The Effects of Hypoproteinemia on Blood-to-Lymph Fluid Transport in Sheep Lung

GEORGE C. KRAMER, BRUCE A. HARMS, ROBERT A. GUNThER, EUGENE M. RENKIN, AND ROBERT H. DEMLING

SUMMARY We studied the effects of reducing the plasma protein concentration on flow and composition of pulmonary lymph in 12 unanesthetized sheep. Whole blood was removed while red cells were returned and lactated Ringers was infused at a rate sufficient to maintain pulmonary vascular pressures at baseline values. A 44-54% reduction in plasma protein concentration resulted in a decrease in the plasma oncotic pressure from 18.6 ± 1.1 to 7.8 ± 0.9 mm Hg. Within an hour after plasmapheresis, lymph flows increased to a maximum of 4 times baseline. Subsequently, lymph flow gradually decreased and were close to baseline at 24 hours. The plasma-to-lymph oncotic gradient was reestablished in 5 hours due to decreased lymph protein. Maintained elevation of lymph flow with hydrostatic and oncotic gradients at baseline values suggest that the blood-to-lymph barrier offers less resistance to fluid transport. The calculated filtration coefficient increased 2- to 3-fold after plasmapheresis. Protein clearances remained normally coupled to lymph flows. Thus the enhanced fluid transport cannot be attributed to a permeability change in the large pore pathways. Hypoproteinemia may alter the interstitial gel so that there is less resistance to fluid movement. Such changes in fluid conductivity between blood capillaries and lymphatics may augment the lymphatic safety factor against pulmonary edema.

MOVEMENT of fluid between vascular and interstitial compartments in the lung are the result of the imbalance of hydrostatic and oncotic forces acting across the microvascular wall. Normally, these forces result in a net fluid filtration equal to lymphatic drainage. Fluid filtration can be increased by raising the microvascular hydrostatic pressure or by lowering the plasma oncotic pressures. If the increase in filtration is greater than the lymphatics' ability to remove fluid, then pulmonary water content increases.

The pulmonary effects of raising microvascular pressure has been extensively studied. Fluid filtration and lymph flow are increased by raising left atrial pressure (Erdmann et al., 1975). However, increases in pulmonary water content were not found until vascular pressures were raised more than 20 mm Hg, Erdmann et al., 1975; Gaar et al., 1966; and Guyton and Lindsay, 1959. In these studies, pulmonary safety factors, which oppose fluid accumulation were attributed to (1) increased lymph flow; (2) a lower interstitial oncotic pressure; and (3) increased interstitial fluid hydrostatic pressure.

The effects of reductions in plasma oncotic pressure on fluid flow are not as well understood. There remains a significant controversy over the importance of this Starling force on the pathogenesis of pulmonary edema. Decreased plasma oncotic pressure has been found to be associated with the formation of pulmonary edema by a number of investigators (Morissette et al., 1975; Rackow et al., 1977). However, other investigators have found a poor correlation between lowered plasma oncotic pressure and indicators of increased pulmonary water content (Lowe et al., 1978; Demling et al., 1980). Guyton and Lindsay (1959) found that pulmonary water content was not increased by a 50% dilution of plasma unless vascular pressure was increased. In anesthetized baboons, reductions of plasma oncotic pressure of 76% resulted in a 7-fold increase in pulmonary lymph flow and no measured increase in pulmonary water content; yet all animals died within 17 hours (Zairns et al., 1978). Unfortunately, none of the above studies determined the effects of solely reducing plasma oncotic pressure. The results were complicated by changes in vascular pressure or the occurrence of circulatory shock.

The present study was undertaken to investigate the effects of a reduction in plasma oncotic pressure alone on pulmonary transvascular fluid flux. In contrast to a gradual reduction of plasma protein, we have studied acute reduction via plasmapheresis. We were interested in both the early response to acute hypoproteinemia as well as any compensatory or sustained effects. We wanted to measure these effects in the absence of any variation in vascular pressure or blood flow. Toward this end, we used Staub's chronic lymph fistula preparation in unanesthetized sheep (Staub et al., 1975). We

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used lymph flow as a sensitive indicator of transvascular fluid flux. We replaced whole blood with packed cells and infused lactated Ringers at a sufficient rate to maintain all measured cardiovascular variables except oncotic pressure.

