The Dynamics of the Lung Fluid Filtration System in Dogs with Edema

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SUMMARY. We studied the relationship between pulmonary microvasculature fluid filtration pressures and lung lymph flow rate ($Q_L$) as filtration pressures increased to determine why lungs with functional lymphatics become edematous and, as filtration pressures decreased, to determine the effect of edema formation on lymphatic function. Edema was induced by rapid intravenous infusion of neutralized Ringer's solution in a volume equivalent to 30% of body weight in seven anesthetized dogs. Pulmonary microvascular pressure (Pmv) and $Q_L$ increased to 58 cm H2O and 40 ml/hr, respectively, during the infusion. Initially, $Q_L$ increased slowly and the estimated net fluid filtration pressure ($\Sigma_P$) increased rapidly with infusion. Later in the 30-minute infusion period, small increases in $\Sigma_P$ produced greater changes in $Q_L$. Over a 3-hour postinfusion period, Pmv and $Q_L$ decreased, but they remained significantly greater than baseline levels. During the postinfusion period, $Q_L$ was a linear function of Pmv and a logarithmic function of $\Sigma_P$. Extravascular lung water content, measured postmortem, was 70% greater than normal. The relationship between $Q_L$ and $\Sigma_P$ during and after the infusion demonstrated marked hysteresis. These results suggest that extravascular fluid accumulated in the lung in part because the lymphatics responded relatively slowly to rapid increases in $\Sigma_P$. Furthermore, the data suggest that, although the lymphatics may not be a quantitatively important route for removal of edema fluid, the pressure-volume characteristics of the pulmonary interstitium seem to have a major influence on lymphatic function.


DURING development of pulmonary edema, lymphatic function may determine in what manner and to what degree fluid accumulates in the extravascular space of the lung. Erdmann et al. (1975) measured lung lymph flow rates in unanesthetized sheep subjected to steady state elevations in left atrial pressure. They found that each cm H2O increase in pulmonary microvascular pressure resulted in an increase in lymph flow rate of about 0.5 ml/hr with no apparent maximum in lymph flow rate over the pressure range studied. However, their data suggest that the rapidity of the response of the lymphatics to a change in transvascular fluid dynamics is a factor that must be considered in studying the relationship between lymph formation and the accumulation of pulmonary extravascular fluid.

After development of pulmonary edema, the lymphatics may continue the normal function of conservation of plasma filtrate. In addition, they may function as conduits for removing accumulated extravascular fluid (Pine et al., 1976). We designed experiments to study the dynamics of transvascular fluid flux and lymph flow during and after development of pulmonary edema. Our results suggest that extravascular fluid accumulated in the lung in part because the lymphatic system responded relatively slowly to a rapid increase in the net fluid filtration rate. Furthermore, the pressure-volume characteristics of the pulmonary interstitium seem to have a major influence on lymphatic function.

Methods

Animal Preparation

We anesthetized seven mongrel dogs with intravenous pentobarbital (30 mg/kg). We secured the dogs in the supine position and made a tracheostomy. The dogs were ventilated on room air using a constant volume pump set to deliver 12 ml/kg, 12 times/min. Airway pressure was measured by placing a catheter in the trachea and attaching it to an appropriate transducer. We cannulated peripheral vessels and advanced catheters to the aorta, left ventricle or left atrium, right atrium and pulmonary artery (Thermodilution catheter, model 1-60-536, 7F, Technology Sales Corp.). Catheters were connected to pressure transducers (Statham, model P23DC, Statham Instrument Co.), and pressures were recorded on a direct-writing oscillograph (model 7, Grass Instrument Co.). We used the most dependent region of the lung as the zero reference level for blood pressures. A large bore catheter was placed in a femoral vein for infusion of fluid. We placed a Foley catheter in the bladder to measure the volume of urine delivered during the experiment. We cannulated the right lymph duct via a cervical lymphatic (Vreim and Ohkuda, 1977). The lymph catheter was Silastic tubing (i.d. 0.020 in., o.d. 0.037 in., or i.d. 0.025 in., o.d. 0.047 in., Dow...
Corning Corp.), filled with heparin (1000 U/ml). After all surgical procedures had been completed, we administered 3000 U of heparin, intravenously. Additional pentobarbital was administered as needed.

