period of ICP elevation during which an increase of 94% was observed. L/P was unchanged from its corresponding baseline value during periods of ICP elevation, although there was a tendency for this parameter to increase slightly in response to the intervention. While mean pulmonary vascular pressures were not increased dramatically by ICP elevation, each period of ICP elevation was associated with marked hemodynamic cycling, i.e., periodic waxing and waning of mean blood pressures, cardiac output, and PVR. Such a response was not observed during baseline periods. No significant changes in measured variables occurred in the sham-control animal.

*Discussion.* The technique of right lymphatic duct cannulation has been used by many investigators to study lung fluid balance[14-17]. Our baseline L/P's are similar to those previously reported for dogs. The initial baseline value of $4.4 \pm 2.7$ ml/h is consistent with RLD flow rates reported in similarly prepared animals[17,18].

Increased pulmonary microvascular permeability has been suggested to occur in response to ICP elevation by several groups of investigators, although in no case has a mechanism by which the alleged increase in permeability occurs been identified. Bowers et al. reported an immediate increase in the flow of protein-rich pulmonary lymph in response to ICP elevation to levels approximating Psa in sheep[9]. Van der Zee et al. also reported an increase in protein-rich lymph flow following intracranial hypertension in sheep, although these investigators observed a more gradual increase in $\dot{Q}_L$ to 2 times baseline levels, presumably since they increased ICP to levels which were 25–40

Lung fluid balance and hemodynamics during successive periods of ICP elevation in dogs

| | Control period | Period 1 ICP | Baseline | Period 2 ICP | Baseline | Period 3 ICP | Baseline |
|---|---|---|---|---|---|---|---|
| Systemic arterial blood pressure (Psa, Torr) | 123 ± 10.2 | 130 ± 21.2 | 111 ± 15.7 | 123 ± 30.2 | 107 ± 21.3 | 129 ± 31.4 | 112 ± 17.9 |
| Cardiac output (CO, L/min) | 3.49 ± 2.01 | 3.65 ± 1.69 | 3.57 ± 2.41 | 3.25 ± 2.05 | 3.59 ± 2.17 | 3.79 ± 2.21 | 3.65 ± 2.40 |
| Pulmonary arterial blood pressure (Ppa, Torr) | 13.6 ± 3.0 | 16.5 ± 3.2 | 14.1 ± 2.5 | 16.6 ± 4.1 | 13.6 ± 2.5 | 17.3 ± 3.3 | 12.7 ± 2.4 |
| Left atrial blood pressure (Lap, Torr) | 4.2 ± 2.7 | 5.1 ± 2.3 | 4.8 ± 3.3 | 5.7 ± 4.0 | 3.8 ± 2.7 | 6.8 ± 4.3 | 3.7 ± 1.8 |
| Pulmonary vascular resistance (PVR, Torr/L/min) | 2.69 ± 0.81 | 3.12 ± 0.96 | 2.61 ± 1.13 | 3.35 ± 1.32 | 2.73 ± 1.12 | 2.77 ± 1.51 | 2.47 ± 1.17 |
| Lymph to plasma protein concentration ratio (L/P) | 0.58 ± 0.07 | 0.60 ± 0.13 | 0.57 ± 0.04 | 0.61 ± 0.05 | 0.60 ± 0.10 | 0.62 ± 0.10 | 0.59 ± 0.06 |
| Right lymphatic duct lymph flow rate (QL, ml/min) | 4.4 ± 2.7 | 8.6 ± 4.1* | 6.1 ± 3.2 | 9.2 ± 3.6* | 6.6 ± 2.9 | 12.6 ± 3.1* | 6.7 ± 3.4 |
| Intracranial pressure (ICP, Torr) | 5.9 ± 2.0 | 134 ± 30.9 | 6.1 ± 3.5 | 143 ± 37.6 | 5.3 ± 3.5 | 136 ± 27.2 | 7.8 ± 3.9 |

