
Contribution of Systemic Venous Hypertension to the Development of Pulmonary Edema in Dogs

WARREN C. MILLER, WARREN W. SIMI, AND DAVID L. RICE

SUMMARY Systemic venous hypertension (SVH) is a frequent finding in pulmonary edema. To study the possible contributory or even causal role of SVH in pulmonary edema, a dog model was developed in which balloon catheters were placed in the left and right atria. Inflation of the left atrial balloon produced a tendency to pulmonary edema by causing pulmonary venous hypertension (PVH) (pulmonary artery wedge pressure of 20 mm Hg). Inflation of the right atrial balloon produced SVH (central venous pressure of 15 mm Hg). After 2 hours, dogs with SVH with or without PVH demonstrated a greater amount of lung fluid accumulation (P < 0.01) compared to controls or PVH alone. There was no significant difference in lung water in SVH dogs with or without PVH. Pulmonary blood flow was not significantly different between the experimental groups, each of which was less than control. Impairment of pulmonary lymphatic flow is one possible mechanism producing the worsening edema; however, bronchial venous hypertension or neurogenic reflexes cannot be excluded. We conclude that the contribution of systemic venous hypertension to the development of pulmonary edema may have therapeutic implications.

INCREASED extravascular lung water (pulmonary edema) has been demonstrated in humans with cor pulmonale, a condition characterized by systemic venous hypertension (SVH), rather than the pulmonary venous hypertension (PVH) seen in classic cardiogenic pulmonary edema due to left heart failure. The latter may additionally show systemic venous hypertension recognized by the clinician as distended neck veins, hepatic congestion and edema of the extremities. Various forms of noncardiogenic pulmonary edema also are accompanied by elevation of central venous pressure (CVP) which is independent of the level of pulmonary venous pressure. It has been postulated that the lung fluid accumulation seen in cor pulmonale is a consequence of SVH which produces back-pressure on bronchial veins that leads to pulmonary edema. Because of the frequent association of an elevated CVP and pulmonary edema and the suggestions that it may play a primary causal role, we have examined the contribution of systemic venous hypertension to the development of pulmonary edema in a canine model.

Methods

Healthy mongrel dogs weighing 22.5-29.3 kg were anesthetized with intravenous pentobarbital (30 mg/kg, iv), secured in a supine position, intubated and ventilated with a volume ventilator (Harvard Apparatus). Control of CVP in the upper body was obtained by variable inflation of a balloon catheter placed at the junction of the superior vena cava and right atrium via a jugular vein. Pulmonary capillary wedge pressure (PCWP), was elevated by a balloon catheter placed directly in the left atrium through a left thoracotomy; the incision was closed airtight.

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without damaging the lung, which was expanded by tube thoracostomy. Pulmonary artery pressures, CVP, and PCWP were measured with transducers (Hewlett-Packard, model 1280) connected to a triple lumen, balloon-tipped, flow-directed catheter inserted via a jugular vein and with the proximal port in the superior vena cava. Cardiac output was determined by injection of indocyanine green dye through the flow-directed catheter and blood withdrawal from the femoral artery through a densitometer (Waters Instruments, model TD-1). Preliminary studies had indicated that, after stabilization, balloon inflation did not cause major modifications in systemic blood pressure. Extravascular lung water (EVLW) was measured postmortem by the methods of Pearce et al. The four groups of six dogs were studied for 2 hours. The control group had catheters inserted but no balloon inflation to modify pressures. The second group had the left atrial balloon inflated so that PVH was maintained with PCWP at 20 mm Hg, a pressure selected to produce a tendency to increased transudation of fluid from pulmonary capillaries without overt pulmonary edema. The third group was similar to the second except that, in addition, the right atrial balloon was inflated to maintain systemic venous hypertension with a CVP of 15 mm Hg (PVH + SVH). The fourth group experienced only right atrial balloon inflation to produce SVH alone. At the end of the experimental period, the above-mentioned in vivo measurements were made. The dogs were killed by intravenous injections of potassium chloride, and EVLW determined. Data were treated statistically by unpaired t-tests.

Results
The results are summarized in Table 1. There was a significant (P < 0.01) increase in lung water with both combined pulmonary and systemic venous hypertension (PVH + SVH) and the systemic venous hypertension (SVH) compared either to controls or the PVH group. There were no differences between SVH and PVH + SVH groups. The PVH group demonstrated slightly, but not significantly, more lung water than controls; this is compatible with results of previous studies. Cardiac output was reduced in all experimental groups with balloon inflation; however, there was no difference among the groups.

