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Pulmonary Transvascular Fluid Dynamics in Sheep During Hemorrhage

Asrar B. Malik, Hoyte van der Zee, Bing C. Lee

Departments of Physiology and Anesthesiology Albany Medical College Albany, New York 12208

Summary

The effects of hemorrhage on pulmonary hemodynamics and lung transvascular fluid dynamics were studied in sheep. We found that 2 hr of hemorrhage caused a fall in lung lymph flow ($p < 0.05$) and no significant change in lymph protein concentration. The fall in lymph flow was not due to decreased vascular surface area since the regional distribution of pulmonary perfusion was not altered during hemorrhage; however, the decrease in lymph flow was associated with decrease ($p < 0.05$) in the calculated pulmonary microvascular pressure. The extravascular lung water lung content per g bloodless dry lung was increased ($p < 0.05$) in the hemorrhaged sheep from the control values. Pulmonary edema was not due to increased lung vascular endothelial permeability since the net transvascular protein flux was not increased. The finding that pulmonary edema occurred despite the consistent decreases in lymph flow suggests that edema may be due to hemorrhage-induced lymphatic "failure" or that edema fluid is sequestered in spaces (e.g., endothelial cells) where it cannot be drained by the lymphatics.

Wheter or not pulmonary edema develops following hemorrhage-induced systemic hypotension and pulmonary hypoperfusion is a controversial question. Studies have indicated both the presence and absence of pulmonary edema following hemorrhage (1, 2, 3, 4, 5). Recently, *Barrios* et al. (6) demonstrated alterations after hemorrhagic shock in the alveolar interepithelial junctions, and to a lesser extent in the pulmonary microvascular interendothelial junctions in dogs suggesting that pulmonary edema may result as a consequence of increased alveolar and lung vascular permeability (7, 8, 9).

The purpose of the present study was to assess the effects of hemorrhage-induced hypotension and hypoperfusion on pulmonary hemodynamics and transvascular fluid dynamics. We studied the sheep because it was possible to sample lung lymph (10).

Methods

Studies were made in 7 Suffolk sheep (mean weight 32 ± 2 kg) anesthetized with 20 mg/kg sodium pentobarbital. All sheep were fasted for 24 hr prior to the study. The endotracheal tube was connected to a Harvard respirator which was adjusted to provide blood gases and pH in the normal range at the start of the experiment. Tidal volume and rate of respirator were determined prior to the experiment using the Collin's spirometer. The lung were inflated with 5 cm H_2O end-expiratory pressure in order to prevent atelectasis during the experiment.

The technique used to sample pulmonary lymph has been described in detail by *Staub* et al. (10). Through a right thoracotomy, the caudal mediastinal node was identified and a portion posterior of the free margin of the pulmonary ligament was resected in order to eliminate systemic lymph input into the node (10).

All identifiable diaphragmatic and chest wall lymph afferent vessels were tied (10). The efferent duct of the node was identified and tied distal to the point of catheterization. The duct was exposed from surrounding tissue, catheterized with a heparin-coated Bardic catheter (C.R. Bard, Inc.), and secured in

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position in the chest. Blood-free pulmonary lymph was obtained successfully in 7 sheep.

The purity of pulmonary lymph samples was assessed by raising either left atrial or systemic venous pressures and determining changes in lymph flow, and lymph/plasma protein concentration ratio. Foley balloon catheters (16-F) were inserted into the right and left atria to raise left atrial and systemic venous pressures. Increase in systemic venous pressure did not alter the resting lymph flow, and lymph/plasma protein concentration ratio, while left atrial hypertension resulted in increased flow, and decreased the lymph protein concentration and lymph/plasma protein concentration ratio. The effects of 5 hr period of anesthesia were studied in one sheep. The initial lymph flow of 11.1 ml/hr and lymph/plasma protein concentration ratio of 0.73 were not markedly different from the final values of 11.4 ml/hr and 0.77.

