Interstitial Pressure of the Lung

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ABSTRACT

The effects of alveolar and pleural pressures on pulmonary interstitial pressure were studied in 36 anesthetized dogs by application of Starling's law of transcapillary exchange. Fluid accumulation in the lung was produced by increasing left atrial pressure to levels always higher than alveolar pressure and by hemodilution with saline. Using a lung divider, a difference in alveolar pressure of from 5 to 14 mm Hg was achieved between the two sides in 24 dogs. Increased alveolar pressure did not reduce the rate of fluid accumulation, indicating its lack of effect on interstitial pressure. A relationship between the rate of fluid accumulation and the forces in the Starling equation was demonstrated when pleural pressure was included as an index of interstitial pressure. The rate of fluid accumulation increased markedly when interstitial pressure exceeded atmospheric. Fluid accumulation was considerably less in lobes statically inflated with plasma than in contralateral lobes ventilated with air (6 dogs); this difference could not be attributed to static inflation as opposed to ventilation (6 dogs). These findings suggest that surface tension opposes the transmission of alveolar pressure to the interstitial space. The interstitial pressure, as measured by application of Starling's law, acts on the small vessels within the alveolar-capillary membrane.

ADDITIONAL KEY WORDS

Starling's law, surface tension, alveolar pressure, interstitial compliance, pleural pressure, pulmonary edema, plasma inflation, static inflation

Estimates of the interstitial pressure of the lung based on the application of Starling's law to the movement of fluid in the lungs have indicated that the pressure surrounding the fluid-exchanging vessels of the lung is normally about 9 mm Hg less than atmospheric pressure (1). A similar value for pulmonary interstitial pressure based on measurements in chronically implanted capsules has been obtained by Guyton (2).

How the different forces in the lung interact to set the interstitial pressure at this level is not entirely clear. Several studies dealing with the effect of alveolar pressure on pulmonary vascular volume (3-6) and resistance (7-12) have led to the general conclusion that the interstitial pressure surrounding the smaller blood vessels of the lung varies directly with alveolar pressure (12) but may be lower than alveolar pressure as the result of surface tension at the alveolar air-liquid interface (13-15). Agostoni, who was concerned with the effects of pleural pressure on the small blood vessels at the surface of the lung, concluded that the interstitial pressure surrounding the fluid-exchanging vessels on the surface of the lung is equal to the pleural fluid pressure and is of the order of -7 to -13 mm Hg (16, 17). This pleural fluid pressure is generated by the balance of hydrostatic and colloid osmotic pressures across the fluid-exchanging vessels on the surface of the
lungs and differs from the pleural surface pressure which is generated by the elastic forces of the lung and chest wall (17). Whether the interstitial pressure at the surface of the lung has the same value and the same determinants as interstitial pressure surrounding the fluid-exchanging vessels within the lung is uncertain for two reasons: (1) pleural pressure over the surface of the lung is not uniform (18, 19), and (2) how pleural pressures are modified within the lung parenchyma is unknown.

The object of the present experiments was to study the effect of alveolar and pleural pressures on the interstitial pressure surrounding the fluid-exchanging vessels of the lung. This involved the application of Starling's equation of transcapillary exchange to the lung. The equation was used in the following form:

\[ F = k (P_c - \pi_{pl} + P_{ct} + \sigma) \]

where \( F \) = fluid flux (ml/sec cm²), \( k \) = filtration coefficient (ml/sec cm² mm Hg), \( P_c \) = capillary hydrostatic pressure (mm Hg), \( \pi_{pl} \) = osmotic pressure of blood plasma (mm Hg), \( P_{ct} \) = interstitial fluid pressure (mm Hg), and \( \sigma \) = osmotic pressure of interstitial fluid (mm Hg).

**Methods**

**GENERAL**

In 36 closed-chest dogs anesthetized with pentobarbital, 25 mg/kg, right and left heart catheterization was performed and catheters were positioned under fluoroscopic control in the pulmonary artery, the left atrium, the right atrium, and the aortic arch. Vascular pressures were measured by Statham P23Db strain gauges positioned at the level of the catheter tips as determined by fluoroscopy. The basic preparation was similar to that previously reported (1, 20). Transudation of fluid into the lung was produced by the combination of inflating a balloon in the left atrium and infusing isotonic saline intravenously. Left atrial pressure (\( P_a \)) was measured from the end-hole of the balloon catheter and was used as a measure of pulmonary capillary pressure (1). In general, the intravenous infusion of 1 to 2 liters of isotonic saline in the first 5 to 10 minutes increased left atrial pressures to more than 20 mm Hg. Left atrial pressure was not only held steady, but was also kept higher than alveolar pressure during the remainder of the 2 hours of the study by regulating the speed of the infusion; the usual infusion rate was 50 to 60 ml/min. This also resulted in mean right atrial pressures above 10 mm Hg in all experiments.

