Lung Fluid Exchange after Uneven Pulmonary Artery Obstruction in Sheep

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SUMMARY We studied steady state transvascular fluid and protein exchange after uneven obstruction of the pulmonary arteries. In anesthetized sheep, ventilated by positive pressure, we measured pulmonary artery and left atrial pressures, cardiac output, lung lymph flow, and lymph/plasma protein ratios. We calculated pulmonary vascular resistance. In 16 sheep we obstructed the pulmonary arteries with various microemboli or balloons in lobar arteries until pulmonary vascular resistance was 2-3 times baseline. In every experiment, lung lymph flow increased as pulmonary vascular resistance increased. The lymph/plasma protein ratio did not change. In four sheep, we increased left atrial pressure by balloon obstruction of the mitral orifice. Pulmonary artery pressure increased as much as in the embolization experiments and lymph flow increased but the lymph/plasma protein ratio decreased, meaning that the increased fluid and protein flux after embolization cannot be due to high pulmonary artery or pulmonary venous outflow pressures alone. In four sheep we compared obstruction of the lower lobe pulmonary arteries by balloons with that of upper lobe pulmonary arteries. Lower lobe arterial obstruction caused the lymph flow which drains predominantly from the lower lobes to decrease whereas upper lobe artery obstruction increased lymph flow. This means that the increased fluid and protein flux occurred mainly in the open, perfused portion of the microvascular bed. The mechanism of the increased fluid filtration and protein permeability may be related to high vascular pressure and high linear blood flow velocity through a markedly restricted microvascular bed, although release of substances that affect endothelial permeability is not ruled out.

IN THE ADULT respiratory distress syndrome, a central feature is the occurrence of interstitial and alveolar edema. Since in pathological sections the edema fluid stains similarly to blood plasma (proteinaceous) and since there are often hyaline membranes in the air spaces, the edema is considered to be of the increased microvascular permeability variety. Hemodynamically, features commonly noted are an increase in pulmonary arterial pressure in the face of a normal pulmonary artery wedge pressure or a directly measured left atrial pressure. The calculated pulmonary vascular resistance is elevated. Numerous investigators have frequently found plugging of pulmonary small arteries and microvessels by various types of microemboli.

How is it that obstruction of pulmonary arteries causes pulmonary edema due to increased microvascular permeability?

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Gibbon and Gibbon made one of the earliest observations on this syndrome. They found that resection of 70% of the lung mass in cats was followed by the development of pulmonary edema, especially if the resection was accompanied by infusions of whole blood or plasma. Although they believed the edema was due to the high pressure in the microvessels, they did suggest that the edema fluid was only slightly diluted plasma (that is, typical of what we call increased permeability edema).

Visscher briefly reported on the effects of microemboli in the isolated dog lung perfused at constant flow. When he injected approximately one billion glass microspheres (25 μm diameter), pulmonary artery pressure rose markedly and edema developed rapidly. He believed that the increased pulmonary artery pressure was transmitted into the microvessels and, together with the increased velocity of blood flow in the patent portions of the microcirculation, caused the edema.

Even pulmonary macroemboli may be associated with acute pulmonary edema if the initial obstruction is not so severe as to cause acute cor pulmonale. Parmley and associates reported pulmonary edema as the immediate cause of death in 8 of 30 dogs given autologous blood clot emboli.

Hultgren and Grover developed the concept of over-perfusion as the mechanism of embolic and high altitude pulmonary edema. In open-thorax dogs, they removed 80% of the lung mass and regularly produced acute pulmonary edema. The total protein concentration of the edema fluid averaged 4.8 g/dl (Hultgren, personal communication). Although he did not measure the plasma protein concentration, based on the usual values in labo-
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monary dogs, the edema fluid protein must have been about 80% of the plasma concentration.

Viswanathan et al.7 hypothesized that uneven pulmonary arterial constriction in acute alveolar hypoxia with resultant overperfusion of some areas of the lung may be the underlying mechanism accounting for high altitude pulmonary edema.