Discussion
Within the bounds of the protocol, our data confirm the significant contribution of systemic venous hypertension per se to the development of pulmonary edema. Mellins et al. demonstrated significant increases in pleural fluid and a tendency to increased lung fluid in the presence of combined systemic and pulmonary venous hypertension compared to pulmonary venous hypertension alone; however, their study used higher pressures and was conducted with baseline venous pressures greater than 8 mm Hg to minimize the loss of pleural fluid by lymphatic drainage into any vein. Our study was designed to compare to normal venous pressures and infer the role of lymphatics. A plausible hypothesis is that elevated CVP impedes flow from the pulmonary lymphatics which empty into the systemic venous system. It has been suggested that such a mechanism aggravates systemic edema by causing venous back-pressure on the thoracic duct and hence impeding systemic lymphatic flow. Staub has amply emphasized the importance of pulmonary lymphatic flow in protecting against pulmonary edema. The exact pumping pressure of pulmonary lymphatics is unknown. Stop-flow techniques suggest about 10 cm H2O, whereas elevated catheter methods suggest about 17 cm lymph. Either would have been exceeded by the level of systemic venous hypertension in our experiments and often observed in patients. Pang et al. were unable to demonstrate differences in lung fluid accumulation between systemic venous pressures of 10 and 25 mm Hg. It is possible that pressures of 10 mm Hg used by Pang et al. and the pressure of greater than 8 mm Hg used by Mellins et al. partially or completely impaired control lymphatic flow. If this occurs, the addition of an even greater systemic venous hypertension might well have no demonstrable effect.

The magnitude of pulmonary lymphatic flow, methods of measurement, and time course of study may be important in the interpretation of such experiments. In the dog, basal right lymphatic duct flow has been determined to be 3–5 ml/hr, but some dogs have higher flows that presumably

### Table 1 Results Obtained in Control Dogs, and in Those with or without PVH and SVH

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 6)</th>
<th>PVH (n = 6)</th>
<th>PVH + SVH (n = 6)</th>
<th>SVH (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVLW (ml/kg)</td>
<td>3.99 ± 0.25</td>
<td>4.49 ± 0.14</td>
<td>6.95 ± 0.99</td>
<td>7.09 ± 0.72</td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>14 ± 0.8</td>
<td>27 ± 0.9</td>
<td>26 ± 0.8</td>
<td>12 ± 1.1</td>
</tr>
<tr>
<td>PCW (mm Hg)</td>
<td>3 ± 0.6</td>
<td>20 ± 0</td>
<td>20 ± 0</td>
<td>2 ± 0.4</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>2 ± 0.4</td>
<td>2 ± 0.4</td>
<td>15 ± 0</td>
<td>15 ± 0</td>
</tr>
<tr>
<td>CO (ml/min per kg)</td>
<td>71 ± 7</td>
<td>60 ± 11</td>
<td>51 ± 8</td>
<td>56 ± 6</td>
</tr>
</tbody>
</table>

EVLW: extravascular lung water; PAP: pulmonary artery pressure; PCW: pulmonary capillary wedge pressure; CVP: central venous pressure; CO: cardiac output.
represent the contribution of systemic lymph via interconnections with the thoracic duct. Moreover, recent experiments suggest that, on the average, only half of lung lymph is carried in the right lymphatic duct and that there is wide individual variation. Granting that the magnitude of basal pulmonary lymph flow in the dog is not precisely known, if a basal flow of 4 ml/hr is assumed and flow completely ceases during a 2-hour experiment, the theoretical accumulation of lung fluid would be only 8 ml. When superimposed on an average total extravascular lung water of 79 ml, the difference from baseline might not be readily apparent. In the basal state after total lymphatic ligation or lung auto-transplantation, a period of several hours is required to demonstrate significant accumulation of lung fluid; yet our dogs with systemic venous hypertension alone developed significant pulmonary edema within 2 hours.

Acute elevation of pulmonary venous pressure augments pulmonary lymph flow, and this probably reaches a maximum at pulmonary venous pressures of 20-25 mm Hg. At pulmonary venous pressures of 30 mm Hg, right duct flow has been measured at more than 11 ml/hr. Under such circumstances, 2 hours of lymphatic obstruction would theoretically produce a 30% increase in extravascular lung water. Magno and Szidon have shown a 16% increase in lung fluid after 2 hours of surgical ligation of lymphatics in the face of pulmonary venous pressures of 20 mm Hg, whereas our dogs with combined systemic and pulmonary venous hypertension experienced a 55% increase in extravascular lung water, which was no greater than the increase seen with SVH alone.

Although impairment of pulmonary lymphatic flow by SVH is an attractive hypothesis and should contribute to pulmonary edema on theoretical grounds, at present it seems inadequate to explain all of our findings in a simplistic fashion. Possibly previous estimates of basal lymphatic flow, its augmentation by PVH, and measurements of extravascular lung water are insufficiently sensitive to confirm this mechanism. Alternatively, additional or other factors may be operative. The concept of bronchial venous hypertension advanced by Turino et al. remains viable. In addition, one cannot exclude some form of neurogenic pulmonary edema related to hypertension in the veins of the central nervous system. Regardless of the exact etiology, the contribution of systemic venous hypertension to the development of pulmonary edema may have therapeutic implications. The effect of potent diuretics, which increase systemic venous capacitance as well as cause diuresis, might be explained in part by alteration in systemic venous pressure. Measurement of CVP may receive new emphasis in coordination with other parameters available from the Swan-Ganz catheter.

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References


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