All values are given as $\bar{X} \pm SD$. * $p \leq 0.05$, compared to control.

mm Hg below Psa[10]. Each of these groups reported L/P's which were either significantly[10] or insignificantly[9] increased during the period of intracranial hypertension. In each of the above reports little change in mean pulmonary blood pressures was observed as a result of ICP elevation. These investigators have interpreted their data as being indicative of a neurally mediated increase in pulmonary microvascular permeability, since ICP elevation produced an increase in protein-rich lymph flow in the face of little change in mean pulmonary blood pressure. Each group however, qualified the alleged increase in lung permeability as being modest and similar to the increase in permeability produced by histamine, an agent which has been reported to produce a small increase in pulmonary vascular permeability[19,20].

Our data are consistent with those of the above studies. The initial period of ICP elevation produced a near doubling of $\dot{Q}L$ (94%) as compared to the initial control period. $\dot{Q}L$ was significantly elevated during each of the two succeeding periods of ICP elevation as compared to the preceding baseline period. During the increased $\dot{Q}L$ caused by ICP elevation, L/P's remained statistically unchanged from control values, although a tendency to increase slightly was observed. These alterations in pulmonary fluid balance occurred concomitantly and with little change in mean Ppa or Pla suggesting that little change in mean pulmonary microvascular pressure occurred during periods of ICP elevation. Thus, these data could be interpreted as suggesting that a modest increase in pulmonary vascular permeability occurred in response to each period of ICP elevation. That such a change could be considered 'reversible' is suggested since $\dot{Q}L$ fell to levels which were statistically unchanged from the initial control value after each period of ICP elevation.

It is, however, unlikely that the sequential increases and rapid decreases in protein-rich lymph flow observed in this study in response to ICP elevation and subsequent lowering represent a rapid reversal in pulmonary microvascular permeability. Most agents that to increase pulmonary microvascular permeability (e.g., alloxan, alphanaphthylthiourea, pseudomonas bacteria) do not produce a rapidly reversible alteration. Pseudomonas bacteremia reportedly produces an alteration in pulmonary microvascular permeability which resolves only within 24–72 h following the insult[20]. That caused by histamine is reported to resolve within 60–90 min following the intervention[20], as compared to our results which indicate that $\dot{Q}L$ had returned to levels not significantly higher than the initial baseline period after each successive period of ICP elevation (within 35 min on average). However, histamine has been shown to increase extravascular lung water content while ICP elevation does not[10].

An alternative explanation to the alleged increase in pulmonary microvascular permeability caused by ICP elevation is that the increase in the flow of protein-rich lymph from the lung is caused by a pressure-dependent recruitment of an otherwise potential microvascular surface area. A recent study by Luce et al., for example, suggests that increasing ICP with air causes pulmonary air embolization in dogs, rather than NPE[22]. That recruitment can cause an increase in the flow of protein-rich lymph from the lung is well known[23], and is a process which was not explicitly ruled out by either Bowers et al. or by Van der Zee et al. as an explanation of their results[9,10]. A recent study from our laboratory, however, has shown that prerecruitment of potential pulmonary microvascular surface area (brought about by elevating Pla before increasing ICP) eliminates the response caused by elevation of ICP alone[11]. These results indicate that a change in pulmonary microvascular surface area, not increased permeability, is the primary mechanism underlying increases in protein rich $\dot{Q}L$ following elevation of ICP.

Increased pulmonary microvascular surface area following ICP elevation is likely explained by both systemic and pulmonary neurohemodynamic events. Primary among these are a central redistribution of blood volume and attendant increases in pulmonary vascular pressures and blood flow which follow the increased systemic vascular resistance caused by increased sympathetic nervous activity during Cushing cycling. Effects of increased sympathetic activity on the pulmonary circulation include decreased vascular compliance, increased arterial pulse pressure and an increase in the ratio of venous to arterial resistance; all of which increase microvascular pressure.