Blood samples were drawn from the aorta during the control period, after 5 minutes of infusion and then at half-hour intervals for the measurement of the osmotic pressure of the plasma proteins (\( \pi_{pl} \)). This measurement was made either directly by means of a Hepp-Brown osmometer or calculated from the equations of Landis and Pappenheimer (21) which had been shown by previous observation in this laboratory to be applicable to the present experimental conditions (1). During the first 5 to 10 minutes of saline infusion the osmotic pressure of the plasma proteins fell to 10 mm Hg or less. The subsequent decrease in colloid osmotic pressure was more gradual, the final value at the end of the 2 hours of saline infusion ranging from 2 to 7 mm Hg.

At the end of each experiment the animals were exsanguinated, the blood was allowed to drain from the cut ends of the pulmonary arteries and veins, and the water content of each lung was determined separately by weighing the entire lung before and after drying to constant weight. The quantity of fluid which accumulated during the experimental period was calculated for each animal as the difference between the water content at autopsy in grams of water per gram of dry lung and the water content of normal dog lung, previously shown to be 3.6 ± 0.2 so of water/g dry lung (1). The rate of fluid accumulation was then obtained by dividing this value by 2, the duration of each experiment in hours, and was expressed in grams of water per gram of dry lung per hour.

**SPECIAL PROCEDURES**

**Effect of Alveolar and Pleural Pressure.—**In 24 of the 36 dogs, a modified Carlens tube was used as a lung divider, so that alveolar pressure could be varied separately on the two sides. Pleural pressures were measured through balloon catheters inserted through specially designed trochars (18) into the left and right pleural spaces. Under the conditions of these experiments, in which fluid accumulated in the pleural space as well as in lung tissue, there is no difference between pleural liquid pressure and pleural surface pressure (17). By regulating the speed of the saline infusion, left atrial pressures were maintained at a constant level, which varied in different experiments from 15 to 25 mm Hg. Previous experiments in this laboratory (20) had shown that left atrial pres-
Mean resistance to airflow was found to be approximately the same during inspiration and expiration (20). Accordingly, the average mean airway pressure was assumed to equal the average mean alveolar pressure in the present study.

**Effect of Surface Tension.**—The contribution of surface tension to the interstitial pressure of the lungs was studied in 6 intact dogs by comparing the rate of fluid accumulation in one lobe in which the alveolar air-liquid interface was eliminated by static inflation with plasma with the rate of fluid accumulation in the contralateral lobe, which was ventilated with air. The basic preparation was the same as that outlined under general methods. Following the rapid infusion of isotonic saline, 200 ml/kg, 160 ml of blood was removed, the plasma separated by centrifugation, and the cells reinfused. Prior to inflation with plasma, the left lower lobe was isolated by means of a modified Carlens tube and was made atelectatic by occlusion of its airway after the animal had breathed oxygen for 30 minutes (22). By means of balloon inflation in the left atrium and saline infusion, the left atrial pressure was then increased over a 10-minute period until it exceeded 20 mm Hg. Since this also resulted in a reduction of the osmotic pressure of the plasma proteins to 10 mm Hg or less, the net intravascular force \( (P_v - \pi) \) favoring filtration exceeded 10 mm Hg. The mean airway pressure of the right lower lobe was maintained at the same level as the left lower lobe. In all 6 dogs the plasma-blue dye mixture was confined to the left lower lobe, and spectrophotometric examination of arterial blood samples collected during and at the end of the experiment failed to reveal any blue dye. The right lower lobe was removed and its water content was determined by weighing the entire lobe before and after drying to constant weight. The rate of fluid accumulation was then calculated as described above. The airway to the left lower lobe was tied off distal to the Carlens tube and the entire lobe was removed for weighing and drying. The fluid remaining in the Carlens tube was measured; this varied from 9 to 12 ml. The amount instilled into the lobe less the amount in the Carlens tube was subtracted from the wet weight at autopsy. The wet weight was further corrected by adding the weight of that volume of fluid which must have moved from the instilled plasma into the blood in order to account for any observed increase in total osmolality of the instilled plasma between the beginning and the end of the experiment. Thus, for example, in dog 73, 70 ml of plasma was used to inflate the left lower lobe. This fluid contained 304 milliosmols/liter at the beginning of the experiment and 323 milliosmols/liter at the end. The loss of 4.1 ml of water from the instilled plasma would account for this increase in osmolality. Accordingly, 4.1 g was added to the wet weight of the lung. This correction is based on the assumption that changes in the osmolality of the instilled plasma were due solely to the movement of water rather than to ion shifts. This assumption is supported by the evidence that the passage of water across the alveolar-capillary membrane is more rapid than sodium or other ions (33). The quantity of fluid which accumulated during the experimental period was then calculated as the difference between the corrected wet weight expressed in grams per gram of dry lung and 3.6 g/g dry lung, the water content of normal dog lung. The rate of fluid accumulation was then obtained by dividing this by 2, the duration of each experiment in hours, and was expressed in grams of water per gram of dry lung per hour.

