Effect of Outflow Pressure upon Lymph Flow from Dog Lungs

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SUMMARY. The pulmonary lymph flow rate \((Q_L)\) should be a function of the lymph vessels' resistance and the pressure gradient along the vessels. We attempted to study how these factors affect lymph flow. We assumed that the lymph system could be represented by a single pressure generated within the lung \((P_L)\) and a single resistance \((R_L)\). Thus, \(Q_L\) should be a function of the lymph vessel outflow pressure \((P_0)\): 
\[
Q_L = \frac{(P_L - P_0)}{R_L}
\]
We cannulated tracheobronchial lymph vessels in eight anesthetized dogs and varied \(P_0\) by raising the outflow end of the cannula. \(Q_L\) decreased linearly when we increased \(P_0\). We estimated \(R_L = -\frac{\Delta P_0}{\Delta Q_L}\) and \(P_L\) as the extrapolated \(P_0\) at which \(Q_L = 0\). At baseline \(P_L = 7.7 \pm 2.7\) (SD) cm H2O and \(R_L = 0.36 \pm 0.25\) cm H2O-min/µl. After we increased capillary pressure to produce edema, \(P_L\) and \(R_L\) averaged 22.8 ± 8.8 and 0.14 ± 0.12, respectively. After we reduced the capillary pressure to baseline in the edematous lungs, \(P_L\) and \(R_L\) averaged 11.6 ± 2.8 and 0.08 ± 0.09, respectively. All changes in \(P_L\) and \(R_L\) were significant \((P < 0.05)\). These results show that (1) lymph flow rate depends upon lymph vessel outflow pressure, and (2) the \(Q_L\) vs. \(P_0\) relationship is changed by edema. \(P_L\) may be equal to the pressure causing lymph to flow and \(R_L\) may equal the lymph vessel resistance. (Circ Res 50: 865–869, 1982)

IN the normal lung, the rate at which fluid is filtered across the capillary membrane is equal to the rate at which fluid is removed from the tissues by the lymphatic system. Thus, there is a steady state in which the tissue volume remains constant. If the capillary filtration rate is increased by moderate increases in capillary pressure, the lymph flow rate will also increase and reestablish a steady state. However, if the capillary pressure is increased above a critical level, the filtration rate will exceed the lymph flow rate and edema will occur. We have previously studied the factors which affect capillary filtration in intact dog lungs (Drake et al., 1980). In the present study, we have attempted to analyze the factors which affect lymph flow.

Several pressures may cause lymph to flow. First, the tissue fluid hydrostatic pressure may push fluid into the terminal lymph vessels. Second, there may be a "pump" mechanism which forces fluid down the lymph vessels. Third, the pressure at the outflow end of the lymph vessels may affect the lymph flow. Lymph flow should also depend upon the hydraulic resistance of the lymph vessels.

A complete study of the factors causing lymph flow would be difficult because direct measurements of tissue fluid pressure and pump pressure are difficult to make. In addition, the resistance of the lymphatic system is the combined resistance of the many interconnecting vessels. However, by using simple circuit analysis techniques it may be possible to resolve the system into a single equivalent pressure \((P_L)\) and a single resistance \((R_L)\), as shown in Figure 1 (Van Valkenburg, 1964). In the equivalent circuit of Figure 1, the lymph flow rate \((Q_L)\) should be a function of the pressure \((P_0)\) at the outflow end of the lymph vessel. Thus:

\[
\dot{Q}_L = \frac{P_L - P_0}{R_L}
\]

In this study, we assumed that the pulmonary lymph system could be represented by an equivalent circuit. We cannulated dog lung lymph vessels and varied \(P_0\) by placing the outflow end of the cannula at various heights above the cannulation site. \(Q_L\) decreased linearly with increases in \(P_0\) (the necessary condition for the equivalent circuit to apply). We estimated \(R_L\) from the relationship \(R_L = -\frac{\Delta P_0}{\Delta Q_L}\) and \(P_L\) as the extrapolated \(P_0\) at which \(Q_L = 0\). We elevated pulmonary capillary pressure and found that the resulting changes in \(Q_L\) were the result of changes in both \(P_L\) and \(R_L\).

Methods

We anesthetized 12 dogs with pentothal and maintained the anesthesia with 1-2% halothane. Catheters were placed into the left femoral artery and vein. The dogs were paralyzed with succinylcholine, and a left thoracotomy was made between the 5th and 6th ribs. In eight dogs we cannulated a tracheobronchial lymph vessel from the lungs and gave the dogs 2000–4000 units of heparin. We measured \(Q_L\) by collecting timed samples into a pipet and varied the outflow pressure \((P_0)\) by adjusting the height of the end of the cannula. We placed a 30-ml Foley balloon catheter and a second catheter to measure pressure in the left atrium. We directed a Swan-Ganz catheter through the left external jugular vein into the pulmonary artery. This catheter was used to measure the pulmonary arterial pressure. The hilus of the lung was used...
The Experiments

In eight dogs, we determined $Q_L$ vs. $P_L$ under baseline conditions, after elevating pulmonary capillary pressure for 1-3 hours to produce edema, and 10-40 minutes after we reduced the capillary pressure. We calculated the capillary pressure as the average of pulmonary arterial and left atrial pressures (Drake et al., 1980). After each experiment, we removed the lymph cannula and placed one end into a beaker of 4-5 g/dl human albumin solution. We measured the flow rate through the cannula with the other end of the cannula at various distances below the beaker. We divided the difference in cannula outflow height by the difference in flow rate to calculate the cannula resistance.

We calculated $P_L$ by adding the product of $Q_L$ and the cannula resistance to the height of the cannula above the cannulation site. To estimate $R_L$ and $P_L$, we determined the regression equation for $Q_L$ vs. $P_L$. The change in $P_L$ divided by the change in $Q_L$ ($\Delta P_L/\Delta Q_L$) was recorded as $-R_L$, and the extrapolated $P_L$ at which $Q_L = 0$ was recorded as $P_L$.

In four experiments we attempted to measure the resistance of the lymph vessels distal to the hilus of the lung. We cannulated tracheobronchial lymph vessels in the direction of flow, and attached the cannula to a pipet which was filled with 4-5 dl albumin solution. The pipet was mounted vertically on a graduated shaft. We measured the flow rate of albumin solution into the lymph vessel with the pipet at several different heights above the cannulation site. At the termination of the experiments, we determined the cannula resistance as described above and calculated the distal lymph vessel resistance as the change in inflow height/flow in rate minus the cannula resistance. We determined the least squares best fit relationship between flow rate and pipet height and extrapolated the flow rate to zero to estimate the minimum pressure required to cause flow into the vessels.

Statistics

All summary data are reported as mean ± s.e. We determined the significance of differences between data with the paired Student’s t-test. Regression equations were determined with the method of least squares, and correlation coefficients ($r$) were calculated with the product moment methods. A $P$ value of less than 0.05 was considered significant.

Results

When we elevated the outflow end of the lymph cannula, there was often a 1- to 5-minute transient period before $Q_L$ stabilized. During this time, there was obvious expansion of the portion of the lymph vessels which were external to the lung. Thus, during the transient, some of the lymph remained in the expanding lymph vessels instead of flowing into the pipet. We believe this caused the flow rate we measured to be too low; therefore, we waited until the transient was completed to record $Q_L$. The lymph flow was always higher in the edematous lungs and the transient time was much less than baseline.

We also observed that if the cannula outflow end was more than approximately 5 cm below the cannulation site, there was no change in $Q_L$ when we changed the catheter height. We attributed this to the “Starling resistor” phenomenon, because a portion of each lymph vessel was exposed to atmospheric pressure and the vessels were collapsible. When we elevated the cannula above 0 cm, $Q_L$ always decreased.

To estimate the $Q_L$ vs. $P_L$ relationships, we used only data in which $Q_L$ decreased when we elevated the cannula outflow end.

Figure 2 shows the $Q_L$ vs. $P_L$ data for a typical experiment. We determined the $Q_L$ vs. $P_L$ relationship 24 times in eight experiments. In 13 determinations, we estimated the relationship from two measurements of $Q_L$ and $P_L$; in the remaining 11 determinations we used three to seven measurements.

Linearity of the $Q_L$ vs. $P_L$ Relationship

The equivalent circuit of Figure 1 is applicable only if the $Q_L$ vs. $P_L$ relationship is linear. For all $Q_L$ vs. $P_L$ determinations based on more than two measurements of $Q_L$, the average correlation coefficient was $-0.984$. All $Q_L$ vs. $P_L$ based upon four or more measurements were significantly correlated with straight lines ($P < 0.05$). The degree of correlation with a straight line shown in Figure 2 was typical.

Changes in $R_L$ and $P_L$

Table 1 shows the calculated data for each experiment. During edema formation, $R_L$ decreased significantly by 60 ± 15% and $P_L$ increased significantly by 15.1 ± 9.9 cm H2O from baseline. When we decreased capillary pressure to the edematous lungs, $P_L$ decreased significantly by 11.2 ± 7.7 cm H2O and $R_L$ decreased significantly by an additional 45 ± 18% from its value at increased capillary pressure. Figure 3 shows the average $Q_L$ vs. $P_L$ data for all eight experiments. Edema fluid was present in the airways of the lungs at the termination of the experiments.

Changes in Lymph Flow Rate

The changes in $R_L$ and $P_L$, which occurred when we increased capillary pressure should both increase $Q_L$ (Eq. 1). However, when we decreased the capillary pressure to the edematous lungs, the resulting changes in $R_L$ and $P_L$ should have had opposite effects upon $Q_L$. The decrease in $R_L$ should increase $Q_L$, but the decrease in $P_L$ should reduce $Q_L$. Thus, in each experiment, the change in $Q_L$ should depend upon...
whether the decrease in $R_L$ or the decrease in $P_L$ dominated.

The effect of the decreases in both $R_L$ and $P_L$ is best illustrated graphically. In Figure 3 the line for edema + high pressure and the line for edema + low pressure cross at $P_0 = -3.5$. The two lines cross because of the differences in $R_L$ and $P_L$ for the two lung states. Thus, in experiments in which $P_0$ was less than the cross-over $P_0$, $Q_L$ should have been lower at the higher capillary pressure than it had been at elevated capillary pressure. In experiments in which $P_0$ exceeded the cross-over $P_0$, $Q_L$ should have been lower at lower capillary pressures.

Table 2 gives the lymph flow rates with the cannula at 0 cm for each experiment. When we increased the capillary pressure, $Q_L$ increased in every experiment ($P < 0.05$). When we decreased the capillary pressure, there was no consistent change in $Q_L$, it increased in two and decreased in six experiments.

We do not believe that the inconsistent $Q_L$ change was due to differences in capillary filtration rate because, in similar experiments, we have shown that the lungs were severely edematous at the high capillary pressures as well as after we decreased the pressures. Thus there was plenty of fluid available to the lymph vessels (Drake et al., 1980).

We believe the inconsistent changes in $Q_L$ were due to the opposing effects of the changes in $R_L$ and $P_L$. To illustrate this, we graphically determined the cross-over $P_0$ for each experiment (as in Fig. 3). We also calculated $P_0$ for each experiment at high capillary pressure by multiplying $Q_L$ times the catheter resistance. $P_0$ and the cross-over $P_0$ for each experiment are given in Table 3. $Q_L$ increased in the experiments in which $P_0$ was less than the cross-over $P_0$. It decreased when $P_0$ was larger than the cross-over $P_0$. Thus, both the paradoxical increase in $Q_L$ in some experiments and the decrease in $Q_L$ in other experi-

### Table 1

<table>
<thead>
<tr>
<th>Experiment no.</th>
<th>Baseline*</th>
<th>Edema + high pressure*</th>
<th>Edema + low pressure*</th>
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</thead>
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<tr>
<td></td>
<td>$P_L$†</td>
<td>$R_L$‡</td>
<td>$P_L$†</td>
</tr>
<tr>
<td>1</td>
<td>3.4</td>
<td>0.42</td>
<td>37.8</td>
</tr>
<tr>
<td>2</td>
<td>3.9</td>
<td>0.27</td>
<td>16.8</td>
</tr>
<tr>
<td>3</td>
<td>8.1</td>
<td>0.13</td>
<td>12.3</td>
</tr>
<tr>
<td>4</td>
<td>8.2</td>
<td>0.69</td>
<td>33.0</td>
</tr>
<tr>
<td>5</td>
<td>9.1</td>
<td>0.15</td>
<td>20.8</td>
</tr>
<tr>
<td>6</td>
<td>9.7</td>
<td>0.35</td>
<td>25.0</td>
</tr>
<tr>
<td>7</td>
<td>11.3</td>
<td>0.76</td>
<td>21.5</td>
</tr>
<tr>
<td>8</td>
<td>8.0</td>
<td>0.096</td>
<td>15.1</td>
</tr>
<tr>
<td>Mean</td>
<td>7.7</td>
<td>0.36</td>
<td>22.8</td>
</tr>
<tr>
<td>±S.E.</td>
<td>2.7</td>
<td>0.25</td>
<td>8.8</td>
</tr>
</tbody>
</table>

* Capillary pressure averaged 19.1 ± 3.9, 48.6 ± 6.1, and 18.6 ± 5.5 cm H$_2$O for the baseline, edema + high vascular pressure, and edema + low vascular pressure states, respectively.
† $P_L$ = effective intrapulmonary pressure causing lymph to flow (cm H$_2$O).
‡ $R_L$ = effective resistance of the lymph system (cm H$_2$O-min/ml).

![Figure 2](http://circres.ahajournals.org/Downloaded.jpg)
ments are easily interpreted in terms of the changes in $R_L$ and $P_L$, which occurred when we decreased the vascular pressure.

**Lymph Vessel Pumping**

Pulmonary lymph may be propelled by active or passive compression of the lymph vessel walls (Hall et al., 1965). We have not ruled out active pumping. However, several of our observations indicate that the pumping was the result of passive compression of the lymph vessel walls caused by inflation and deflation of the lungs. First, lymph moved into our collecting pipet during part of the respiratory cycle (expiration). Second, when we turned off the respirator, $Q_L$ was usually substantially decreased. Third, we saw no active contractions of the exposed portion of the lymph vessels.

**Distal Lymph Vessel Resistance**

The average distal lymph vessel resistance was $0.04 \pm 0.036$ cm H$_2$O min/μl. The estimated minimum pressure required to cause fluid to flow into the distal lymphatic vessels was $5.4 \pm 3.1$ cm H$_2$O.

We measured the inflow pressure and resistance of the distal portion of the lymph vessels so that we could estimate $Q_L$ in uncannulated vessels. In uncannulated vessels, the lymph must flow through the distal portion of the lymph vessels as shown in Figure 4. Thus, the lymph flow rate should be:

$$Q_L = \frac{P_L - \text{distal vessel inflow pressure}}{R_L + \text{distal vessel resistance}}.$$  (2)

We used $R_L$ and $P_L$ data of Table 1 and the data from the distal lymph vessel experiments to calculate $Q_L$ in uncannulated vessels. For the baseline, edema plus elevated capillary pressure and edema plus low capillary pressure states, we calculated the lymph flow rates to be $9.6 \pm 8.0$, $107 \pm 39$, and $60 \pm 27$ μl/min respectively. These lymph flow rates are much different ($P < 0.05$) from the $31 \pm 22$, $184 \pm 69$, and $162 \pm 99$ μl/min flow rates we measured with the cannula outflow at 0 cm in the same experiments (Table 2).

**Discussion**

The two basic findings in this study are (1) there is a linear relationship between lymph flow rate and the pressure at the outflow of the lymph vessel, and (2) this $Q_L$ vs. $P_L$ relationship is changed by high vascular pressures and edema formation. We chose to represent the $Q_L$ vs. $P_L$ relationship in terms of $R_L$ and $P_L$ because these two parameters completely define the

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**Table 1**

<table>
<thead>
<tr>
<th>Experiment no.</th>
<th>Change in lymph flow*</th>
<th>$P_L$ at high pressure (cm H$_2$O)</th>
<th>$P_L$ - Cross-over (cm H$_2$O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Decrease</td>
<td>6.3</td>
<td>-10.5</td>
</tr>
<tr>
<td>2</td>
<td>Decrease</td>
<td>1.8</td>
<td>-8.3</td>
</tr>
<tr>
<td>3</td>
<td>Increase</td>
<td>1.3</td>
<td>+11.5</td>
</tr>
<tr>
<td>4</td>
<td>Decrease</td>
<td>2.4</td>
<td>-36.2</td>
</tr>
<tr>
<td>5</td>
<td>Decrease</td>
<td>8.7</td>
<td>+6.5</td>
</tr>
<tr>
<td>6</td>
<td>Decrease</td>
<td>6.2</td>
<td>-5.9</td>
</tr>
<tr>
<td>7</td>
<td>Increase</td>
<td>2.8</td>
<td>+4.2</td>
</tr>
<tr>
<td>8</td>
<td>Decrease</td>
<td>5.9</td>
<td>-5.1</td>
</tr>
<tr>
<td>Mean</td>
<td>-5.5</td>
<td>±2.7</td>
<td>±14.6</td>
</tr>
</tbody>
</table>

* The change in lymph flow rate when we decreased the vascular pressures to the edematous lungs.

† $P_L$ at high pressure is the pressure at the outflow end of the lymph vessel when the pulmonary capillary pressure was elevated (edema + high pressure). It is equal to the catheter resistance times $Q_L$ in the edema + high pressure state.

‡ The cross-over $P_L$ is the pressure at the outflow end of the lymph vessels at which the edema + high pressure and edema + low pressure $Q_L$ vs. $P_L$ relationships cross (Fig. 3).
"equivalent circuit" of the pulmonary lymph system (Van Valkenburg, 1964). Thus, no matter how complicated the lymphatic system is, it can be represented by R_L and P_L, as shown in Figure 1. In terms of the circuit in Figure 1, we found that Q_L changed during edema formation because of changes in both R_L and P_L.

Possible Relationship between R_L and P_L and the Resistance and Pressures of the Lymph System

There is another advantage of representing the lymph system by an equivalent circuit. R_L and P_L may be related to the basic factors which cause lymph to flow. We believe that R_L represents the hydraulic resistance of the lymphatic vessels and P_L may equal the tissue fluid pressure plus the pressure generated by the lymph pump mechanism. These relationships are based upon the assumption that when we raised the outflow pressure, there was no significant change in the tissue fluid pressure, the pump pressure, or the lymph vessel hydraulic resistance. We believe that these assumptions are correct because the Q_L vs. P_o relationships were linear. Thus, if tissue pressure, pump pressure, or lymph vessel resistance did change when we changed P_o, they must have changed by the same percent of each change in P_o.

Another possible source of error in relating P_L and R_L to the basic factors causing lymph flow could occur if lymph flow was shunted into other lymph vessels when we increased P_o. We do not believe that lymph shunting occurred because, in most experiments, we ligated lymph vessels which we found near (1 cm) the site of cannulation. However, we cannot rule out the possibility of shunting to more distant lymph vessels.

Interpretation of the Changes in P_L and R_L

If our assumptions are correct and P_L and R_L are directly related to the basic factors affecting lymph flow, then it may be possible to interpret the changes in P_L and R_L in terms of changes in tissue pressure, pump pressure, or lymph vessel hydraulic resistance. For instance, when we elevated vascular pressures, R_L decreased. This may be due to an increase in lymph vessel diameter. Staub et al. (1967) has shown that in edema formation, fluid collects first in the perivascular spaces. Most of the lymph vessels are located in these spaces. Other investigators have shown that lymph vessels are attached to surrounding tissue fibers (Casley-Smith, 1980). When the tissue becomes edematous, the fibers are pulled apart, and consequently the lymph vessels are pulled open. We have previously shown that there is a progressive accumulation of perivascular edema fluid at elevated vascular pressures in our preparation (Drake et al., 1980). This perivascular edema could have caused the decrease in R_L because it may have pulled the vessels open.

P_L increased when we increased the vascular pressures. This may be due to an increase in tissue fluid hydrostatic pressure which occurs when capillary pressure is increased (Parker et al., 1978). There may also have been an increase in the pressure generated by the lymph pump mechanism. The decrease in P_L after we decreased vascular pressure may have resulted from a decrease in tissue fluid pressure, or a decrease in pump pressure.

When we decreased vascular pressure in the edematous lungs, R_L decreased. We do not know the reason R_L decreased; however, it may be that at the high vascular pressures, the swollen blood vessels compressed the nearby lymph vessels and increased R_L. Thus, when the vascular pressures were decreased to baseline, the lymph vessels may have expanded, and their resistance would have decreased. Another possible reason for the decrease in R_L may be that the site of edema fluid accumulation may have changed when we reduced vascular pressures. If R_L is affected by the perivascular fluid volume, an increase in this volume could reduce R_L.

In this study we have shown that the lymph flow rate from tracheobronchial lymph vessel depends upon the pressure at the outflow of the vessels. We have also shown that changes in Q_L occur because of changes in both effective lymph vessel resistance and lymph driving pressure. Based upon certain assumptions, P_L and R_L may be related to the basic factors which cause lymph to flow. Thus it may be possible to interpret changes in P_L and R_L in terms of changes in tissue fluid pressure, lymph pump pressure, or lymph vessel resistance.

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