Protocol

We waited until lymph cleared the cannula to begin a 30- to 60-minute baseline period. Lymph was collected in graduated, heparinized centrifuge tubes and the flow rate calculated in ml/hr. At the midpoint of the lymph collection, we measured cardiac output (Q) by the thermodilution method (Thermodilution Computer, model 3500, KMA, Technology Sales Corp.) and took a 2-ml systemic arterial blood sample. We also measured left ventricular end-diastolic pressure or mean left atrial pressure (Pla) and mean pressures in the aorta (Pa), right atrium (Pra), and pulmonary artery (Ppa). Mean pressures were recorded by electronic integration.

After baseline measurements, we began infusion of Ringer's solution at 37°C and brought to pH 7.40 with bicarbonate. We infused a volume equivalent to 30% of the dog's body weight by gravity feed at pressures of 30-40 cm H2O. The average infusion rate was 9.3 ± 0.5 (se) ml/min per kg (Table 1). The infusion was complete in about 30 minutes. During the infusion, we collected lymph in 15-minute samples. Midway in each collection, we recorded pressure and sampled arterial blood. We did not attempt to measure cardiac output during the infusion period. We continued to use 15-minute data collection periods for the first hour after the infusion. For the last 2 hours of the experiment we used 30-minute lymph collection periods. Three hours after completing the infusion, we opened the chest, clamped the lungs at the hila, and excised them to measure extravascular lung water (Pearce et al., 1965; Gee et al., 1978; Eilers, 1967).

Analysis of Samples and Data

After centrifugation, we measured the protein concentrations in duplicate samples of lymph (Cly) and plasma (Cp) (Lowry et al., 1951). The concentrations of albumin and globulin were calculated after cellulose acetate electrophoresis of duplicate samples of the two fluids (Grunbaum and Kirk, 1960). We used the albumin and globulin concentrations to calculate the oncotic pressures in plasma (πp) and lymph (πl), using the equations of Landis and Pappenheimer (1963). We calculated the pulmonary microvascular pressure (Pmv) by assuming that 60% of the total pulmonary vascular resistance is precapillary (Gaar et al., 1967) and that the distribution of vascular resistance does not change. These data were used to estimate the net pulmonary microvascular fluid filtration pressure (ΣF) as follows: ΣF = Pmv - (πp - πl). Since we did not have estimates of interstitial hydrostatic pressure in these experiments, we assumed that interstitial pressure for the fluid exchange vessels was equal to end-expiratory alveolar pressure (Woolverton et al., 1978). We also assumed that the reflection coefficients for albumin and globulin were unity and remained constant throughout the experiment.

Numerical data are reported as means ± sem. We compared groups of data using an unpaired t-test after determining that the variances were homogeneous (Snedecor and Cochran, 1967). Relationships between variables were determined by regression analyses. Unless stated otherwise, we accepted P < 0.05 as indicating statistical significance.

Results

As shown in Figure 1, rapid intravenous infusion produced marked transient increases in cardiac output and mean blood pressures. The exception was the mean systemic arterial pressure. Pa averaged 137 ± 8 torr at baseline and did not change significantly during or after the infusion. In contrast, the infusion-induced increase in Ppa was only partially reversed, since Ppa remained significantly higher than the baseline value throughout the postinfusion period. As shown in Figure 2, Pmv increased 4.5-fold during the infusion and, although pressure decreased rapidly after the infusion, Pmv remained significantly greater than the baseline level. The plasma protein concentration (Cp) decreased by about 60% during the infusion (Fig. 3). However, as