To rule out any systematic difference in fluid accumulation which might arise from nonventilation of the plasma-filled lung, in 6 other dogs the rate of fluid accumulation in a lobe statically inflated with ambient air was compared with the contralateral lobe ventilated with ambient air. The airway to the left lower lobe

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was isolated by means of a modified Carlens tube and was occluded by a cork; air could be introduced or withdrawn from a side-arm distal to the occlusion. The right lung was ventilated with a Harvard pump. The mean airway pressure of the right lower lobe was maintained between 4 and 7 mm Hg by adjusting the volume and rate of the Harvard pump. The mean airway pressure in the occluded left lower lobe was held equal to that of the right lower lobe by adding or removing air by way of the side tap of the Carlens tube. In 5 of the 6 dogs the position of the Carlens tube was such that the left upper lobe ventilated with the right lung; in 1 dog the left upper lobe was atelectatic.

Results

EFFECT OF ALVEOLAR AND PLEURAL PRESSURE

Four experimental protocols were used (Fig. 1) to test the effect of different alveolar and pleural pressures on the interstitial pressure of the fluid-exchanging vessels. The levels of airway and pleural pressure achieved by these different experimental arrangements are shown in Table 1 and are summarized in Figure 1.

A. Closed-Chest Spontaneously Breathing Dogs.—One bronchus (lung L) was connected to a chamber maintained at subatmospheric pressures ranging from −5 to −12 mm Hg by a duoseal vacuum pump (Welch Scientific Co., Model 1400); the mean airway pressure of this lung was −9.3 (SE = 1.1), and the mean pleural pressure was −3.0 (SE = 1.1). The other bronchus (lung H) opened to ambient pressure; the mean airway pressure was zero and the mean pleural pressure was −2.8 mm Hg (SE = 0.6). The swings in airway pressure during the experiment and the absence of atelectasis at autopsy indicated that lung L was ventilating.

B. Closed-Chest Dogs Ventilated by Constant-Volume Pumps.—Each lung was ventilated by a separate Harvard pump. An expiratory resistance to one bronchus (lung H) was produced by connecting the expiratory limb of the pump to a tube, the end of which was maintained under water; the mean airway pressure of this lung was 16.8 mm Hg (SE = 0.2) and the mean pleural pressure was 3.0 mm Hg (SE = 0.6). The other bronchus (lung L) opened to ambient pressure during expiration; the mean airway pressure was 5.7 mm Hg (SE = 0.5) and the mean pleural pressure was 2.2 mm Hg (SE = 0.8).

C. Closed-Chest Spontaneously Breathing Dogs in a Body Plethysmograph.—The dog was enclosed in a body plethysmograph (24) after all catheters had been placed. The plethysmograph lid contained special adaptors so that vascular, pleural, and airway pressures could be monitored throughout.