Arfors and co-workers11 have measured pulmonary vascular resistance following fibrin microemboli in dogs. Although they did not relate the degree of edema directly to the amount of obstruction, their data show a correlation between these two variables. Saldeen12 attributed the edema following microemboli principally to the biochemical action of fibrin metabolic products acting to increase microvascular permeability.

In the experiments reported here, we have studied the relationship between pulmonary embolism and lung fluid and protein exchange using a sheep model13 in which we can obtain nearly pure lung lymph. We have tried to answer the following three questions: (1) can acute pulmonary edema reliably be produced by uneven obstruction of the pulmonary arteries? (2) is the edema of the increased permeability type? (3) do the edema fluid and protein escape from the occluded portion or the perfused portion of the lung?

Methods

We prepared yearling female sheep (weight, 25-58 kg; average, 38 kg) in order to collect pure lung lymph and to measure pulmonary hemodynamics as previously described.13,14 We did our experiments in anesthetized sheep rather than in chronically instrumented, unanesthetized ones, for convenience and also because we were uncertain as to the animals' response.

At preliminary surgery, we resected the distal portion of the caudal mediastinal lymph node to remove essentially all of its systemic lymph input. We placed a catheter in the left atrium to record pressure and, in some sheep, a balloon catheter in the left atrium for later use in obstructing the mitral valve orifice in a controlled fashion.14

On the day of study, we anesthetized the sheep with intravenous sodium pentobarbital (30 mg/kg), tracheally intubated them, and ventilated them with 0.5–1.5% oxygen using a positive pressure ventilator (Ventimeter, Air Shields Co.) set at 15 cycles/min to deliver a tidal volume of approximately 600 ml at a peak airway pressure of 30 cm H2O. Through a right thoracotomy (5th interspace) we cannulated the efferent duct of the caudal mediastinal lymph node with a small silastic catheter.13 We did not close the thorax but continued with the experiment. We placed the sheep in the supine position.

Under fluoroscopic control, we passed a double lumen catheter with a thermister bead near the tip via the right external jugular vein into the main pulmonary artery (7F, Kimray Medical Assoc.). We also passed a large polyvinyl catheter via a systemic artery into the aorta. We attached the aortic, left atrial, and distal lumen of the pulmonary arterial catheters of strain gauges (Statham P23G) to record pressures on a direct-writing polygraph (model 7, Grass Instruments). Pressures were measured relative to atmospheric pressure and to the base of the lung.

Through the proximal lumen of the thermister catheter, which was in the right atrium, we injected 5 ml of iced saline and determined cardiac output by the thermal dilution method, using a cardiac output computer (model 2800, Kimray).

Experimental Procedure

After the surgical preparation was completed, we studied each sheep for a baseline period of at least 2 hours, after which we made a variety of interventions. There were 28 sheep in the entire study; four in each of seven groups. The first group consisted of our experimental controls. In these, we followed lung lymph flow and hemodynamics for 6–8 hours. We did not obstruct the pulmonary circulation.

In 16 sheep, we obstructed the pulmonary arterial circulation in one of four different ways. In four sheep we made mineral oil emboli (200 ± 10 μm in diameter) prepared by the method of Sackner and associates.15 In four sheep we used silicone-coated glass beads (215 ± 15 μm in diameter) (glass type IV A, unispheres, Ferro Corp.). In four we gave an intravenous infusion of tranexamic acid to inhibit fibrinolysis (150 mg/kg iv initial bolus followed by 15 mg/kg per min continuous iv infusion) and thrombin (5000 U.S. N.I.H. units intravenously as a bolus followed by approximately 3000 U iv in boluses every 15 minutes until the maximum increase in pulmonary vascular resistance was achieved) (Park Davis) in order to form fibrin microemboli in the pulmonary circulation.11

In four sheep, we passed small balloon catheters via the external jugular vein to obstruct lobar pulmonary arteries. We obstructed the entire left main pulmonary artery as well as the right upper and right middle lobe pulmonary arteries. Right ventricular output then was forced through the right lower and cardiac lobes which together account for approximately 30% of lung mass in the sheep. We will call this group, "upper lobe obstruction," even though the left lower lobe was included. We want to differentiate this group from another one which we will call "lower lobe obstruction." This is important because the lymph in the caudal mediastinal efferent duct, which we cannulated, comes predominantly from the lower lobes of the lung, as indicated in Figure 1. It was necessary in this macroballoon obstruction to leave as much as possible of the lung from which lymph flow came, open for blood flow.