The edemogenic mechanism which follows ICP elevation evidently differs from that of fulminating neurologic pulmonary edema. This can develop after acute, massive brain injury and is characterized by rapid onset, extraordinary systemic hypertension, and alveolar flooding with fluid having a high protein content, presumably reflecting increased pulmonary microvascular and airway permeability. The mechanism is unknown but is thought to be multifactorial, involving not only hemodynamic processes which cause increased pulmonary microvascular pressure, but

other neural and humoral factors such as the direct action of 'permeability nerves', the possibility of 'stretched pores' under extremely high pressure transients, and the influence of a variety of agents which may damage the air-blood barrier[6-10].

In conclusion, the results of the present study are consistent with other recent evidence[11,22,24] and further suggest that the increase in the flow of protein-rich lymph produced by intracranial hypertension is more likely explained by a recruitment of pulmonary microvascular surface area than by an increase in pulmonary microvascular permeability.

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## Can blocking the Na/K exchange pump lead to a reduction in intracellular sodium?[1]

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*Summary.* It has been assumed that a rise in intracellular sodium should follow inhibition of the Na/K exchange pump. However, under certain conditions a reduction in intracellular sodium following pump blockage is possible. Many results postulating 'stimulation' of the Na/K exchange pump by low doses of the cardiac glycosides can be explained in this manner.

It has been assumed that a rise in intracellular sodium should follow the inhibition of the Na/K exchange pump[2-6]. In cardiac muscle, this rise in intracellular sodium is postulated to be an important first step leading to the increase in contractile force produced by cardiac glycosides[2,4]. However there are reports that following the application of low concentrations of the glycosides there is a decrease in intracellular $[Na^+]$ or $Na^+$ activity, or a rise in intracellular $[K^+]$[7-11]. These results have led to the suggestion that low concentrations of the glycosides can stimulate the Na/K exchange pump[7,9,12]. Another explanation is possible. The low concentrations of the glycosides by partially inhibiting an electrogenic Na/K exchange pump, will change the membrane potential[13-16]. The change in membrane potential will lead to changes in $[Na^+]_i$ and in $[K^+]_i$. A simple model shows the conditions under which low concentrations of glycosides could lower $[Na^+]_i$ owing to this effect.

For simplicity the model will be developed by considering only the Na and K currents and the Na/K pump. The steady state current due to sodium, which is known in cardiac muscle as the inward background current, $I_{inb}$, is assumed to follow the constant field equation[6,21], and therefore is monotonically rising with an increase in the negativity of the membrane potential (fig. upper panel). The potassium current, $I_K$, is assumed to depend on membrane potential as shown in the figure, middle panel (inwardly rectifying at negative potentials ($< -30$ mV) and outwardly rectifying at more positive potentials[17,18]). The Na/K pump is assumed to be potential independent[14], depend linearly on $[Na]_i$, and to have a fixed coupling ratio of 3 $Na^+$/2 $K^+$ (fig., lower panel). The pump is therefore electrogenic, with a current $I_p$. These assumptions are most parsimonious with the available data, although a window

Na/K pump blockage can lead to a reduction in $[Na]_i$

| A) Rest | B) Immediately following a 5% pump blockage | C) Later, new steady state* |
|---|---|---|
| $V = -90$ mV | $V = -80$ mV | $V = -75$ mV |
| $I_K = 2$ | $I_K = 1.76$ | $I_k = 1.71$ |
| $I_p = 1$ | $I_p = .95$ | $I_p = .855$ |
| $I_{inb} = -3$ | $I_{inb} = -2.71$ | $I_{inb} = -2.565$ |
| $[Na]_i = 7$ mM | $[Na]_i = 7$ mM | $[Na]_i = 6.3$ mM |

*The time necessary to achieve this new steady state is dependent on the cell surface to volume ratio. The steady state achieved is independent of that ratio. $I_K$, $I_{inb}$ and $I_p$ as given in the figure. The units are arbitrary, and would have to be scaled to the size of the preparation.