By lowering the plasma oncotic pressure in the absence of a shock state, we hoped to address the following questions:

1. What is the effect of reductions in plasma oncotic pressure on pulmonary transvascular fluid flux?
2. How do the increased filtration rates due to a given lowering of plasma oncotic pressure compare with those produced by an equivalent increase in hydrostatic pressure?
3. What are the compensatory mechanisms which oppose fluid accumulation following acute hypoproteinemia?

Methods

Animal Preparation

Twelve adult sheep (45-65 kg) were prepared with chronic lung lymph fistulas according to the method of Staub et al. (1975). Briefly, the efferent lymphatic of the caudal mediastinal lymph node, draining lung lymph, was cannulated through a right thoracotomy with a Silastic catheter (no. 602-015, Dow Corning). A second thoracotomy was performed through which the distal end of the lymph node was transected near the diaphragm to eliminate systemic lymph components. The cannula was externalized on the chest wall. Polyvinyl catheters were placed in the aorta and superior vena cava through a neck incision. A Swan-Ganz thermomodulation catheter (Edwards model 93A 1317F) was advanced into the pulmonary artery via the jugular vein. Experiments were conducted after steady state lymph flows and lymph protein concentrations were reached, generally 5 days postsurgery. Studies were performed with the sheep in a metabolic cage with free access to food and water.

Measured Variables

Aortic, central venous (right atrial), pulmonary artery, and pulmonary wedge pressures were measured with calibrated pressure transducers (Statham P23) and monitored on a strip chart recorder (Gilson model ICT-5H). All transducers were leveled with the tuberosity of the humerus which was taken as the level of the left atrium. Cardiac output was measured by the thermal dilution technique using a cardiac output computer (Edwards model 9520). Lymph was collected each half hour in heparinized tubes and the volume measured to determine lymph flow. Venous blood samples were drawn from the superior vena cava during each lymph collection for plasma samples and to monitor hematocrit. All plasma and lymph samples were analyzed for total protein (biuret) and oncotic pressure (Weil Oncometer, Instrument Laboratories).

Plasmapheresis

Plasmapheresis was performed by replacing whole blood with red cells and lactated Ringers. Animals were bled from the arterial line into standard 500-ml blood packs containing 63 ml of anticoagulant citrate phosphate dextrose solution (Fenwal). Bags were spun in a refrigerated centrifuge (Damon CRU 500) at 2000 rpm for 10 minutes. Plasma was removed and packed red cells were promptly returned. Lactated Ringers was infused continuously via the venous cannula at a rate sufficient to maintain central venous pressure. Generally, 1 liter of lactated Ringers was given for each unit of blood removed. Samples were collected and systemic variables were continuously monitored during a baseline period (2-4 hours) before plasmapheresis, until at least 10 hours after plasmapheresis, and intermittently over the next 14 hours.

Calculations

To evaluate the overall fluid conductivity between plasma and the cannulated lymphatic, we have calculated a plasma-lymph filtration coefficient $k_l$. We determined $k_l$ as follows;

$$K_l = \frac{L}{Pw + \frac{1}{3}(Pa - Pw) - (\pi_p - \pi_l)}$$

where $Pw$ = pulmonary wedge pressure (mm Hg), $Pa$ = pulmonary artery pressure, $\pi_p$ = plasma oncotic pressure, $\pi_l$ = lymph oncotic pressure, $L$ = lymph flow (ml/hr).

Calculation of a filtration coefficient based on lymph flow requires the following assumptions. First, the water content of the lungs is not increasing; therefore, filtered fluid per time equals lymph flow. Second, the forces that move fluid from the blood to the lymphatic are the hydrostatic pressures in the exchange vessels and the oncotic pressure difference between the plasma and lymph. This assumes that interstitial pressure is zero and the microvascular reflection coefficient for protein is equal to one. The consequences of these two assumptions will be addressed in the Discussion.