The five groups of four sheep each described above form the primary experimental study. The experiments were done in random fashion. The following two groups of experiments were done subsequently.

In four sheep, we inflated a balloon in the left atrium to raise pulmonary artery pressure passively to approximately the same value as was achieved during the arterial obstruction experiments.

In the seventh and last group of four sheep, we passed balloon catheters via the external jugular veins into the lower lobe pulmonary arteries and selectively occluded these. This is the "lower lobe obstruction" group, as previously mentioned (Fig. 1). The purpose of this group...
Figure 1 Schema of lung lymph drainage in the sheep. The upper (anterior) lobe drains predominantly via the lung hilum and tracheobronchial lymph nodes into both the right lymph duct and thoracic duct. The lower (posterior) lobes drain predominantly over the pleural surface, through the pulmonary ligament to the large caudal mediastinal lymph node. The lymph cannula, through which we measured lung fluid flux, was in the main efferent duct of the caudal mediastinal lymph node.

was to determine whether the increased fluid exchange occurred in the open or occluded portions of the pulmonary vascular bed.

In all of these experiments, after the baseline period, there was a transition period of up to 2 hours during which new steady state conditions were established. For example, in the pulmonary arterial obstruction experiments, we embolized the lungs at intervals until we had achieved increases in calculated pulmonary vascular resistance of 2-3 times baseline. We then followed the parameters of lung fluid exchange over a period of approximately 2 hours of relatively stable lymph flow, which we defined as a lymph flow whose variance does not exceed that of the baseline period.

Terminally, all sheep were killed as follows. We opened the thorax widely, extending the original thoracotomy incision across the sternum. We isolated and clamped the right and left lung hila separately. We removed the lungs, took samples for histology, and homogenized the remainder in order to determine extravascular lung water.16

Statistics

We compared the experimental data between the baseline and steady state experimental periods in each sheep by the paired t-test. The summary data in the text and tables give the average ± 1 standard deviation of the sample of each group of four animals. We made comparisons between experimental groups by an unpaired t-test and comparison of the slopes of regression lines by the F-test. We accepted \( P < 0.05 \) as indicating statistical significance.

Results

General

Within each group, the responses of the four sheep were qualitatively similar. All animals remained fully anesthetized and in relatively stable condition throughout the experiments. Arterial oxygen tension was usually above 200 torr during the baseline period. Following embolization, arterial oxygen tension sometimes decreased to less than 100 torr. Although we did not measure lung mechanics, total pulmonary resistance tended to increase after embolization as judged by an increase in the inflation pressure at constant tidal volume. Published data concerning microemboli indicate that their main effect is to induce alveolar duct constriction within the terminal respiratory unit, thereby decreasing lung compliance.18,19

Lung lymph was generally free of red blood cells during the baseline period. Sometimes it became slightly sanguinous after embolization. The lymph hematocrit, however, never exceeded 2%.

At postmortem examination, we did not find any significant accumulation of pleural fluid and the lungs were not grossly edematous. Histologically, we saw only small
perivascular or peribronchial fluid cuffs. There was no alveolar edema.