<p>| Table 1  Effect of Rapid Fluid Infusion on Lung Fluid Balance in Anesthetized Dogs |
|---------|------|-------------|--------|-----------|-----------------|</p>
<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Body wt (kg)</th>
<th>Infusion rate (ml/min per kg)</th>
<th>Volume infused (% B.W.)</th>
<th>Volume retained* (% B.W.)</th>
<th>Extravascular lung water (g/g dry lung)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D82-77</td>
<td>12.3</td>
<td>7.7</td>
<td>30.0</td>
<td>27.0</td>
<td>7.15</td>
</tr>
<tr>
<td>D83-77</td>
<td>12.2</td>
<td>12.6</td>
<td>30.0</td>
<td>26.3</td>
<td>5.23</td>
</tr>
<tr>
<td>D84-77</td>
<td>14.5</td>
<td>9.5</td>
<td>27.6</td>
<td>24.2</td>
<td>6.51</td>
</tr>
<tr>
<td>D89-77</td>
<td>20.0</td>
<td>7.5</td>
<td>30.1</td>
<td>27.6</td>
<td>6.03</td>
</tr>
<tr>
<td>D96-77</td>
<td>15.0</td>
<td>8.6</td>
<td>30.0</td>
<td>21.7</td>
<td>7.13</td>
</tr>
<tr>
<td>D14-78</td>
<td>14.7</td>
<td>10.0</td>
<td>29.9</td>
<td>23.8</td>
<td>5.11</td>
</tr>
<tr>
<td>D18-78</td>
<td>18.1</td>
<td>9.1</td>
<td>30.0</td>
<td>21.7</td>
<td>6.23</td>
</tr>
<tr>
<td>Mean</td>
<td>15.3</td>
<td>9.3</td>
<td>29.7</td>
<td>24.6</td>
<td>6.20</td>
</tr>
<tr>
<td>SE</td>
<td>1.1</td>
<td>0.7</td>
<td>0.3</td>
<td>0.9</td>
<td>0.31</td>
</tr>
</tbody>
</table>

* Volume retained is the difference between the volume infused and the volume excreted. B.W. = body weight.
FIGURE 1 Changes in cardiac output (Q) and mean pressures in the pulmonary artery (Ppa), left atrium (Pla), and right atrium (Pra) induced by rapid intravenous fluid infusion equivalent to 30% of body weight. The bars indicate the infusion period. Data shown are means ± SEM of measurements made in seven dogs.

FIGURE 2 Effect of rapid intravenous fluid infusion on pulmonary microvascular pressure (Pmv), right duct lymph flow rate (QL) and the protein concentration ratio in lymph (CL) and plasma (CP). Data reporting lymph and plasma protein concentrations are shown in Figure 3. The bars indicate the infusion period. Data shown are means ± SEM of measurements in seven dogs. Standard error bars were omitted when the statistic was too small to illustrate with the scales used.

FIGURE 3 Effect of rapid intravenous fluid infusion on albumin and globulin concentrations in plasma and right duct lymph. The bars indicate the infusion period. Data shown are means and standard errors of measurements in seven dogs.

the fluid load distributed, CP increased to 65% of baseline. The lymph flow rate (QL) increased 50-fold during the infusion. QL decreased gradually after the infusion although extravascular lung water was 70% greater than normal (Table 1) (Gee et al., 1978). However, lymph flow rate remained about 16 times greater than baseline flow. The lymph: plasma protein concentration ratio (CL:CP) increased during the infusion, since CP decreased very rapidly and CL decreased slowly (Fig. 3). However, these data may not represent maximum changes since we did not specifically attempt to measure the maximum changes in protein concentrations. Furthermore, we assumed that the protein concentration in aortic blood was the same as that in the pulmonary exchange vessels, which may not be a valid assumption (Friedman and Garza, 1976). After the infusion, CP increased while CL was essentially constant. Therefore, CL:CP decreased early in the postinfusion period.

Figure 4 illustrates the relationships between the lymph flow rate, expressed in ml/sec, and the estimated transvascular pressure gradients during the baseline and postinfusion periods. QL decreased linearly as Pmv decreased after the infusion. The equation describing the relationship is $QL = 0.51 \times Pmv - 5.48$, $r = 0.96$. There was an inverse linear relationship between QL and the transvascular oncotie pressure gradient ($\Delta \pi = \pi_L - \pi_T$) during the
in the pulmonary circulation, where both hemodynamic effect of the fluid load is most pronounced. Fluid filtration protocol should minimize cardiac contaminations concerning the lymphatic drainage system. Since the lung is the only organ to receive the entire cardiac output, the lymphatic pump to changes in \( \Sigma P \) is at least, in part, a function of the fluid filtration history of the pulmonary circulation.