![Figure 1](http://circres.ahajournals.org/)

*FIGURE 1*

The four experimental preparations used to vary alveolar and pleural pressures; level of airway and pleural pressures achieved is shown below. See text for description.
All measurements were made relative to ambient pressure. The vacuum pump was adjusted to maintain pressure in the plethysmograph at subatmospheric levels ranging from $-6$ to $-11$ mm Hg. One bronchus (lung L) was exposed to plethysmographic pressure; the mean airway pressure was $-9.8$ mm Hg ($\sigma = 0.8$) and the mean pleural pressure was $-6.0$ (SE = 1.0). The other bronchus (lung H) was exposed to ambient pressure; the mean airway pressure was zero and the mean pleural pressure was $-5.5$ mm Hg (SE = 1.0). The presence of swings in airway pressure during the experiment and the absence of atelectasis at autopsy indicate that lung L was ventilating. By providing a small leak of air into the plethysmograph from the outside in conjunction with the constant suction by the vacuum pump, fresh air was made to circulate in the plethysmograph and CO₂ accumulation did not occur. The effect of procedure C on the relationship between airway and pleural pressures is similar to that of procedure A except that the lower pressure produced around the body by procedure C resulted in lower pleural pressures.

D. Open-Chest Dogs Ventilated by Constant-Volume Pumps.—Each lung was ventilated by a separate Harvard pump. Different expiratory resistances were produced on the two sides by connecting the expiratory limbs of the pumps to tubes, the ends of which were submerged to different levels. The mean airway pressure of lung H was 18.5 mm Hg ($\sigma = 0.2$) and the mean pleural pressure was zero. The mean airway pressure of lung L was 6.1 mm Hg (SE = 0.3) and the mean pleural pressure was zero. With respect to the relationship between airway and pleural pressures, procedure D was similar to procedure B except that the pleural pressure was lower in procedure D because the chest was open bilaterally.

The right lung was exposed to the lower airway pressure in half of the 24 experiments and the left lung in the other half. Since the results were not affected by which side was exposed to the higher or lower airway pressure, for simplicity the results have been given in terms of lung H (lung under higher airway pressure) and lung L (lung under lower airway pressure).

Comparable levels of vascular and of plasma colloid osmotic pressures were obtained during the four procedures. Mean left atrial pressure for the four procedures ranged from 18.8 to 24.0 mm Hg. Mean plasma colloid osmotic pressure varied from 4.0 to 6.9 mm Hg. The intravascular force favoring filtration of fluid ($P_a - \pi_{pl}$) ranged from 13.9 to 17.1 mm Hg. The difference in airway pressure between the two lungs in any given animal varied from 5 to 14 mm Hg; the pleural pressure of the two lungs remained similar.

In Figure 2, the rate of fluid accumulation in lung H is compared to that in lung L for all 24 dogs. The line of identity is shown for reference. Nine points fall below and 15 above the line of identity. A t-test on the paired observations was performed and shows that the rate of fluid accumulation in lung H is significantly greater than that in lung L ($P < 0.01$).
In Figure 3, the rate of fluid accumulation in the closed-chest dogs is related to the intravascular and extravascular forces responsible for fluid movement. On the left, the rate of fluid accumulation has been plotted against the intravascular forces, namely, pulmonary capillary pressure minus plasma colloid osmotic pressure ($P_c - \pi_P$), disregarding the differences in pleural pressure induced in these experiments. There is a poor correlation ($r = 0.16; P > 0.05$). The plot on the right is similar but includes mean pleural pressure ($P_{PL}$) on the abscissa to test the idea that the interstitial pressure is related to pleural pressure. A significant relationship exists ($r = 0.75; P < 0.01$).

**EFFECT OF SURFACE TENSION**

Table 2 shows the results of the studies in which fluid accumulation in the left lower lobe statically inflated with either plasma (group I) or ambient air (group II) is compared with the contralateral lobes ventilated with ambient air. Mean right and left airway pressures were equal in each experiment and varied from 6 to 8 mm Hg in group I and from 4 to 7 mm Hg in group II. In Figure 4, the rate of fluid accumulation in the left lower lobe is compared to that in the right lower lobe. The difference in the rate of fluid accumulation between the right and left lower lobes in group II was very small in all experiments but was significant ($0.05 > P > 0.01$). On the other hand, in group I the rate of fluid accumulation was considerably less in the left lower lobes statically inflated with plasma than in the contralateral lobes ventilated with ambient air ($P < 0.01$). The difference in the
TABLE 1
Summary of Experiments Comparing Fluid Accumulation in Lungs Exposed to Different Airway Pressures