Control Experiments

The time course of one control experiment is shown in Figure 2A. The summary data for pulmonary hemodynamics and lung fluid balance for the baseline period and for the last 2 hours of the "experimental" period are shown in Table 1A. There were no significant differences between the baseline and later observation periods. The lung water content was in the normal range reported by our laboratory.14-20

Microemboli

Examples of the time course of the microemboli experiments are shown in Figure 2B (mineral oil), 2C (glass beads), and 2D (fibrin). The summary data for the baseline and 2-hour steady state periods after obstruction are in Table 1B. Pulmonary artery pressure and calculated pulmonary vascular resistance were increased in all embolization experiments. The rise following the fibrin microemboli was less than with the other two types. Lung lymph flow increased in every experiment after emboli whereas the lymph protein concentration, expressed as the lymph-to-plasma protein ratio, did not change significantly. Not listed in the table are the data for the lymph/plasma ratios of the subfractions of albumin and globulin which averaged 0.77 ± 0.05 and 0.53 ± 0.05, respectively, in the baseline periods. Neither of these changed significantly after embolization. The lung water contents in these animals were increased approximately 10% above the control value.

Upper Lobe Pulmonary Artery Balloon Obstruction

Figure 3 shows the time course of one experiment in which we obstructed the pulmonary arteries to the entire left lung and the right upper and middle lobes with balloon catheters, leaving only the right lower and cardiac lobe perfused. The summary data are in Table 1C. In every sheep, the pulmonary artery pressure and vascular resistance increased. Lung lymph flow increased significantly but the lymph/plasma protein ratios did not change. In these sheep, we measured postmortem water content of the perfused right lower and cardiac lobes separately from those that had been obstructed. In every sheep, the perfused lobes averaged 10% more water than the obstructed portions of lung; the same difference as found between the control and microembolized animals.

![Graphs showing time course of lung lymph flow, calculated pulmonary vascular resistance, and lymph protein concentration expressed as lymph/plasma ratio for albumin and globulin, in one control sheep (A) and three sheep with different types of emboli; mineral oil (B), silicone-coated glass microspheres (C), and fibrin (D).]
TABLE 1 Effects of Uneven Lung Vascular Obstruction on Pulmonary Hemodynamics and Lung Fluid Balance in Anesthetized Sheep

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pulmonary artery pressure (cm H2O)</th>
<th>Left atrial pressure (cm H2O)</th>
<th>Cardiac output (liters/min)</th>
<th>Calculated resistance [cm H2O/liters/min]</th>
<th>Lymph flow (ml/hr)</th>
<th>Lymph protein concentration (lymph/plasma)</th>
<th>Lung water content (g/g dry lung)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Controls</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Baseline*</td>
<td>25.3±2.1†</td>
<td>14.9±1.0</td>
<td>3.7±0.6</td>
<td>3.7±0.3</td>
<td>5.1±0.9</td>
<td>0.73±0.03</td>
<td></td>
</tr>
<tr>
<td>Experimental</td>
<td>27.7±2.2</td>
<td>15.0±0.9</td>
<td>4.1±0.4</td>
<td>3.5±0.4</td>
<td>6.3±0.6</td>
<td>0.68±0.02</td>
<td>4.2±0.1</td>
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<tr>
<td>B. Microemboli</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Mineral oil</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>26.5±0.7</td>
<td>16.8±0.6</td>
<td>3.8±0.4</td>
<td>2.6±0.3</td>
<td>5.0±0.5</td>
<td>0.64±0.02</td>
<td>4.6±0.2</td>
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<tr>
<td>Experimental</td>
<td>41.1±2.1(s)‡</td>
<td>16.9±0.6</td>
<td>3.6±0.3</td>
<td>7.6±0.5(s)</td>
<td>15.2±1.0(s)</td>
<td>0.62±0.02</td>
<td>4.6±0.2</td>
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<tr>
<td>2. Glass beads</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>25.6±2.3</td>
<td>13.6±1.4</td>
<td>4.2±0.6</td>
<td>2.8±0.6</td>
<td>7.6±1.4</td>
<td>0.64±0.03</td>
<td>4.6±0.1</td>
</tr>
<tr>
<td>Experimental</td>
<td>44.9±2.1(s)‡</td>
<td>13.7±2.0</td>
<td>3.5±0.3</td>
<td>9.6±0.8(s)</td>
<td>20.5±2.1(s)</td>
<td>0.69±0.02</td>
<td>4.6±0.1</td>
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<tr>
<td>3. Fibrin</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>24.7±1.2</td>
<td>15.0±0.6</td>
<td>3.8±0.5</td>
<td>2.6±0.3</td>
<td>4.8±0.8</td>
<td>0.61±0.05</td>
<td>4.8±0.2</td>
</tr>
<tr>
<td>Experimental</td>
<td>33.8±1.3(s)‡</td>
<td>14.4±0.5</td>
<td>3.1±0.2</td>
<td>5.7±0.5(s)</td>
<td>7.9±1.2(s)</td>
<td>0.63±0.03</td>
<td>4.8±0.2</td>
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<td>C. Balloon occlusion</td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>24.9±1.0</td>
<td>15.9±1.1</td>
<td>3.4±0.4</td>
<td>2.8±0.4</td>
<td>5.7±0.4</td>
<td>0.72±0.02</td>
<td>4.0±0.2</td>
</tr>
<tr>
<td>Experimental</td>
<td>33.0±1.3(s)‡</td>
<td>13.7±0.6</td>
<td>3.0±0.3</td>
<td>6.9±0.4(s)</td>
<td>9.3±0.7(s)</td>
<td>0.70±0.03</td>
<td>4.4±0.3§</td>
</tr>
</tbody>
</table>