**Discussion**

In relating lung lymph flow rate to pulmonary microvascular hemodynamics, we made several assumptions concerning the lymphatic drainage system in dogs and the variables in the fluid filtration equation that we could not measure. We assumed that the lymph we collected from the right lymph duct originates primarily in the lung. In our experiments, we were very careful to ligate lymphatic vessels draining the head, neck, and forelimb during the cannulation procedure. Additional important sources of nonpulmonary lymph include the heart and the abdominal structures drained by the thoracic duct. Moreover, there is no satisfactory procedure for eliminating cross-over between cardiac and pulmonary lymphatics. However, the fluid infusion protocol should minimize cardiac contamination of right duct lymph. Since the lung is the only organ to receive the entire cardiac output, the hemodynamic effect of the fluid load is most pronounced in the pulmonary circulation, where both arterial and venous pressures increased dramatically. Therefore, the proportion of right duct lymph that might have been cardiac in origin would decrease with volume expansion. Contamination by the thoracic duct can be detected and eliminated. We did not fast dogs prior to the experiment, so thoracic duct lymph, if it had been present, would have been milky and easily detected. Furthermore, we have shown that the flow and composition of right duct and thoracic duct lymph are significantly different before, during, and after rapid fluid infusion (Gee and Donovan, 1979). Finally, other studies have shown that, in dogs with edema, the protein concentration of pulmonary interstitial edema fluid and right duct lymph are the same (Vreim and Staub, 1976; Gee and Donovan, 1979). However, as discussed below, it is likely that lymph protein concentration probably was not the same as that in perimicrovascular fluid during parts of our experiment.

In estimating the net fluid filtration pressure, it was necessary to make certain assumptions. First, we used values for pre- and postcapillary vascular resistances suggested by Gaar et al. (1967). More importantly, we assumed that the distribution of vascular resistance did not change sufficiently during the experiment to alter the basic relationships we described. Since, through most of our experiment, the entire lung was in zone III (West et al., 1978), it is certainly likely that as the fluid filtration rate increased, perimicrovascular pressure increased (Taylor et al., 1973). This local increase in interstitial pressure would aid fluid flow through the interstitial space resulting in formation of perivascular and peribronchial fluid cuffs (Staub, 1978). The extent to which fluid flow through the interstitium may modulate changes in interstitial pressure around exchanging vessels during formation of pulmonary edema is unknown. However, the volume of fluid in perivascular cuffs can be quite large (Gee and Williams, 1979). Therefore, the changes in perimicrovascular pressure with an increased filtration rate may not be as rapid or severe as might occur if fluid cuffs did not form. Furthermore, we assume that the physical properties of the pulmonary endothelium were not altered during the experiment and that the reflection coefficients for albumin and globulin were unity. The reflection coefficients are more likely less than unity. However, assuming a different positive number for the reflection coefficients would only shift the relationships we described without changing their character.

If permeability increased during the fluid load, the lymph flow rate at a given \( P_{mv} \) would increase,
since the effective reabsorptive pressure exerted by plasma proteins would be reduced and the hydraulic conductivity of the membrane would be increased. We found that the postinfusion relationships between \( Q_L \) and \( \Sigma_P \) or \( P_{mv} \) also described the preinfusion data (Fig. 4). These data suggest that if endothelial permeability increased as a result of high vascular pressures, the increase was reversible.