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<th>Dog</th>
<th>Wt (kg)</th>
<th>Mean blood pressures (mm Hg)</th>
<th>Mean plasma colloid osmotic pressure (eone)</th>
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<th>Rate of accumulation of lung water (g/g dry lung/hr)</th>
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B. Closed-Chest Dogs Ventilated by Constant-Volume Pumps

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C. Closed-Chest Spontaneously Breathing Dogs in a Body Plethysmograph

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D. Open-Chest Dogs Ventilated by Constant-Volume Pumps

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PA = pulmonary artery; LA = left atrium. Lung H is the lung under higher airway pressure, and Lung L is the lung under lower airway pressure.
rate of fluid accumulation between the left and right lower lobes in group I was significantly greater than in group II ($P < 0.01$).

**Discussion**

In the present study, the Starling equation for transcapillary exchange was used as the basis for comparing the effects of alveolar pressure and of pleural pressure on the interstitial pressure of the lungs. By using one lung as a control for the other, the same intravascular forces ($P_c - P_{et}$) could be assumed to be operating bilaterally despite wide differences in airway pressures on the two sides. This assumption is based on the observations that (1) mean left atrial pressures were consistently above the alveolar pressure of both sides, thereby excluding "waterfall" or "sluice" effects in the lungs (10, 11), and (2) the difference between pulmonary arterial and left atrial pressure was relatively small (of the order of 7 mm Hg) in the presence of a distended pulmonary vascular bed, and this makes it unlikely that there could be a significant difference between the pressures of the small blood vessels of the two lungs.

Several other reasonable assumptions were involved in this comparison. The filtration coefficient was assumed to be constant, on the basis of the theoretical considerations of Landis and Pappenheimer (21) and previous experiments with the same preparation (1). The lymphatic drainage was discounted as a significant variable because right lymphatic duct obstruction did not affect the rate of fluid accumulation during acute experiments (1), and the mean right atrial pressure was elevated above 10 mm Hg in the present experiments, opposing lymph drainage from any route. The colloid osmotic pressure of the interstitial fluid proteins was discounted as a significant variable in these experiments for two reasons: the albumin and globulin concentrations of the plasma were very low as a result of hemodilution, and pleural and alveolar fluid collected at the end of a number of these experiments had an even lower protein concentration than the plasma (Table 3). If the protein concentration of the interstitial fluid approximated that of alveolar and pleural fluid in these experiments, the colloid osmotic pressure of the interstitial fluid would be about 3 mm Hg. This value is of the same order of magnitude as that estimated for normal pulmonary interstitial fluid (1). From these considerations, a difference in the rate of fluid accumulation between the two lungs was considered to depend on differences in interstitial pressures.

**EFFECT OF ALVEOLAR AND PLEURAL PressURES**

The failure of an increase in airway pressure to reduce the rate of fluid accumulation indicates that under the conditions of the present experiments an increase in alveolar pressure did not increase the interstitial pressure of the vessels involved in fluid exchange. These findings are in agreement with those of Wagner et al. (25), who demonstrated that the rate of fluid accumulation into the isolated canine lung was not influenced by variations of the airway pressure (static or intermittent) or by collapse of the lung. On the other hand, the results of studies by others, in which interstitial pressure has been evaluated on the basis of changes in vascular volume (3-6) or resistance (7-12), have led to the conclusion (12) that the pressure surrounding the small blood vessels of the lung ("alveolar vessels") varies directly with alveolar pressure. In the latter studies, alveolar pressure compressed small blood vessels only when it exceeded pulmonary venous pressure. Thus, oppor-

<table>
<thead>
<tr>
<th>Protein Concentration in Blood Plasma, Pleural Fluid and Alveolar Fluid</th>
<th>Plasma</th>
<th>Pleural fluid</th>
<th>Alveolar fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/100 ml)</td>
<td>1.1</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Globulin (g/100 ml)</td>
<td>1.0</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Values are averages for 10 experiments.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
tunity for collapse of the small pulmonary vessels did not exist in our experiments since, by experimental design, left atrial pressure was consistently higher than alveolar pressure. We did not study the movement of fluid in the lung when alveolar pressure exceeded left atrial pressure because under this condition it would have been impossible to know what value to use for pulmonary capillary pressure in the Starling equation.