* 2-hr baseline period and 2-hr steady state period after obstruction.
† Average ± standard deviation. Pressures measured relative to atmospheric pressure and the base of the lung.
‡ (s) = statistically significant at P < 0.05 by paired t-test between baseline and experimental periods.
§ Lobes with arteries occluded are listed above the perfused lobes.

Increased Left Atrial Pressure

Figure 4A shows the time course of one of these experiments. Qualitatively, it is not different from our previous experiments in unanesthetized animals. Nevertheless, it seemed necessary to test the effects of pulmonary venous hypertension under the conditions of our experiments. We raised left atrial pressure until the pulmonary artery pressure was in the same range as in the microemboli and balloon obstruction experiments. The data are summarized in Table 2A. In every experiment, lung lymph flow increased but, what is more important, the lymph/protein ratio decreased. This is different from all of the pulmonary artery obstruction experiments (Table 1).

Lower Lobe Pulmonary Artery Balloon Occlusion

We selectively occluded the pulmonary arteries to the right and left lower lobes and the cardiac lobe with balloon catheters in four sheep. Under these conditions, the portion of lung from which most of the caudal mediastinal lymph drainage comes was obstructed.

The time course of one of these experiments is shown in Figure 4B and the data are summarized in Table 2B. The protocol of these experiments was slightly different in that there is a recovery period after the period of occlusion. In each animal, lung lymph flow decreased during occlusion in spite of the rise in pulmonary artery pressure and pulmonary vascular resistance. The pressure in the pulmonary artery in the occluded lobes was approximately left atrial pressure.

Lung water content is for the entire lung 2 hours after the occlusion had been released. That is not very informative and may be a protocol error on our part. Nevertheless, we felt that it was more important to have good before-and-after lung lymph flows in this group than to have the extravascular lung water content at the end of the occlusion period.
Concentration Protein (cardiac output) may be an important factor, as Gibbon, 6 artery pressure to emphasize that microvascular flow rate among the slopes of lines. We correlated the change in and lung lymph flow. There are no significant differences were selectively occluded.

Vascular (lymph /plasma) /cm H 2 O /
l/min / cm H 2 O /ml/h

A: Time course of pulmonary venous congestion. Rising pulmonary vascular pressures increased lung lymph flow but decreased lymph protein concentration. B: Time course of lower lobe pulmonary artery balloon obstruction. The regions of lung from which the caudal mediastinal lymph emanates were selectively occluded.

Discussion

General

The control sheep (Fig. 2 and Table 1A) establish the stability of our experimental model over a time course in excess of 8 hours.