We still must resolve why extravascular lung water nearly doubled in dogs with a 50-fold increase in lymph flow rate. Clearly, the filtered load through the lung exchange vessels must have exceeded the lymph flow rate at some point during the experiment. Part of the answer may be found if we extend the relationship between lymph flow rate and microvascular fluid filtration pressure shown in Figure 4 to include data obtained during the infusion period (Fig. 5). There is a pronounced hysteresis in the response of lymph flow rate to changes in \( \Sigma_P \) depending on whether filtration pressure was increasing or decreasing. Initially, increases in \( \Sigma_P \) seemed to have little effect on \( Q_L \). Therefore, as \( \Sigma_P \) increased, the net transvascular fluid filtration rate must have exceeded the lymph flow rate, and fluid accumulated in the extravascular space. However, as \( \Sigma_P \) continued to increase, \( Q_L \) increased at a much faster rate. The lymphatic pump may require priming. That is, it may be necessary to have distension of the lymph vessels or some accumulation of fluid in the interstitial space before the lymphatics respond adequately to an increase in the fluid filtration rate. Perhaps distension of the lymphatics initiates more effective pumping or fluid accumulation expands interstitial channels reducing the resistance to fluid flow from the perimicrovascular space to the terminal lymphatics. Although the response time of the lymphatics to rapid increases in \( \Sigma_P \) may be partly responsible for the edema formation, the magnitude of the response may also play a role. Edema fluid may accumulate because the ability of the lymphatic pump to remove fluid is exceeded by the filtration rate. The lymph flow rates we measured are much higher than previously reported right duct flow rates (Drinker and Hardenbergh, 1947; Rabin and Meyer, 1960). Obviously, the lymphatics are capable of transferring a very large volume of fluid.

The validity of this interpretation of our results depends in large part on the relationship between lymph and perimicrovascular fluid protein concentrations. Early in the infusion period before the lymph flow rate increased dramatically, \( C_L:C_P \) increased because plasma protein concentration decreased about 50% with no change in lymph protein concentration. If we assume that the perimicrovascular fluid became increasingly protein poor as the net fluid filtration rate increased, the lymph protein concentration must have exceeded that in perimicrovascular fluid for part of the infusion period. In this case, the calculated interstitial fluid oncotic and net fluid filtration pressures would be overestimates of these pressures for the fluid-exchanging vessels. However, this error could not be of sufficient magnitude to explain the hysteresis in the lymph flow rate curve. If we assume that the perimicrovascular fluid protein concentration decreased by the same amount as the plasma concentration early in the infusion, the estimated net fluid filtration pressure would decrease from 55 to about 45 cm H2O. Even with this change, the increase in lymph flow rate early in the infusion was delayed relative to the rapid increase in the net fluid filtration pressure. In fact, we suggest that the delayed changes in \( C_L \) and \( Q_L \) are due to the same mechanism. It is apparent that the transvascular filtration rate exceeded the rate of fluid flux from the perimicrovascular space to the right lymph duct during the infusion. Furthermore, it seems reasonable that the primary resistance to fluid flux in this system may be in the interstitial pathway from the perimicrovascular space to the level of the terminal lymphatics. Accumulation of fluid in this space may reduce interstitial resistance, hence decreasing the transit time for flow through the interstitium.

Finally, we have the question of whether the flow and composition of lymph from edematous lungs reflects microvascular events or the accumulation of extravascular fluid. As shown in Figure 5, as \( \Sigma_P \) decreased from the maximum, the relationship between \( \Sigma_P \) and \( Q_L \) was essentially the reverse of that seen with increasing \( \Sigma_P \). That is, \( Q_L \) decreased at a
relatively slow rate as $\Sigma_p$ fell below the maximum value, which again suggests a slow lymphatic response to rapid changes in $\Sigma_p$. However, as $\Sigma_p$ approached the baseline fluid filtration pressure, the lymphatics became much more sensitive to small changes in $\Sigma_p$. These data demonstrate that, although the pressure-volume characteristics of the interstitium play a role, the lymphatics are sensitive to changes in the net fluid filtration pressure even when the lungs are edematous.

It is apparent that the dynamics of the pulmonary microvascular-lymphatic system are complex. A complete description of this system must await development of new methods to study pressure-flow relationships in the microvascular and interstitial spaces. However, we can make two conclusions based on our results. Edema fluid accumulated in the lungs, at least in part, because the lymphatics responded slowly to rapid, large increases in the fluid filtration pressure. Also, the lymphatics were sensitive to changes in the net fluid filtration pressure even though the lungs were edematous. It seems that, whereas the lymphatics may not be a quantitatively important route for removal of edema fluid, the volume of fluid in the pulmonary interstitium may be an important determinant of lymphatic function.

**References**


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