We have used $\pi_l$ as representative of pulmonary interstitial oncotic pressure. The interstitium includes both a free fluid phase and a gel phase containing collagen and glycosaminoglycans. Within the interstitium, free fluid and gel must be in osmotic balance, else water would move until they were. Since lymph is a sample of free interstitial fluid, it is reasonable to assume that it has the same oncotic pressure as the interstitium as a whole. We have further assumed that lymph is not altered during transport through lymphatics or lymph nodes of the lung.

Decreased plasma oncotic pressure would not be expected to affect blood flow zones in the lung which are determined solely by vascular and extravascular hydrostatic pressures. A change in $\pi_p$ would have no direct effect on hydrostatic pressures and would affect fluid filtration in the three zones
as zone 1 with collapsed capillaries and no filtration before or after change in \( \pi_p \), while in zone 2 and 3 there would be increased filtration directly proportional to change in \( \pi_p \).

The hydrostatic pressures of the pulmonary capillaries are the result of 39% of total resistance acting distal to the capillary midpoint (Bhattarcharya and Staub, 1980). We calculated the microvascular hydrostatic pressure as pulmonary wedge pressure plus one-third of the difference between pulmonary artery and pulmonary wedge pressure. This assumes the pulmonary wedge pressure is only slightly greater than left atrial pressure (Malik and Kidd, 1976). We used \( K_l \) only to determine apparent changes in the relative fluid conductivity of each sheep.

Statistics

Average values are expressed as mean ± standard error. Differences were considered significant when \( P < 0.05 \). To test for an overall difference with time in averaged variables, we used analysis of variance (Wallerstein et al., 1980). If the overall difference was significant, the paired Student's t-test was used to determine differences between baseline and specific times post plasmapheresis. Least-squares regression lines were fitted to paired data and correlation coefficients were determined (Snedecor and Cochran, 1967).

Results

Table 1 lists individual experiments with the percentage decrease in plasma protein concentration, and the baseline and maximum lymph flow rate. Four to 6 units of blood were replaced during plasmapheresis, except in animal 301 in which only 1-2 units were removed due to centrifuge failure. Plasma protein concentration was reduced from 15% to 54% and was a function of the amount of blood replaced and the weight of the animal. Plasmapheresis required from 2 to 3 hours. We chose a level of plasmapheresis, 4 to 6 units replaced, which resulted in significant reductions in oncotic pressure without any other measured or observable effects on cardiovascular variables. The increases in lymph flow for the 12 sheep correlated \( r = 0.74 \) with reductions in oncotic pressure.

Figure 1 shows a representative experiment in which the concentration of plasma protein was reduced about 50%. In this experiment, as in all, lymph flow rapidly increased during plasmapheresis and reached its maximum level within 1-3 hours after the first fluid exchange. Subsequently, lymph flow gradually decreased and returned close to baseline within 24 hours. The rapid reduction in plasma protein resulted in a transient and probably artificial increase in lymph to plasma protein concentration (L/P) ratio, because no allowance was made for the time lag between lymph formation and collection. The L/P ratio then fell below baseline, reaching minimum values within 1-3 hours after plasmapheresis. Subsequently, the plasma protein concentration slowly rose toward baseline. At 24 hours, plasma protein concentration was halfway back to normal and the L/P ratio was 0.64, slightly less than the average baseline value of 0.68.

Table 2 lists the time course of the averaged data of experiments with five sheep, each with 6 units of blood removed. We averaged the response in these five animals as plasma protein was similarly reduced over a range of 44-54%. Baseline lymph flow was 4.6 ± 0.8 ml/hr and had increased to 15.7 ± 1.2 ml/hr at the end of plasmapheresis. The responses in the other sheep with less plasma dilution were qualitatively similar, but quantitatively reduced. Lymph flow remained significantly increased at 10 hours, but returned close to baseline by 24 hours. The oncotic pressure of both plasma and lymph was significantly reduced at all times following plasmapheresis due to decreased protein concentrations. However, the plasma-to-lymph oncotic gra-

### Table 1 Summary of Experiments

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<td>Plasma protein (mg/ml)</td>
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### Figure 1

Time course of the effects of reductions in plasma protein (P) on pulmonary lymph flow (L) and the lymph-to-plasma protein ratio (L/P). Six units of blood were removed over 24 hours and simultaneously replaced with cells and enough lactated Ringers to maintain central venous pressure.
gradient was reestablished by 2½ hours post plasmapheresis. The reductions in oncotic pressure are proportionally greater than the reductions in plasma or lymph protein due to the nonlinear relationship between the two variables (Landis and Pappenheimer, 1963).