Catheters (7-F) were positioned in the main pulmonary artery, pulmonary arterial wedge, aortic arch and jugular vein. Pulmonary arterial, pulmonary arterial wedge and aortic pressures were recorded using Statham P23Db pressure transducers referred to the level of left atrial appendage. The reference level was verified at autopsy. Pulmonary perfusion pressure was calculated as the difference between pulmonary arterial and pulmonary arterial wedge pressures. Pulmonary blood flow was determined in triplicate using the indicator-dilution technique. Cardiogreen dye was injected into the right atrium and dilution curves were recorded from the aorta using the Gilford Instruments 1031R cuvette-densitometer and Harvard infusion-withdrawal pump. A Godard NV infra-red capnograph recorded the end-tidal CO_2 concentration from a port on the airway. The pressures, dye curves, and CO_2 concentrations were recorded on Electronics for Medicine PR-7 recorder and Grass 7B polygraph.

The PO_2, P_{CO_2} and pH of arterial blood samples were determined using the Radiometer BMS-3 blood gas and pH analyzer, and corrected to body temperature determined with a rectal thermometer. Blood gas and pH samples were analyzed within 5 minutes after withdrawal. The measured PO_2 was converted to oxygen saturation using sheep P_{50} of 33.8 mm Hg with the Severinghaus blood gas calculator (BCG 1, Radiometer).

Regional pulmonary perfusion was determined using labelled microspheres as described by *Reed* and *Wood* (11). Microspheres 15 ± 5 μm in diameter and labelled with ^{85}Sr or ^{51}Cr were injected into the right atrium to allow adequate mixing during a 40 to 60 second period. Regional pulmonary blood flow was obtained by the reference sample method (12).

Hemorrhage was induced by bleeding the non-heparinized animals from the femoral arterial catheter into a reservoir containing acid citrate dextrose solution. The arterial pressure was decreased to 55 mm Hg within 10 minutes, and it was maintained at this level for 2 hours. It was necessary to return 15% of the shed blood volume in 1 sheep near the end of the 2 hr period in order to maintain blood pressure, but this was not necessary in others. In each case, steady-states in lymph flow and lymph/plasma protein concentration ratios were attained within the 2 hrs of hypotension.

Lymph and plasma samples were collected at 15 min intervals during the hemorrhage after the steady-state baseline period of 2 hrs. Protein concentrations were determined using the Biuret method, and albumin and globulin fractions were determined by cellulose acetate electrophoresis (Microzone 110, Beckman Instruments).

At the end of the experiment, sheep were killed with bolus injection of KCl, the chest was quickly opened and lungs were inflated to 30 cm H_2O *in situ*. Right and left lungs were marked at 2 cm intervals above and below the left atrial appendage reference level. Lungs were then quickly removed, drained for 3 min, blotted of surface blood and weighed. Needle holes were placed in the visceral pleura to allow passage of air through the lungs. Lungs were reinflated to 30 cm H_2O from a constant pressure source and air dried to a constant weight for 2 to 4 days. The drying did not alter the lung geometry since the 2 cm marks remained 2 cm apart following

drying. Each lung was sectioned into slices at the marked 2 cm lines and were compacted into plastic tubes. Radioactivity for each of the two isotopes in each level was counted in the Nuclear-Chicago gamma well counter. The pulse height analyzer was set to count the photopeak of each isotope. The overlap of the isotopes was removed by a matrix solved on a PDP-12 digital computer.

Lung water was determined by the extravascular lung water/blood-free dry lung weight ratio (13, 14). The correction for residual blood in the lungs was made by determining hemoglobin concentration in the supernatant fluid following rehydration and homogenization of the dried inflated lungs. The lungs were homogenized in a blender (Waring Products), and 5 ml duplicate samples of the homogenate were centrifuged at 35,000 x g for 1 hr at 5 °C to obtain a clear red supernatant extract. Water contents of the homogenate and supernatant samples, and mixed venous blood were determined by drying in an oven at 95 °C for 48 hours. Hemoglobin concentrations of supernatant fluid and blood were determined by the standard cyanmethemoglobin method.