There are at least two possible explanations for the unexpected trend for more fluid to accumulate in the lungs subjected to higher airway pressures. (1) The interstitial pressure of the fluid-exchanging vessels may decrease with increasing alveolar pressure. Although evidence has been provided that interstitial pressure surrounding large blood vessels decreases as alveolar pressure increases, the opposite effect presumably occurs around the small blood vessels (5, 6). (2) The alveolar capillary surface available for fluid exchange may increase with lung inflation.

Although previous experience with the basic preparation used for these experiments provided evidence that the filtration coefficient remains constant (1), the effects of differences in the degree of lung inflation on fluid movement were not examined. To distinguish between the effects of lung inflation and those of alveolar pressure on fluid movement would require that lung volume be held constant at different alveolar pressures. Since this can only be achieved by varying pleural pressure, interpretation of the results of such experiments would be extremely difficult.

Because of uncertainties with respect to changes in capillary geometry and volume with lung inflation, a precise calculation of the change in capillary surface area with lung inflation is not possible. However, using several simplifying assumptions, it is possible to estimate the change in capillary surface area with lung inflation and thus to compare the rate of fluid accumulation of the two lungs at comparable capillary surface areas (Appendix). When this is done the rate of fluid accumulation in the two lungs is similar (Fig. 5).

In a previous study (1), a nonlinear relationship was observed between the rate of accumulation of water in the lungs and the intravascular forces favoring fluid movement ($P_c - \pi_p$). This relationship was not observed in the present study. The difference seems attributable to the difference in the basic design of the experiments. Thus, in the previous study, in which pleural pressure was not varied deliberately, it could well have changed proportionally to the rate of water accumulation as the lungs became waterlogged and less compliant with time. On the other hand, in the present experiments in which pleural pressure was deliberately varied, it and the rate of water accumulation were dissociated.

However, when pleural pressure is included in the calculations as an index of interstitial pressure, the rate of fluid accumulation in the lung can be accounted for.
by the forces represented in the Starling equation. That interstitial pressure is not identical to pleural pressure in these experiments is indicated in Figure 6, which includes the observations illustrated in the right panel of Figure 3 plus other observations in spontaneously breathing dogs in which the intravascular force was smaller, i.e., $P_c - \pi_pl$ varied from $-12.8$ to $+4.4$ mm Hg (Table 4). In addition, the abscissa of Figure 6 now includes interstitial colloid osmotic pressure ($\pi_if$), which, as indicated above, is of the order of 3 mm Hg in these experiments. If interstitial pressure were identical to pleural pressure, one would expect to see an increase in the rate of fluid accumulation in Figure 6 when the pressure $(P_c - \pi_pl - P_{PL} + \pi_if)$ exceeds zero. The observation that an appreciable increase in the rate of fluid accumulation does not occur until the pressure exceeds $+9$ mm Hg suggests that the interstitial pressure may be as much as 9 mm Hg greater than pleural pressure at the point of inflection of the curve. Since the mean pleural pressure of those experiments to the left of the inflection of the curve was of the order of $-6$ mm Hg (Table 4), this suggests that appreciable quantities of fluid do not accumulate in the lung until the interstitial pressure exceeds atmospheric pressure. This agrees with Guyton's observations using implanted capsules: subcutaneous tissues had a low compliance at subcutaneous fluid pressures ranging from $-7$ to 0 mm Hg, and compliance increased markedly when interstitial pressure exceeded atmospheric pressure (26, 27); the interstitial pressure of the lung exceeded atmospheric pressure when pulmonary edema was induced (2). The abrupt increase in fluid accumulation as $P_c - \pi_pl - P_{PL} + \pi_if$ exceeds $+9$ mm Hg in the present experiments suggests that either the compliance of the interstitial tissues increases or fluid now accumulates in some other compartment, e.g., the alveolar spaces (28).