Aortic and central venous pressures did not deviate significantly from their baseline values, 97.7 ± 4.6 and 3.1 ± 0.7 mm Hg, respectively. Cardiac output was measured in five sheep and had a baseline average of 98.0 ± 7.5 ml/min per kg. During plasmapheresis average cardiac output was decreased to 85.8 ± 12.5 ml/min per kg, but the difference was not statistically significant. After completion of plasmapheresis cardiac output varied little and averaged very close to baseline. At no time were any of the mean pulmonary pressures significantly different from their baseline values (Table 2).

Clearly, an acute removal of protein did not result in a constant lowered plasma protein concentration (Table 2). After plasmapheresis, as plasma protein concentration slowly increased, lymph flow and the L/P ratio also returned towards baseline levels. The time course of return was much slower than the rate of response to the initial protein concentration fall (Fig. 1). Thus, all measured variables were changing slowly enough so that it seemed reasonable to refer lymph flow at anytime to the direct balance of Starling forces measured at that time. As individual oncotic pressures were changing at a rate substantially less than 1 mm Hg/hr, any errors caused because of lag time between lymph formation and lymph collection would be small.

Figure 2 is a plot of baseline and maximum lymph flows for individual experiments plotted against the corresponding change in plasma oncotic pressure. For comparison with equivalent hydrostatic pressure increases, we have also plotted a regression analysis of the data of Erdmann et al., 1975. For their data, the abscissa represents the change in microvascular pressure which was increased with inflation of a left atrial balloon. In Erdmann's study, an increase in microvascular pressure of 20 mm Hg typically increased lymph flow about 3-fold; this is less than the average response obtained by reducing plasma oncotic pressure 10 mm Hg. Regression analysis shows that lymph flow was increased 21.3 µl/min for each mm Hg decrease in plasma oncotic pressure. This compares to a lymph flow increase of 9.2 µl/min for each mm Hg in microvascular hydrostatic pressure.

Figure 3 shows the average plasma to lymph oncotic gradient and lymph flow response in the five animals with plasma protein reductions of 44-54%. Also plotted in this figure is the change in the apparent lymph filtration coefficients. Lymph flows...
Flow. Furthermore, we wanted to measure these in plasma oncotic pressure on pulmonary lymph was to determine the effects of an acute reduction mann et al., 1975). The goal of the present study are a more sensitive measure of transvascular fluid increases in pulmonary water content are probably the result of a reduced oncotic gradient. However, lymph flows remain significantly elevated even after the oncotic gradient has returned to baseline. Increased lymph flow, when the hydrostatic and oncotic gradients appear to have returned to baseline, suggests that the fluid conductivity has increased. The baseline lymph filtration coefficients exhibited a large variance between animals, but calculated $K_L$ was always increased following plasmapheresis and remained greater through 10 hours. The time of maximum $K_L$ did not coincide with the time of greatest lymph flow.

**Discussion**

Reductions in the concentrations of plasma protein are reported to result in no change in pulmonary water content for either the isolated lung or intact animal (Gaaz et al., 1966; Guyton and Lindsay, 1959; Zairns et al., 1978). However, measurable increases in pulmonary water content are probably a late development in the pathogenesis of pulmonary edema (Staub, 1974). Changes in lymph flow are a more sensitive measure of transvascular fluid flow than standard water content methods (Erdmann et al., 1975). The goal of the present study was to determine the effects of an acute reduction in plasma oncotic pressure on pulmonary lymph flow. Furthermore, we wanted to measure these effects without changing hydrostatic pressures or blood flow. We found that if we varied infusion rate to maintain central venous pressure, then the pulmonary hydrostatic pressures and cardiac output remained at baseline levels.