The hemodynamic and fluid balance data for all four types of uneven pulmonary artery obstruction were similar (Table 1B). Figure 5 is a graphic demonstration of the relationship between pulmonary vascular resistance and lung lymph flow. There are no significant differences among the slopes of lines. We correlated the change in lymph flow to resistance rather than to the pulmonary artery pressure to emphasize that microvascular flow rate (cardiac output) may be an important factor, as Gibbon, 6 Visscher, 7 and Hultgren 9 have suggested, and that the response is not due to increased pressure alone (Table 2A).

We conclude that in terms of lung fluid exchange there are no differences among the four types of uneven pulmonary artery obstruction.

A remarkable but perhaps not obvious fact is that lung lymph flow increased, although much of the lung's microvasculature had been occluded; that is, the surface area for fluid exchange must have decreased markedly. In the first stages of embolization, recruitment of additional microvessels occurs and pulmonary vascular resistance does not rise very much. When microvascular recruitment is nearly complete, however, resistance increases rapidly with further obstruction. The pressure-flow relation is very nearly linear so that changes in resistance are a reasonable index of the changing fraction of the microvascular cross section that is obstructed. Thus, a 2-fold rise in pulmonary vascular resistance means that 50% of the microvascular cross-section has been obstructed and 50% of fluid exchange area has been sequestered. Likewise, a 3-fold increase in calculated resistance means a 67% decrease in the available exchange area. If there is too much reduction in surface area, lymph flow may decrease, as is clearly demonstrated by our experiments with the selective lower lobe occlusions (Table 2B).

Site of Increased Fluid and Protein Exchange

Although the obvious site of the altered fluid exchange would be in the open, perfused microvessels, three alternate possibilities ought to be considered, namely, fluid leakage (1) directly through the thin walls of pulmonary arteries proximal to the embolization sites; (2) at the site of embolic impaction due to local injury and (3) in the microvessels beyond the sites of occlusion due to accumulation of chemically active substances.

1. The pressure increased in all pulmonary arteries proximal to the occlusion sites. Whayne and Severinghaus, 21 Iliff, 22 and Butler and associates 23 have evidence that fluid leakage may occur in the arteriolar portion of the lung's microvessels, that is, proximal to the main alveolar wall capillary network. In their various experiments, vessels only slightly larger than 15-20 µm in diameter (alveolar wall corner vessels) were suspected. Iliff, using Evans blue dye, has the most direct evidence for the size of vessels leaking. On the arterial side, she detected possible leakage only from vessels <75 µm in diameter.

Since our mineral oil and glass bead microemboli were 200 µm in diameter, such small pulmonary arteries could not have been involved except for those in the perfused portions of lung.

Vessels larger than 200 µm in diameter have not been seriously considered in terms of transarterial leakage and, if they were, the internal evidence from our lobar artery balloon occlusion experiments would tend to rule that out because the response is not different from the microemboli occlusions, although the surface area available for transarterial leakage is 3-fold different. Even firmer evidence that transarterial leakage is not occurring in vessels remote from alveolar walls (<200 µm) is our recent investigation of acute and chronic alveolar hypoxia in sheep. 24
In those experiments, pulmonary artery pressures were elevated to levels similar to those in the microemboli experiments, and yet there was no change in lung lymph flow or its protein composition. We interpreted the hypoxia-induced pulmonary artery hypertension as due to active vasoconstriction proximal to the sites of fluid exchange.\(^2\) Thus, although pulmonary vascular resistance was increased, neither microvascular flow rate nor microvascular distending pressure was affected.

2. Injury at the site of embolic impaction is possible. Following the initial impaction, as pulmonary artery pressure rises, the emboli may be pushed downstream, thereby exposing the original damaged area. Although we cannot rule out this possibility, it certainly cannot be the explanation in those animals with the main lobar pulmonary arteries occluded by balloons.

3. Although the arterial end of the microvessels is occluded, the leakage could be from the occluded microvessels. They are open to pressure from the left atrium or the bronchial circulation. As noted above, pressure distal to balloon occlusions was approximately left atrial pressure which, as Table 1 shows, is not insignificant at the base of the lungs in these supine animals.