### Table 4

<table>
<thead>
<tr>
<th>Dog</th>
<th>Wt (kg)</th>
<th>Mean blood pressure (mm Hg)</th>
<th>Mean plasma colloid osmotic pressure (mm Hg)</th>
<th>Mean airway pressure (mm Hg)</th>
<th>Mean pleural pressure (mm Hg)</th>
<th>Rate of accumulation of lung water (g/g dry lung/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>18</td>
<td>22</td>
<td>12</td>
<td>7.5</td>
<td>0</td>
<td>-6</td>
</tr>
<tr>
<td>24</td>
<td>16</td>
<td>21</td>
<td>11</td>
<td>12.5</td>
<td>0</td>
<td>-6</td>
</tr>
<tr>
<td>25</td>
<td>20</td>
<td>12</td>
<td>4</td>
<td>16.4</td>
<td>0</td>
<td>-7</td>
</tr>
<tr>
<td>28</td>
<td>13</td>
<td>15</td>
<td>5</td>
<td>12.6</td>
<td>0</td>
<td>-4</td>
</tr>
<tr>
<td>29</td>
<td>14</td>
<td>16</td>
<td>5</td>
<td>15.2</td>
<td>0</td>
<td>-6</td>
</tr>
<tr>
<td>30</td>
<td>14</td>
<td>11</td>
<td>4</td>
<td>16.8</td>
<td>0</td>
<td>-6</td>
</tr>
<tr>
<td><strong>MEAN</strong></td>
<td></td>
<td>16.1</td>
<td>6.8</td>
<td>13.5</td>
<td>0</td>
<td>-6.0</td>
</tr>
<tr>
<td><strong>SE</strong></td>
<td></td>
<td>1.9</td>
<td>1.5</td>
<td>1.4</td>
<td>0</td>
<td>0.4</td>
</tr>
</tbody>
</table>

PA = pulmonary artery; LA = left atrium; LL = left lung; RL = right lung.

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EFFECT OF SURFACE TENSION

The failure of high airway pressures to decrease the rate of fluid accumulation suggests that the increase in alveolar pressure was not transmitted to the interstitial space surrounding the fluid-exchanging vessels. One force which could have counterbalanced the heightened alveolar pressure, thereby leaving the interstitial pressure unaffected, is the surface tension at the alveolar air-liquid interface. The observation that fluid accumulation was considerably greater in the air-filled lobe than in the contralateral plasma-filled lobe supports this view. That the absence of ventilation was not the cause for the decreased rate of fluid accumulation in the plasma-inflated lobes is indicated by the observation that there was very little difference in fluid accumulation between lobes statically inflated with ambient air and contralateral lobes ventilated with ambient air (Fig. 4).

Although the possibility exists that increases in the total osmolality of the circulating blood plasma during the experiment accounted for the decrease in the rate of fluid accumulation in the plasma-filled lobes, this possibility seems unlikely for two reasons: (1) the weight of the volume of water that would account for increases in the total osmolality of the plasma in the plasma-filled lobe was included in the calculation of the rate of fluid accumulation, and (2) in two experiments (dogs 77 and 78) in which the total osmolality of the plasma used for inflation exceeded that of the circulating blood plasma, the rate of fluid accumulation in the left lower lobe was also decreased.