Fluid filtration can be increased by reducing the plasma oncotic pressure, as we did, or by raising microvascular hydrostatic pressure. A study of increased hydrostatic pressure on pulmonary lymph flow, which is directly comparable to ours, is that of Erdmann et al. (1975). We compare our data to theirs in Figure 2. The regression line for Erdmann's data ($r = 0.60$) is for change in lymph flow vs. increase in microvascular pressure. It is drawn with its endpoints being representative of the typical baseline and maximum lymph flows that they reported. It is apparent that the reductions in the plasma oncotic pressure increased lymph flow more than a comparable increase in hydrostatic pressure. This is a consequence of two factors. First, as was pointed out by Erdmann et al., the increases in microvascular hydrostatic pressure are opposed by increases in the oncotic gradient due to washout of interstitial protein, whereas reductions in plasma oncotic pressure are not opposed by reductions in the microvascular pressure. In fact, both hydrostatic and oncotic increases in fluid filtration were opposed by reductions in the oncotic pressure of lymph and presumably interstitial fluid. This change constitutes an important defense against fluid accumulation. However, even after correction is made for this oncotic feedback, the lymph flow response appears greater for plasmapheresis than for elevations in vascular pressure. The second factor is an apparent increase in plasma-lymph fluid conductivity. In Figure 3 relative change in $K_L$ is compared with lymph flow. At all times post-plasmapheresis, $K_L$ is significantly greater than baseline. Using similar calculations, Erdmann et al. (1975) found no change in $K_L$ following increases in hydrostatic pressure.

Our calculation of $K_L$ requires two assumptions: (1) the hydrostatic interstitial pressure is constant and equal to zero, and (2) the microvascular reflection coefficient to protein is equal to one. Interstitial pressure may be negative and increase with enhanced transvascular flux (Guyton et al., 1975), and the reflection coefficient is probably less than one (Staub, 1974). An increase in $P_i$ would oppose fluid filtration and $K_L$ would increase more than we calculated. If the reflection coefficient is less than one, only part of the reduction in plasma oncotic pressure would contribute to an increase in net filtration force; again, $K_L$ would increase more than we calculated. Thus our calculated increase in $K_L$ is a conservative estimate of the actual increase in plasma-lymph fluid conductivity.

Apparent increases in $K_L$ could be the result of increased microvascular surface area, decreased fluid viscosity, or increases in fluid conductivity...
between the capillary wall and the cannulated lymphatic. Pulmonary vascular pressures and cardiac output remained at baseline values throughout the experiments. This suggests that the surface area of the exchange vessels has not changed. Reduced viscosity of filtered fluid would produce a proportional increase in calculated $K_L$. Plasma protein concentrations directly affect fluid viscosity. However, reductions of protein concentration of 50% reduce viscosity only about 20% (Bayliss, 1952). Only a small part of the observed increase in $K_L$ can be attributed to viscosity change.

Another possible explanation of increased fluid conductivity is an increase in the "large pore" pathways of the capillary wall. To examine this permeability factor, we have plotted plasma clearance ($L \times L/P$) against lymph flow in Figure 4. As lymph flow increases over baseline, the protein clearance likewise increases, but the coupling of fluid and protein transport remains low as the $L/P$ ratio falls. This is the typical pattern seen when fluid filtration increases with no increase in permeability (Taylor et al., 1978). Studies of the effects of increased hydrostatic pressure in unanesthetized sheep show that, as pulmonary lymph flow increases, the lymph protein concentration falls (Brigham and Owen, 1975; Erdmann et al., 1975). On Figure 4, the shaded area represents the 95% confidence limits for the increased pressure studies of Brigham and Owen (1975). Lymph flow and plasma clearance are similarly coupled in their study and ours. Comparison of Figure 4 with a plot constructed of the increased pressure data of Erdmann et al. (1975), not shown, also indicates a similar coupling of fluid and protein transport. These comparisons suggest that the increases in fluid conductivity are not the result of a permeability increase of the "large pore" pathways; neither can they be the result of increases only in the "small pore" transendothelial pathways. If capillary permeability is increased, both pathways must be equally increased so as to retain normal coupling of water and protein transport.