Clearly, in the experiments of Gibbon\(^4\) and Hultgren,\(^5\) the increase in fluid flux had to come from vessels with blood flow, since the remaining lung had been removed. Because of the pattern of lymph drainage from the sheep lung, we have been able to make a direct determination of the principal fluid exchange sites. As Figure 1 showed, lymph from the caudal mediastinal efferent duct comes principally from the lower lobes of the lung. Occluding the lower lobe arteries with balloons decreased the measured lymph flow. Thus, the leakage could not have come from the occluded vessels.

It is possible that the primary injury was in the occluded portions of the microvessels but that there was diffusion of chemically active substances through the lungs interstitium to other perfused vessels which were then made permeable. Since the microemboli are distributed throughout the lung, occluded vessels were intermixed with those open to perfusion. The microemboli were distributed initially in proportion to blood flow distribution; but, since the lungs were embolized repeatedly, the emboli eventually were distributed in all lobes. On the other hand, the interstitial diffusion of vasoactive substances does not fit with our lobar artery balloon occlusion experiments, nor with previously published studies involving lung resection.

### Nature of the Increased Fluid Exchange

In Figure 6, we have compared the relative protein clearance for the four uneven arterial obstruction groups (Table 1) with that of the sheep with increased left atrial pressure (Table 2A). All of the uneven obstruction experiments show the same increases in protein clearance with respect to lymph flow, whereas the protein clearance with increased left atrial pressure is significantly less even though the pulmonary artery and microvascular pressures generated were as high as the emboli experiments.

The protein clearance is a key differential point be-
definitive evidence that this material functions as a permeability-increasing factor in the lung. The pulmonary permeability increasing factor in the lung is not surprising that due to increased endothelial permeability. 2,14,20

We conclude that the increased fluid and protein exchange associated with uneven pulmonary artery obstruction involves elevated microvascular pressures which are transmitted into the open, perfused regions from the pulmonary artery. We also conclude that the edema following pulmonary microembolism is chiefly one of increased microvascular fluid and protein permeability and that the changes in permeability cannot be accounted for solely by the elevated vascular pressure.

What is the Mechanism for the Increased Permeability?

Is there any mechanism that is common to all of the experiments which will account for the observed results? To indicate the direction in which our research is headed, we offer the following speculative review of two different but not mutually exclusive possibilities.

Biochemical Factors

Lindquist and associates5,26 have identified a permeability-increasing factor that is released from the lungs of dogs into right duct lymph in the microembolism syndrome. They have tentatively identified it as a fibrin degradation product (FDP), slowly released from the persistent fibrin microemboli in the pulmonary vessels. The material increases vascular permeability in the hamster cheek pouch and in the abdominal skin of the rat. The fact that FDP is released in the lung is not surprising since their emboli were predominantly fibrin. However, altered permeability in the hamster cheek pouch is not definitive evidence that this material functions as a permeability increasing factor in the lung. The pulmonary vasculature is notorious for behaving differently from systemic blood vessels.

On the other hand, our mineral oil and Silastic-coated glass microsphere emboli are probably not as inert as we had originally thought. For example, Piper and Vane27 reported the release of prostaglandins from lungs after a variety of microemboli.

Recently, Malik and Van der Zee28 presented evidence that heparin can partially block the increase in pulmonary vascular resistance and completely block the increase in lung water content and tracer fibrinogen deposition after glass microemboli in dog lungs. Their results support Saldeen's view that the fibrinogen system is involved in the altered permeability.3 The difficulty remains, however, in trying to explain the results of our pulmonary artery balloon occlusion experiments. If an FDP is released downstream from the occlusion site, how does it reach the open microvessels in another lobe? One would have to invoke recirculation to explain it.

Lung mechanics have been shown to be affected by active substances formed or released after microembolization.18,19 In our sheep, we did not measure lung mechanics specifically but noted that peak inflation pressure increased after emboli, indicating an increase in total pulmonary resistance. In addition, arterial oxygen tension usually decreased, indicating an increased right-to-left shunt-like effect.