The significance of changes from control levels was determined by the paired t-test and mean values were compared by the Student's t-test.

Results

The blood volume in the reservoir at the end of the 2 hr period of hemorrhage (H) averaged 27.5 ± 4.0 ml/kg. The mean arterial pressure decreased from 105.8 ± 5.8 to 51.2 ± 2.0 mm Hg 10 minutes after the beginning of H; after 1 hr of H the pressure was 57.5 ± 5.7 mm Hg, and at 2 hr the pressure was 58.8 ± 6.2 mm Hg. Pulmonary blood flow decreased progressively ($p < 0.05$) over the 2 hr period of H from baseline value of 115.0 ± 12.5 ml/min/kg to 59.2 ± 18.5 ml/min/kg at 1 hr of H, to 41.3 ± 15.8 ml/min/kg at 2 hr of H. Pulmonary arterial pressure (P_{pa}) decreased during the initial hemorrhage period from baseline value of 21.8 ± 1.1 mm Hg; it was decreased to 16.8 ± 1.4 ($p < 0.01$) from baseline levels at 1 hr and by 2 hrs the pressure had returned to 18.7 ± 2.2 mm Hg. Pulmonary arterial wedge pressure at 1 hr of H of 2.3 ± 0.6 mm Hg was not significantly different from baseline value of 2.9 ± 1.1 mm Hg, but was decreased ($p < 0.05$) to 1.0 ± 0.6 mm Hg at 2 hr of H. Pulmonary vascular resistance increased progressively ($p < 0.01$) during the 2 hr period of hemorrhage-induced systemic hypotension from the baseline value of 5.9 ± 1.1 mm Hg/l/min to 11.3 ± 3.3 at 1 hr of H, to 19.1 ± 4.5 mm Hg/l/min at the end of 2 hr of H. Arterial Pa_{O_2} and Pa_{CO_2} did not change significantly from baseline values of 63.4 ± 9.4 mm Hg and 39.1 ± 3.5 mm Hg respectively, but pH decreased progressively ($p < 0.05$) from baseline value of 7.30 ± 0.023 to 7.21 ± 0.014 at 2 hr of H.

Figure 1 shows the changes observed during one experiment. Pulmonary blood flow and aortic pressure both decreased following the initiation of hemorrhage and were unchanged thereafter. Pulmonary arterial and pulmonary arterial wedge pressure initially decreased and returned towards control levels at the end of the 2 hr period of hypotension. Pulmonary lymph flow decreased to a new steady-state at the end of period of systemic hypotension. Plasma protein concentration decreased while the lymph protein concentration did not change significantly. Figure 2 indicates the steady-state lymph flow, lymph protein clearance (lymph flow x lymph/plasma protein concentration ratio) and lymph protein flow (lymph flow x lymph protein concentration) data for each animal. Lymph flow and protein flow decreased ($p < 0.01$) in most animals (6/7), while lymph protein clearance decreased in 4 of 7 animals.

Table 1 summarizes the mean steady-state data in the 7 hemorrhaged sheep. Pulmonary lymph flow and plasma protein concentration decreased significantly ($p < 0.05$), while the lymph protein concentration did not change. The pulmonary microvascular pressure as calculated from the *Gaar* et al. equation (15) decreased ($p < 0.05$) from 7.60 ± .62 to 5.89 ± 1.03 mm Hg.