SITE OF INTERSTITIAL PRESSURE AS DETERMINED BY STARLING'S LAW

Observations on edematous lungs by light microscopy have demonstrated that fluid accumulates in the interstitial tissues around larger blood vessels and airways (28, 29) before fluid enters the air spaces. These findings raise the possibility that fluid may be filtered directly through the walls of the large pulmonary vessels. However, two lines of evidence favor the conventional view that fluid is filtered predominantly at the level of the alveolar vessels, and then traverses the tissue spaces around the larger vessels and airways as it progresses along drainage pathways toward the systemic veins. First, electron microscopic observations of lungs in which hemodynamic pulmonary edema has been produced in the same manner as in the present experiments (30) have demonstrated that fluid accumulates between the basement membranes of the capillary endothelium and the alveolar epithelium in the portions of the alveolar-capillary membrane containing collagen bundles (Fig. 7). However, further studies are needed to ascertain the sequence of fluid accumulation in the various anatomic subdivisions of the interstitial space. Second, in lobes inflated with plasma, a maneuver which should raise the interstitial pressure only at the level of the small pulmonary vessels, the rate of fluid accumulation was less than in the contralateral air-filled lobes. If the pressure surrounding the larger vessels and airways were a major determinant of fluid filtration, either by direct effect on the transmural pressure of the larger blood vessels or by direct fluid continuity with the interstitium of the alveolar-capillary membrane, one would have expected a greater rate of fluid accumulation in the plasma-filled lobes because at any given alveolar pressure, lung inflation is greater in fluid-filled lungs than in air-filled lungs and the pressure surrounding the larger blood vessels is thought to decrease with lung inflation (5, 6), and because the large, extra-alveolar vessels would not be expected to be appreciably affected by the changes in alveolar surface tension produced by inflation with plasma (12). On the other hand, the decrease in the rate of fluid accumulation noted in the plasma-filled lobes suggests that the interstitial pressure in the alveolar-capillary interfaces is a major determinant of fluid filtration in the lung and that this pressure is higher when the alveolar air-liquid interface is eliminated. Thus, the interstitial pressure as measured by application of Starling’s law to the pul-
Electron micrograph of a normal dog lung (top) and one in which hemodynamic pulmonary edema has been produced in the same manner as the present experiments (bottom). ALV = alveolar space, CAP = capillary, E = erythrocyte, and IS = interstitial space between the basement membranes of the capillary endothelium and the alveolar epithelium. During edema formation, fluid accumulated in the portions of the interstitial space containing collagen bundles.
defined by Starling. Because there is a net absorptive force under normal conditions, this pressure is subatmospheric (1, 2). Also, under normal conditions, the interstitial fluid pressure can remain lower than alveolar surface pressure because of the retractive force of the alveolus, as modified by surface tension. How surface tension modifies the retractive force under normal conditions, as well as during the formation of pulmonary edema, remains unknown because of uncertainties as to the precise geometry of the alveolar surface and the width of the fluid lining this surface. The failure to demonstrate an increase in interstitial fluid pressure with increasing alveolar pressure in the present experiments suggests that under conditions promoting the accumulation of fluid in the lung, the predominant curvature of the alveolar air-liquid interface is concave to the alveolar lumen so that surface tension would oppose the transmission of alveolar surface pressure to the interstitial fluid.

Appendix

The change of surface area of the pulmonary capillaries due to inflation of the lungs from a volume $V_1$ (lung L) to a volume $V_2$ (lung H) is here estimated on the basis of a constant pulmonary capillary blood volume. Although the exact change in the geometry of the capillaries with lung inflation is unknown, it is likely that the change in capillary blood volume is small under the conditions of the present experiment because left atrial pressure is held well above alveolar pressure.

Considering a single segment of capillary to be a circular cylinder whose length and radius are altered due to inflation, let

\[ v_1 = \pi r_1^2 l_1 = \text{volume of the capillary segment at lung volume } V_1 \]

\[ v_2 = \pi r_2^2 l_2 = \text{volume of the capillary segment at lung volume } V_2 \]

where $r_1$, $r_2$, and $l_1$, $l_2$ are the radii and lengths of the capillary segment at lung volumes $V_1$, $V_2$ respectively.

The surface areas of the capillary wall at lung volumes $V_1$, $V_2$ are $S_1 = 2\pi r_1 l_1$ and $S_2 = 2\pi r_2 l_2$.

If the blood volume is constant, then $v_1 = v_2$ and hence

\[ r_1^2 l_1 = r_2^2 l_2. \]

The ratio of $S_1$ to $S_2$ is

\[ \frac{S_2}{S_1} = \frac{r_2 l_2}{r_1 l_1}. \]

Solving equation (1) for $r_2^2/r_1$ and substituting into equation (2) leads to

\[ \frac{S_2}{S_1} = \left( \frac{l_2}{l_1} \right)^{1/2}. \]

It is now assumed that the length of any capillary varies as the cube root of the lung volume, i.e.,

\[ l_2 \left/ l_1 \right. = \left( \frac{V_2}{V_1} \right)^{1/3}. \]

Equation 4 is exactly fulfilled if the configurations of the vascular networks at volumes $V_1$ and $V_2$ are geometrically similar so that all dimensions along the axes of capillaries are extended by the same percentage. Substituting equation 4 into equation 3 gives

\[ \frac{S_2}{S_1} = \left( \frac{V_2}{V_1} \right)^{1/6}. \]

The lung volumes $V_1$ and $V_2$ are approximated using the lung volumes and pressure-volume characteristics of a group of dogs with comparable amounts of pulmonary engorgement and edema (20). In this group of dogs, the mean functional residual volume was 34.3 ml/kg and the pulmonary compliance was 2.3 ml/mm Hg/kg. