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Lymph and Pulmonary Response to Isobaric Reduction in Plasma Oncotic Pressure in Baboons

CHRISTOPHER K. ZARINS, CHARLES L. RICE, RICHARD M. PETERS, AND RICHARD W. VIRGILIO

SUMMARY Plasma colloid osmotic pressure was reduced by 76% (from 19.6 ± 0.6 to 4.7 ± 1.5 mm Hg) in five baboons while pulmonary capillary hydrostatic pressure was maintained at a normal level. This resulted in fluid retention, weight gain, peripheral edema and ascites, but no pulmonary edema. Thoracic duct lymph flow increased 6-fold and pulmonary lymph flow 7-fold. Thoracic duct lymph had a lower colloid osmotic pressure (2.0 ± 0.7 mm Hg) than plasma (4.7 ± 1.5 mm Hg), whereas the colloid osmotic pressure of pulmonary lymph (4.7 ± 0.7 mm Hg) was the same as that of plasma. The lymph-plasma ratio for albumin fell in thoracic duct lymph but remained unchanged in pulmonary lymph. The difference between plasma colloid osmotic pressure and pulmonary artery wedge pressure decreased from 15.3 ± 1.9 to −0.7 ± 2.9 mm Hg. Despite this increase in filtration force, the lungs were protected from edema formation by a decrease of 11 mm Hg in pulmonary interstitial colloid osmotic pressure and a 7-fold increase in lymph flow.

FLUID movement across capillary membranes is governed by a precise balance between hydrostatic and osmotic forces across the capillary wall and by the permeability characteristics of the capillary membrane. The Starling equation describes this balance and is of central importance in the regulation of tissue fluid volume. Increased capillary hydrostatic pressure, decreased plasma colloid osmotic pressure, increased interstitial fluid osmotic pressure, and decreased lymphatic flow all tend to promote edema formation. The systemic lymphatics can compensate for conditions causing increased interstitial fluid by great increases in flow. A similar increase in lymph flow occurs in the lung when microvascular pressure is elevated and occurs at a lower microvascular pressure when combined with a decreased colloid osmotic pressure. However, reduced colloid osmotic pressure alone rarely causes pulmonary edema despite the fact that marked peripheral edema and ascites may be present. To determine the effects of isobaric reduction in plasma colloid osmotic pressure on edema formation, we studies systemic and pulmonary lymphatic flow in baboons.

Methods

Five healthy male baboons (Papio anubis) weighing 21-28 kg were sedated with phencyclidine hydrochloride (Sernylan, 1 mg/kg). Under local 1% lidocaine anesthesia, catheters were introduced through the femoral vessels and positioned under fluoroscopic control in the descending aorta, right atrium, and pulmonary artery. The pulmonary artery catheter was a 7F flow-directed, balloon-tipped catheter (Edwards Laboratories) which allowed measurement of pulmonary artery wedge pressure. Additional phencyclidine was given (0.5-1 mg/kg), and the baboons were paralyzed with pancuronium bromide (Pavulon, 0.1 mg/kg). Respiration was controlled using a cuffed endotracheal tube and Harvard volume ventilator delivering room air (12 ml/kg tidal volume). Respiratory rate was adjusted so that arterial PCO2 remained between 30 and 40 mm Hg for 30 minutes and was not changed thereafter.

A supraclavicular incision was made under 1% lidocaine anesthesia. The sternocleidomastoid muscles were divided at their sternal and clavicular origins and the medial two-thirds of each clavicle...
excised. The thoracic duct was cannulated at the left jugular-subclavian venous junction with a 16-gauge Teflon catheter. A venous pouch was created at the right jugular-subclavian junction for collection of right-sided lymph (Fig. 1). Nonpulmonary components of right-sided lymph were minimized by dividing the right descending cervical lymphatic chain and ligating the right subclavian lymphatics. Lymph drained by gravity into EDTA tubes placed at the level of the right atrium and the volume was recorded every 15 minutes.

During a baseline period lasting 1 hour, lymph was collected and intravascular pressures and urine output were monitored. Baseline measurements included heart rate, arterial pressure, pulmonary artery pressure, pulmonary artery wedge pressure, central venous pressure, cardiac output, arterial and mixed venous blood gas tensions, dynamic compliance, plasma and lymph colloid osmotic pressure, plasma and lymph total protein and albumin concentrations, and rate of lymph flow.