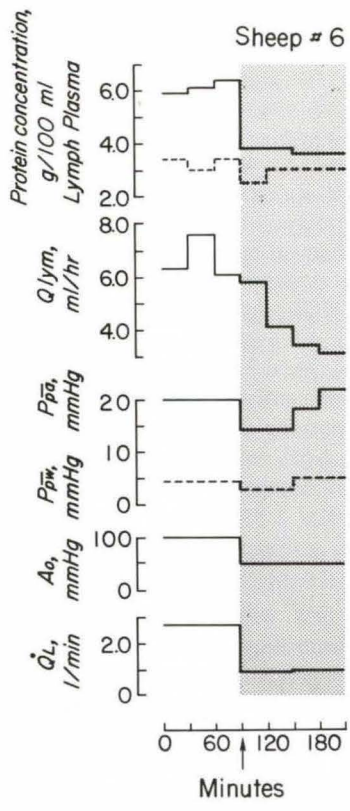

Fig. 1 Changes during hemorrhage in plasma and lymph protein concentration, pulmonary lymph flow ($\dot{Q}_{lym}$), pulmonary arterial pressure ($P_{\overline{pa}}$), pulmonary arterial wedge pressure ($P_{\overline{pw}}$), aortic pressure (A_o), and pulmonary blood flow ($\dot{Q}_L$) in one experiment. The hemorrhagic period is darkened

Figure 3 describes the relationship between the decreases in the calculated pulmonary microvascular pressure (P_{mv}) and the lymph flow ($\dot{Q}_{lym}$) during hemorrhage and the increase in lymph/plasma protein concentration ratio. The decreases in P_{mv} and $\dot{Q}_{lym}$ were both associated with increase in lymph/plasma protein concentration ratio ($p < 0.05$).

Figure 4 shows the regional distribution of pulmonary perfusion as percent of pulmonary blood flow at 2 cm levels above and below the left atrial reference. Hemorrhage did not significantly alter the baseline pattern of pulmonary perfusion.

The mean extravascular lung water/dry blood-free lung weight ratio in 7 hemorrhaged sheep of 4.87 ± .50 was greater ($p < 0.05$) than the value of 3.58 ± .14 in 10 similarly anesthetized and operated control sheep.

Discussion

The data on the changes in extravascular lung water content following hemorrhagic shock are equivocal (1, 2, 3, 4, 5). Some evidence indicates that pulmonary edema does not develop following hemorrhagic shock in heparinized animals (1, 4, 5, 12). Unfortunately, many of these studies have been made in animals administered anticoagulants prior to hemorrhage (1, 4, 5, 12); hence they are difficult to interpret since some pulmonary complications of hemorrhage may have been

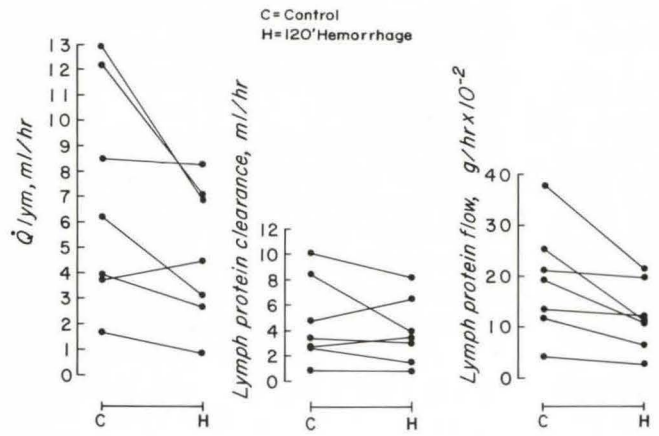

Fig. 2 Lymph flow ($\dot{Q}_{lym}$), lymph protein clearance, and lymph protein flow during the control baseline period (C) and steady-state hemorrhage (H) in each experiment

Tab. 1 Steady state lymph flows ($\dot{Q}_{lym}$), protein and albumin concentrations in plasma and lymph, and pulmonary microvascular pressure (PmV) calculated using the equation of *Gaar* et al. (15) (Mean ± 1 SE; n = 7)

	Q_{lym} (ml/hr)	Protein Concentration (g/100 ml)		Albumin Concentration (g/100 ml)		Pmv (mm Hg)
		Lymph	*Plasma*	*Lymph*	*Plasma*	
Baseline	7.03 ± 1.6	2.85 ± .18	4.44 ± .38	1.65 ± .10	2.14 ± .11	7.60 ± .62
Hemorrhage	4.79* ± 1.03	2.72 ± .18	3.35* ± .21	1.62 ± .094	1.76* ± .063	5.89* ± 1.03

* $p < 0.05$

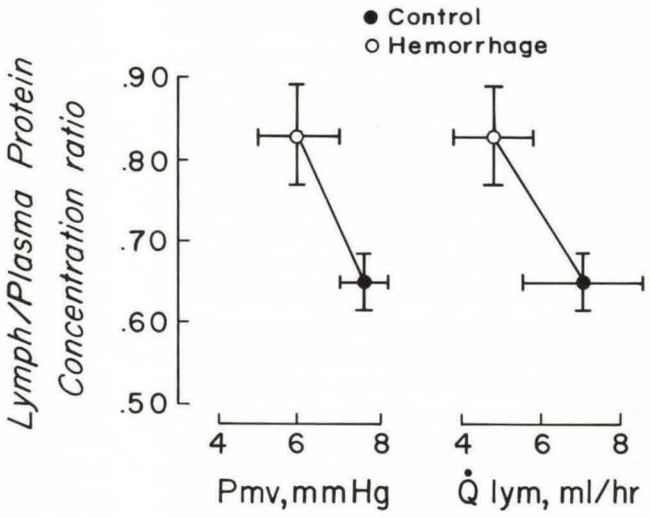

Fig. 3 Relationships between hemorrhage-induced decrease in the calculated pulmonary microvascular pressure (P_{mv}) and the decrease in pulmonary lymph flow ($\dot{Q}_{lym}$), and the decrease in P_{mv} and the increase in lymph/plasma protein concentration ratio

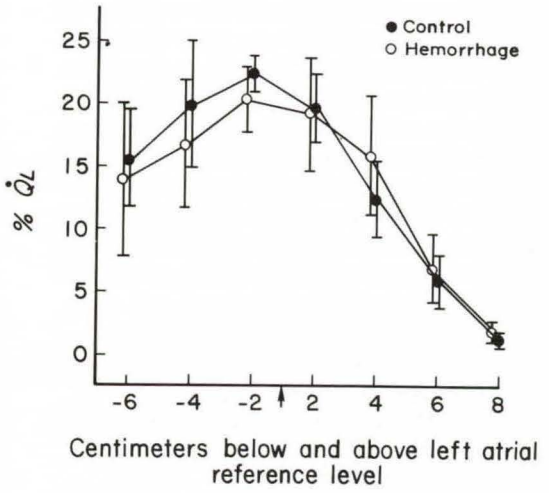

Fig. 4 Regional pulmonary perfusion expressed as % of pulmonary blood flow ($\dot{Q}_L$) at 2 cm levels below and above the left atrial reference. The distributions of flow during the control period and at 2 hr of hemorrhage are shown. Bars represent ± 1 SE

prevented by heparin-induced inhibition of intravascular coagulation and resulting thromboembolization (14). In contrast to studies in which lungs were unaffected, several experiments have indicated varying degrees of pulmonary edema following hemorrhage (2, 3, 16, 17). Morphological studies demonstrated interstitial edema suggesting that discrete pulmonary lesions may develop following hemorrhage (2, 4). Studies using tracers indicated that sodium and water accumulated in the lung interstitium during hemorrhagic shock and that these changes persisted after resuscitation (2). Lung oxygen consumption and substrate utilization were decreased during hemorrhage suggesting that early metabolic derangements may lead to non-cardiogenic cellular edema since normal metabolism is required to maintain transmembrane ion gradients (18). Pulmonary extravascular water volume measured in non-heparinized dogs during hemorrhagic shock by the double indicator-dilution technique was unchanged while pulmonary blood volume was decreased, suggesting extravascular fluid accumulation (17).

In the present study, we examined the effects of hemorrhage on lung fluid exchange in non-heparinized sheep to obviate any possible effect of heparin in inhibiting intravascular coagulation often associated with the low flow state during hemorrhage (19). Our previous studies indicated that heparin pre-treatment in dogs (14) and rats (unpublished observation) markedly reduced the degree of pulmonary edema following pulmonary thromboembolization. We studied the effects of hemorrhage by rapidly bleeding the animals into a reservoir to a pressure of 50 to 60 mm Hg in 10 minutes. We observed significant increase in the extravascular lung water/dry blood-free lung weight ratio in the animals subjected to 2 hrs of hemorrhage. The development of mild pulmonary edema during hemorrhage was associated with a decrease in the steady-state plasma protein, albumin and "globulin" concentrations, while the lymph concentrations did not change significantly and the lymph/plasma concentration ratios increased. The decrease in the plasma protein concentration supports the observations indicating greater reabsorption of fluid from the interstitial space due to decrease in the peripheral capillary hydrostatic pressure during the compensated phase of hemorrhage (i.e., so-called "autotransfusion") (20). The decrease in the capillary pressure is likely due to the sympathetic-mediated peripheral vasoconstriction (20). These peripheral vascular adjustments are responsible for the well-known hemodilution that occurs during hemorrhage (20). The observation that the steady-state pulmonary lymph protein concentration was unaltered during hemorrhage is consistent with the fndings of *Erdmann* et al. (21) that pulmonary lymph protein concentration is inversely related to the net fluid filtered (lymph flow) and pulmonary microvascular pressure (21). These workers demonstrated that an increase in microvascular pressure resulted in increase in lymph flow and decrease in the lymph protein concentration due to ultrafiltration of protein-poor fluid (21). Although they did not specifically study the effects of decrease in the pulmonary microvascular pressure, the unchanged steady-state lymph protein concentration and resulting increase in lymph/plasma ratios during hemorrhage in the present study may also be due to the decreases in pulmonary microvascular pressure and filtration rate.

Todd et al. (7) using horseradish peroxidase demonstrated increased lung microvascular endothelial permeability during hemorrhage in dogs, and their calculations suggested that number of endothelial "pores" increased while their average size remained the same. The same group also demonstrated abnormalities in the endothelial junctions of the lung vessels (although the abnormalities were greater in the alveolar epithelial junctions) following hemorrhagic shock (6), and increased lymph protein transport in the dog (7). They suggested that increased capillary permeability after hemorrhage could be explained by these ultrastructural alterations. However, we observed a decrease in the lymph flow and lymph protein transport during hemorrhage in the sheep; these data do not suggest increase in lung vascular permeability. The reason for the conflicting results may be due

to differences in the response to hemorrhage in the two species. Hemorrhagic shock in dogs clearly results in marked hepatic and intestinal ischemia due to constriction of hepatic venous sphincters which may release permeability-increasing factors (20). The present data are, however, support the studies in sheep by *Demling* et al. (5) indicating that pulmonary vascular permeability does not increase during hemorrhagic shock.

Demling et al. (5) did not observe changes in the pulmonary lymph flow during hemorrhagic shock in sheep, although both the pulmonary arterial and left atrial pressures decreased. They attributed the lack of decrease in lymph flow to maintenance of the pulmonary microvascular pressure due to an increase in the pulmonary venous resistance during hemorrhage. In the present study, we observed decrease in pulmonary lymph flow which was associated with decrease in the calculated pulmonary microvascular pressure. The microvascular pressure calculation is, however, based on the assumptions that pulmonary venous resistance represents 40% of the total lung vascular resistance (15) and that it does not change during hemorrhage. Decrease in lymph flow may also be due to decrease in the vascular surface area available for filtration (i.e., increased Zone I); however, the present data do not support this contention since regional distribution of pulmonary blood flow as measured by the distribution of labelled microspheres was not measurably altered during hemorrhage.

The mechanism of the increase in extravascular lung water/blood-free dry lung weight ratio during hemorrhage when the calculated pulmonary microvascular pressure and lung lymph flow are decreased is altogether unclear, although the occurrence of pulmonary edema after hemorrhage is consistent with some other observations (2, 3, 16, 17). It is also not clear whether the fluid accumulation was interstitial or intracellular. Interstitial fluid accumulation is likely to result in increase in pulmonary lymph flow provided the lymphatics are patent and their pumping ability is unaltered during hemorrhage, and provided that the fluid is not sequestered in the interstitial gel matrix and lung cells where it cannot be drained by the lymphatics. There is also circumstantial evidence suggesting that lymphatic function may be impaired during hemorrhagic shock (22); therefore lymphatic "failure" could be another mechanism contributing to increase fluid accumulation.

Since lung lymph flow did not increase in the face of increased extravascular lung water content, pulmonary edema may also be due to fluid accumulation in the endothelial cells which represent approximately 30% of the total extravascular tissue mass (34) rather than accumulation in the interstitial space (23). *Roghati* et al. (18) have demonstrated impairment in the metabolic activity and substrate utilization by lung slices in rats subjected to hemorrhage. Since normal cellular metabolism is required to maintain the transmembrane ion gradients, there may be impairment in lung endothelial Na^+-K^+ pump resulting in fluid accumulation and swelling of these cells as demonstrated in liver parenchymal cells during hemorrhagic shock (24). *Sayeed* et al. (25) were unable to demonstrate alterations in water accumulation and Na^+-K^+ transport in rat lung slices during hemorrhagic shock, although the effects of pulmonary hypoperfusion and hemorrhage on specifically the endothelial cell were not studied. There is ultrastructural evidence that endothelial cells from patients in respiratory distress are enlarged (26) and cellular edema occurs in various forms of pulmonary edema (27). Distortion of these cells may result in reduction of pulmonary blood flow, increased PVR, and alterations in dimensions of the inter-cellular junction (28). Infusion of hypertonic mannitol solution reduced the PVR in patients with post-traumatic insufficiency suggesting that decrease in resistance may be due to decreased cellular swelling resulting from dehydration of the cells (29).

In the present study, PVR was increased three- to four-fold from baseline levels at the end of the hemorrhagic period. It is unlikely that the marked increase in resistance was due solely to metabolic acidosis since decrease in pH to 7.21 evoked 25% increase in resistance (30). Increase in Pa_{CO_2} and de-

crease in Pa_{O_2} also cannot explain the large increase in PVR since neither changed markedly. The regional distribution of pulmonary blood flow was not significantly altered after 2 hrs of hemorrhage, suggesting that the increase in PVR was also not due to increased Zone I in the lung. The unchanged distribution of perfusion despite the increase in PVR supports our earlier observation suggesting that regional perfusion is unaltered during hemorrhage due to the acidosis-induced maintenance of pulmonary arterial pressure at control levels (12). It is conceivable that perivascular "cuffing" of vessels with edema fluid or alveolar edema may result in increased PVR. If this is the case, then greater flow reduction is expected in the dependent lung due to preferential fluid accumulation in this region (31, 32). Since we did not observe flow redistribution away from the dependent lung, the results suggest that the increase in PVR was also not due to interstitial or alveolar edema. However, it is possible that the progressive increase in PVR during hemorrhage, which appeared to be uniform throughout the lung since flow was not redistributed, may be due to decrease in vascular calibre caused by swelling of endothelial and vascular smooth muscle cells (33).

In summary, the results indicate decrease in the pulmonary lymph flow and increase in lymph/plasma protein, albumin and "globulin" concentration ratios during hemorrhage. The decrease in lymph flow may be due to decrease in filtration pressure rather than vascular surface area and the increased lymph/plasma protein ratio may reflect the decrease in the rate of fluid filtration. Hemorrhage was not associated with increase in lung vascular permeability consistent with previous findings in sheep (5). However, hemorrhage resulted in the development of mild pulmonary edema. The mechanism and site of edema are unclear; evidence suggests that it may be due to lymphatic "failure" and to swelling of lung vascular endothelial and smooth muscle cells.

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Dr. A.B. Malik, Department of Physiology, Albany Medical College of Union University, 47 New Scotland Avenue, Albany, New York 12208