Finally, blood-to-lymph fluid conductivity may be altered downstream of the site where protein sieving occurs. Hypoproteinemia may alter either the interstitial gel or the walls of the terminal lymphatics. The capillary wall may be the primary determinant of protein selectivity, but series resistances between the capillary wall and the terminal lymphatic may determine fluid fluxes. Granger et al. (1975) measured convective water flows across a model interstitium of human umbilical connective tissue. From their study, it appears that initial small increases in gel hydration may increase hydraulic conductivity several-fold. The increased conductivity does not appear to be offset by increased dimensions of the gel phase.

We would like to know what factors might have affected plasma-lymph fluid conductivity. We performed a series of regression analyses of the changes in $K_L$ with other variables. The ratio of lymph filtration coefficients before and after plasmapheresis ($K_L/K_L'$) compared with the changes in lymph protein, plasma protein, lymph flow, and the $L/P$ ratio (Fig. 5). There were significant correlations with lymph protein ($r = 0.74$) and plasma protein ($r = 0.62$); the correlations with increased lymph flow ($r = 0.35$) and $L/P$ ratio ($r = 0.47$) were not significant. The values of $K_L/K_L'$ most closely correlated with the decrease in lymph protein. The low protein concentration in the interstitial fluid may have resulted in an oncotic expansion of the interstitial gel matrix. In the studies of Erdmann et al. (1975), lymph protein concentrations decreased following elevations in microvascular pressure, whereas on the average, the apparent filtration coefficients showed no change. However, reductions in the concentration of lymph protein were greater in our study than in Erdmann's. The regression analysis of Figure 5 suggests that protein concentrations of lymph must be reduced more than 20 mg/ml before there are substantial increases in $K_L$. In Erdmann's study, only rarely was lymph protein decreased by more than 20 mg/ml, and in the cases where it was, the filtration coefficient always increased.

While it can be hypothesized that alterations in the interstitial gel are responsible for the apparent increases in blood-to-lymph fluid conductivity, it remains to be shown if the observed changes occur at the capillary wall, interstitial gel, or terminal lymphatic. The decreases in $K_L$ remain a puzzle. However, the phenomenon is not a special characteristic of the pulmonary circulation. We observed a similar effect in a systemic vascular bed when we compared the effects of venous congestion and plasmapheresis on lymph flow from the hindpaw of the anesthetized dog. Renkin et al., 1981. Hargens and Zweifach (1976) reported that the calculated $K_L$ for cat mesentery increased about 3-fold following a
plasma dilution by saline replacement of 35% of blood volume.

The lungs are able to withstand moderate increases in microvascular pressure without a measurable increase in water content or alteration of pulmonary function. We found the lungs to be protected acutely by the same safety factors following plasmapheresis as with increased vascular pressure. These are an increase in lymph flow and a decrease in interstitial oncotic pressure. An increase in interstitial fluid pressure (Pi) also has been suggested as a safety factor, (Guyton et al., 1975). Whether Pi increases or not, another previously unrecognized contribution to overall protection against edema may be an increase in interstitial hydraulic conductivity which would facilitate lymphatic drainage.

Following plasmapheresis, the plasma-lymph oncotic gradient rapidly returned to baseline and was fully reestablished in 2½ hours. However, lymph flow remained significantly elevated for up to 24 hours following plasmapheresis. Thus, it cannot be assumed that return of a normal oncotic gradient negates the effects of a reduced plasma oncotic pressure on fluid flux. After plasmapheresis, plasma protein concentration returned toward normal due to an apparent redistribution of protein from the systemic extravascular compartment to the plasma (Yuile et al., 1959). The role that return of protein to the circulation and restoration of plasma protein concentration plays in reestablishing pulmonary fluid flux was not determined in our study. However, it may be important if either plasma or interstitial protein concentration can modulate Kt.

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