Plasma oncotic pressure then was lowered by plasmapheresis while pulmonary artery wedge pressure was maintained at the baseline level by intravenous infusion of Ringer's lactate. Twenty percent of the estimated blood volume was allowed to flow into an acid-citrate-dextrose collection bag while pulmonary artery wedge pressure was continually monitored and adjusted if necessary. Shed blood was centrifuged and the packed red blood cells reinfused slowly to avoid alteration in pulmonary artery wedge pressure. Fifteen minutes after red cell reinfusion, all measurements made under baseline conditions were repeated. Samples of right- and left-sided lymph were collected continuously and the volume, colloid osmotic pressure, total protein and albumin concentrations determined for each 30-minute sample.

The plasmapheresis process then was repeated and data again collected 15 minutes after reinfusion. Twenty percent blood volume plasmapheresis was performed five times in the first two baboons. No further reduction in plasma colloid osmotic pressure occurred after the third exchange, and hemodynamic instability developed after the fourth exchange, causing death within 4-6 hours. Therefore, plasmapheresis was performed only three times in the remaining three baboons. The final data point was obtained 1 hour after the third exchange and analyzed together with data for the fourth exchange from the first two baboons.

The plasma that had been removed was then reinfused in an attempt to obtain survival. Plasma reinfusion resulted in cardiovascular stabilization and eliminated the need for continued Ringer's lactate infusion. The pancuronium bromide was reversed with neostigmine, and after the baboons were awake and breathing spontaneously, they were returned to their cages.

At the conclusion of the study, each baboon was weighed. After death an autopsy was performed. The lungs were excised, weighed, and -examined, and then allowed to air-dry. Wet lung-baseline body weight ratio and wet lung-dry lung weight ratio were calculated.

Intravascular pressures were measured with Statham P23 transducers and amplified and recorded on a Hewlett-Packard eight-channel recorder. Cardiac output was determined by indocyanine green dye dilution using a Waters densitometer and a Beckman optical recorder. Arterial and mixed venous blood gas tensions were measured with an Instrumentation Laboratory model 213 blood gas analyzer. Intrapulmonary shunt was calculated using the standard shunt equation. Respiratory mechanics and dynamic compliance were determined using the automated system described by Hilberman. Plasma and lymph albumin and total protein concentrations were measured by the Hycel-Biuret technique. Plasma and lymph colloid osmotic pressure were measured by a transducer membrane system as described by Weil.

Results were expressed as the mean for the five baboons ± the standard error of the mean (SEM).

Figure 1. Lymph cannulation: Right lymph was collected from a right jugular-subclavian venous pouch after ligation of right cervical and subclavian lymphatics. Left lymph was collected by direct cannulation of the thoracic duct.
Differences from the baseline measurement were determined using the paired t-test, and significance was attributed to \( P < 0.05 \).

Results

Hemodynamics

Plasmapheresis removed 1040 ± 55 ml of plasma containing 40.5 ± 1.5 g of protein, of which a total of 24.1 ± 1.1 g was albumin. The baboons received 5700 ± 730 ml of Ringer’s lactate and maintained a urine output of 30–80 ml/hr. There was no change in hematocrit, heart rate, arterial pressure, pulmonary artery pressure, central venous pressure, arterial \( P_{O_2} \), or \( P_{CO_2} \). Cardiac output and pH were unchanged after the first three exchanges, but both decreased after the fourth exchange (Table 1). Plasma colloid osmotic pressure decreased by 76%, from 19.6 ± 0.6 to 4.7 ± 1.5 mm Hg (\( P < 0.001 \)) after plasmapheresis. The resultant gradient between colloid osmotic pressure and pulmonary artery wedge pressure (COP minus PAW) decreased from 15.3 ± 1.9 to -0.7 ± 2.9 mm Hg (\( P < 0.01 \)) (Fig. 2).

Plasma albumin and total protein concentration decreased significantly after each exchange (Table 2). At the final measurement, total plasma protein had decreased by 71% from 5.5 ± 0.3 to 1.6 ± 0.4 g/dl (\( P < 0.001 \)) and albumin had decreased by 72% from 3.2 ± 0.1 to 0.9 ± 0.3 g/dl (\( P < 0.001 \)).

Pulmonary Function

There was no significant change in pulmonary function during the course of the study and no clinical evidence of the development of pulmonary edema. Intrapulmonary shunt (Fig. 2), peak inspiratory pressure, and dynamic compliance remained unchanged throughout the study (Table 1).

Lymph

Right lymph flow before plasmapheresis was 0.14 ml/kg per hr, which is consistent with the volume of right lymph flow found by others. Both right and left lymph flow increased in each baboon after each plasmapheresis. By the end of the experiment, right lymph flow had increased 7-fold (from 0.06 ± 0.03 to 0.43 ± 0.11 ml/min; \( P < 0.001 \)), and left lymph flow had increased 6-fold (from 0.27 ± 0.04 to 1.51 ± 0.29 ml/min; \( P < 0.001 \)) (Fig. 3). This increase was accompanied by a marked decrease in total protein concentration, albumin concentration, and colloid osmotic pressure in both right and left lymph (Table 2). Right lymph albumin was not significantly different from plasma albumin at baseline or during plasmapheresis. Left lymph albumin, however, was significantly lower than plasma at baseline and decreased to barely measurable levels after plasmapheresis (Fig. 4). This is illustrated by the lymph-to-plasma albumin ratio. After plasmapheresis, right lymph-plasma albumin ratio was unchanged (from 0.87 ± 0.06 to 0.83 ± 0.05) but the left lymph-plasma albumin ratio fell markedly from 0.76 ± 0.05 to 0.05 ± 0.03 (\( P < 0.001 \)). Albumin flow was estimated from the product of lymph flow (ml/min) and lymph albumin concentration (mg/ml). Left lymph albumin flow decreased from 6.5 to 0.8 mg/min, whereas right lymph albumin flow increased 2-fold from 1.7 to 3.4 mg/min (Fig. 5).

**TABLE 1** Effect of Plasmapheresis on Hemodynamic and Respiratory Function

<table>
<thead>
<tr>
<th></th>
<th>Before plasmapheresis</th>
<th>After plasmapheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAW (mm Hg)</td>
<td>4 ± 1</td>
<td>6 ± 2</td>
</tr>
<tr>
<td>Cardiac output (liters/min)</td>
<td>3.4 ± 0.8</td>
<td>1.4 ± 0.3*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>117 ± 10</td>
<td>140 ± 16</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>116 ± 3</td>
<td>105 ± 7</td>
</tr>
<tr>
<td>Mean PA (mm Hg)</td>
<td>10 ± 1</td>
<td>10 ± 2</td>
</tr>
<tr>
<td>( P_{O_2} ) (mm Hg)</td>
<td>62 ± 4</td>
<td>70 ± 10</td>
</tr>
<tr>
<td>( P_{CO_2} ) (mm Hg)</td>
<td>34 ± 2</td>
<td>37 ± 3</td>
</tr>
<tr>
<td>pH</td>
<td>7.46 ± 0.03</td>
<td>7.34 ± 0.03*</td>
</tr>
<tr>
<td>COP-PAW gradient (mm Hg)</td>
<td>15.3 ± 1.9</td>
<td>-0.7 ± 2.9*</td>
</tr>
<tr>
<td>Peak inspiratory pressure (cm H2O)</td>
<td>4 ± 0.6</td>
<td>6 ± 1</td>
</tr>
<tr>
<td>Intrapulmonary shunt (%)</td>
<td>19.6 ± 4.2</td>
<td>14.3 ± 2.7</td>
</tr>
<tr>
<td>Dynamic compliance (liters/cm)</td>
<td>0.068 ± 0.002</td>
<td>0.060 ± 0.005</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM. PAW = pulmonary artery wedge pressure, BP = arterial pressure, PA = pulmonary artery pressure, COP = colloid osmotic pressure.

* \( P < 0.05 \) (paired t-test).
Table 2  Effect of Plasmapheresis on Colloid Osmotic Pressure and Plasma Proteins

<table>
<thead>
<tr>
<th></th>
<th>Before plasmapheresis</th>
<th>After 3rd plasmapheresis</th>
<th>Final measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma COP (mm Hg)</td>
<td>19.6 ± 0.6</td>
<td>5.6 ± 1.8*</td>
<td>4.7 ± 1.5*</td>
</tr>
<tr>
<td>(R) Lymph COP (mm Hg)</td>
<td>16.3 ± 2.7</td>
<td>5.9 ± 0.7†</td>
<td>4.7 ± 0.7†</td>
</tr>
<tr>
<td>(L) Lymph COP (mm Hg)</td>
<td>12.1 ± 1.0</td>
<td>2.5 ± 0.9†</td>
<td>2.0 ± 0.7*</td>
</tr>
<tr>
<td>Plasma albumin (g/dl)</td>
<td>3.2 ± 0.1</td>
<td>1.1 ± 0.2†</td>
<td>0.9 ± 0.3*</td>
</tr>
<tr>
<td>(R) Lymph albumin (g/dl)</td>
<td>2.8 ± 0.2</td>
<td>1.0 ± 0.2†</td>
<td>0.8 ± 0.2*</td>
</tr>
<tr>
<td>(L) Lymph albumin (g/dl)</td>
<td>2.4 ± 0.1</td>
<td>0.1 ± 0.1*</td>
<td>0.05 ± 0.03*</td>
</tr>
<tr>
<td>Plasma total protein (g/dl)</td>
<td>5.5 ± 0.3</td>
<td>2.1 ± 0.4†</td>
<td>1.6 ± 0.4*</td>
</tr>
<tr>
<td>(R) Lymph total protein (g/dl)</td>
<td>3.9 ± 0.3</td>
<td>1.5 ± 0.2†</td>
<td>1.2 ± 0.2*</td>
</tr>
<tr>
<td>(L) Lymph total protein (g/dl)</td>
<td>4.1 ± 0.4</td>
<td>0.5 ± 0.1*</td>
<td>0.4 ± 0.1*</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM. COP = colloid osmotic pressure. Significance compared to baseline value (paired t-test):
* P < 0.001.
† P < 0.01.

Postmortem
All baboons died within 17 hours of completion of the experiments despite reinfusion of shed plasma at the end of the experiment in three. Postmortem examination revealed marked peripheral edema, massive ascites, and small pleural effusions in all baboons. Body weight increased by 16% (3.5 ± 0.8 kg). Small areas of atelectasis were present in three baboons, but none had gross or microscopic evidence of pulmonary edema, and tracheal aspiration did not recover any fluid. Wet lung weight was 274 ± 29 g. The wet lung-body weight ratio was 0.010 ± 0.001. Dry lung weight was 53 ± 5 g, and the wet lung-dry lung weight ratio was 5.13 ± 0.25. The three baboons in which plasma was reinfused had heavier lungs and higher wet lung-dry lung ratios (5.5) than the two that did not (4.6).

Discussion
The thoracic duct drains essentially all lymph from the lower part of the body plus that from the left arm, left thoracic region, and the left side of the head.16 The majority of pulmonary lymph drains to the right lymphatic duct,16 with some pulmonary lymph draining to the thoracic duct.12 This was confirmed in two additional baboons in which Evans blue dye was instilled into the trachea. Dye was noted to drain predominantly to the right lymphatics. In one baboon, the cannulas to collect lymph were inserted as described, and the right lymph was...
found to be stained dark blue, whereas there was only a faint blue tinge in the left duct. Right lymph contains, in addition to pulmonary lymph, lymph from the right arm, right side of the head and neck, and right chest wall. Division of the right cervical lymphatic chain and interruption of the right arm lymphatics eliminated these sources of contamination of pulmonary lymph. The right lymph collected in this experiment probably contained some cardiac lymph and thus cannot be considered pure pulmonary lymph. However, it was found to be strikingly different from thoracic duct lymph and thus seems to represent principally pulmonary lymph.

The absence of pulmonary edema in the presence of massive peripheral edema and ascites was documented by pulmonary function and autopsy examination. Pulmonary insufficiency did not develop during the study, with no change in intrapulmonary shunt or dynamic compliance. Intrapulmonary shunt rises with acute pulmonary edema and compliance falls with pulmonary engorgement and edema.

At autopsy, the fraction of lung water (0.81) was normal. Wet lung-body weight ratio was 0.010, which is below the upper limit of normal (0.012). Wet lung-dry lung weight ratio was 5.13, which is similar to the normal human ratio of 5.2 and different from the ratio of 7.6 found in acute pulmonary edema. It was less than the normal value of 5.4 in dogs reported by Guyton.

The lung weight-to-body weight ratio does not take into account residual blood volume. Since hematocrit did not change, the 3.5-liter net increase in total body water must be presumed to have been distributed through the extra vascular fluid compartment, making an increase in pulmonary blood volume unlikely. However, the lung weight-to-body weight ratio is an insensitive test of interstitial edema, and it is possible that some interstitial edema did occur in our baboons. Snashall measured extravascular lung water after acute volume expansion in dogs and found interstitial edema, in spite of wet-to-dry lung weight ratios of less than 6.

According to the Starling equation, a number of factors can act to oppose edema formation in tissues when plasma oncotic pressure is low and capillary hydrostatic pressure is constant. These include decreased interstitial colloid osmotic pressure, increased interstitial tissue hydrostatic pressure, and increased lymph flow. In these experiments, the volume of lymph flow increased and lymph colloid osmotic pressure decreased on both the right and left sides. The absolute increase in flow was greater in left lymph than right, but the fractional increase was similar on the two sides. Colloid osmotic pressure decreased more in left lymph than right lymph, suggesting a lower systemic than pulmonary interstitial colloid osmotic pressure.

Numerous investigators have produced pulmonary edema by elevation of pulmonary capillary hydrostatic pressure. Reduced plasma protein or colloid osmotic pressure results in pulmonary edema at a lower hydrostatic pressure than when colloid osmotic pressure is normal. Guyton demonstrated a direct relation between the development of pulmonary edema and the difference between plasma colloid osmotic pressure and pulmonary hydrostatic pressure, but Levine found that water accumulation in the lung was significantly affected by changes in pericapillary forces in the pulmonary interstitium. Our study is unique in that an increase in filtration force was produced by reduction of plasma oncotic pressure alone, with no change in hydrostatic pressure.

Staub found a linear increase in pulmonary lymph flow with increased hydrostatic pressure along with a linear decrease in the lymph colloid osmotic pressure. The lymph-plasma albumin ratio decreased as a protection against edema formation. We too found an increase in right lymph flow and a decrease in right lymph colloid osmotic pressure. However, the lymph-plasma albumin ratio did not fall but remained constant. Protein and albumin flow increased despite the decrease in lymph protein concentration because of the increase in lymph flow. Brigham reported findings similar to ours when capillary permeability was altered by Pseudomonas bacteremia.

The increase in lymph albumin flow suggests an increase in pulmonary capillary protein permeability. An alternative explanation is that albumin present in the pulmonary interstitium at the start of
plasmapheresis was removed by pulmonary lymph at a rate necessary to prevent the development of an adverse plasma-to-interstitial colloid osmotic pressure gradient. Thus we may not have reached a steady state, and the removal of pulmonary interstitial protein by the lymph may have continued after the completion of the study. If the experiments had continued for a longer time, further removal of protein by pulmonary lymph might have resulted in a decrease in lymph-plasma albumin ratio.

The absence of pulmonary edema implies that any increase in fluid filtered into the interstitial space was removed by the lymph. The demonstrated decrease in interstitial colloid osmotic pressure would tend to oppose the increase in filtration further.

Thus an increase in fluid filtration would result in a steady state, and the removal of pulmonary interstitial space was  removed by the lymph. The demonstrated decrease in interstitial colloid osmotic pressure would tend to oppose the increase in filtration forces as described by the Starling equation. In addition, there may have been an increase in pulmonary interstitial pressure to limit edema formation further.

In a theoretical analysis of the lung, Fung has concluded that the lung's interstitium remains small even in the supercritical pressure range. In most tissues, the interstitial space is capable of great expansion and offers little resistance to fluid entry. The pulmonary interstitial space, however, is bound by tight junctions of epithelium, the geometry of the alveolar network, and a collagen frame work. Thus an increase in fluid filtration would result in a rapid rise in interstitial pressure resisting further filtration.

Findings similar to our observations in baboons have been reported for humans. In patients undergoing acute hemodynamic resuscitation with colloid-containing or colloid-free solutions, we found that a low plasma colloid osmotic pressure was associated with peripheral edema, but found no evidence of pulmonary edema despite great reduction in the gradient between colloid osmotic pressure and pulmonary hydrostatic pressure. The observation by others of pulmonary edema in patients with low colloid osmotic pressure during volume infusion and after myocardial infarction may be related to an increase in hydrostatic pressure or a change in capillary permeability rather than to a reduction in plasma colloid osmotic pressure.

In the face of decreased plasma oncotic pressure, when there is no increase in hydrostatic pressure, the lung appears to be able to resist edema formation by increasing lymph flow and decreasing interstitial colloid osmotic pressure.

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References

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