Craddock and associates29 have evidence that complement-activated plasma acts to trap circulating neutrophils in the lung's microcirculation with subsequent increase in microvascular permeability, presumably due to release of lysosomal enzymes. Be et al.30 find that platelets are necessary for at least part of the microembolism response. Although Saldeen31 tends to discount the role of white cells and platelets in the increased permeability of the microembolism syndrome, further evaluations by specific depletion experiments are necessary before their role can be completely defined.

It is possible that local or circulating vasoactive substances released or generated by the microvascular obstruction (for example, histamine31) contribute to the changes in vascular permeability.

Physical Factors

An increased driving pressure is not the only physical factor that has been altered in the uneven obstruction experiments. The linear velocity of blood is also increased, since cardiac output remained nearly normal in spite of the decrease in the vascular cross-section.7 This is different from the increase in pulmonary blood flow seen in exercise. There the increase in cardiac output (linear velocity of blood flow) is largely offset by the expansion of the pulmonary microvascular bed.25 In addition, pulmonary vascular resistance decreases so that the distending pressure in the microvessels is not increased; at least, that is the interpretation we place on Marshall's32 finding of no increase in lung water content in exercising dogs. Unfortunately, measurements of steady state lung lymph flow during exercise have not been made.

How does an increased blood flow rate alter microvascular permeability? Fry34 and Patel and associates35 have evidence that local stress on endothelial surfaces, at critical points in the circulation, can lead to rapid and marked
changes in endothelial permeability to proteins and other molecules. Figure 7 is a hypothetical scheme denoting some of the "stress" points that may occur in the pulmonary microvascular bed. These are analogous to stresses described by Fry. The critical areas appear to be at branches, sharp bends, or where there is direct impaction of blood flow jets.

Substantial evidence for injury in large blood vessels, such as the aorta and coronary arteries, exists, but there is no direct evidence for injury at the microvascular level. In the Appendix we have calculated both circumferential and shear stresses within the alveolar wall microvessels based upon estimates of the necessary parameters. Both stresses increase with uneven pulmonary artery obstruction. The tangential stress increased 7-fold between the two conditions but was always less than one-tenth the values for large arteries. This is consistent with our data that distending pressure alone does not increase the lung's microvascular permeability.

The shear stress increased 4-fold but, more important, it exceeds values that cause increased endothelial fluid and protein permeability in large arteries. Admittedly speculative, the concept of physical injury by high velocity and high pressure flow in the pulmonary microcirculation is able to account for all forms of pulmonary edema following uneven arterial obstruction.

Appendix

Estimates of endothelial stresses in the lung's microcirculation provide a basis for comparison between different conditions. We cannot place too much reliance upon the absolute numbers because of the complex geometry of the microvascular bed (Fig. 7) and the many simplifying assumptions involved.

The two major stresses are (1) the tangential stress tending to rupture the vessel wall and (2) the shear stress due to viscous drag along the luminal surface of endothelium.

Tangential stress ($\sigma_t$) in a cylindrical, thin-walled vessel is directly proportional to the distending pressure ($P_{tm}$), the radius (r), and inversely proportional to the wall thickness (h).

$$\sigma_t = \frac{r(P_{tm})}{h}$$

Shear stress ($\tau$) varies directly with driving pressure ($P_d$) along the vessel, the radius (r), and inversely with vessel length (L).

$$\tau = \frac{r(P_d)}{2L}$$

To obtain numbers, we have assumed the lung's microcirculation to consist of uniform cylindrical tubes with characteristic length based on measurements in dogs, cats, and rabbits and whose radius varies with distending pressure according to the equation of Sobin and coworkers. In Table 3 are listed the necessary parameters and the calculated values of tangential and shear stress for two conditions; baseline and after glass bead microemboli (Tables 1B and 2).

References


![Figure 7](image-url)


Lung fluid exchange after uneven pulmonary artery obstruction in sheep.
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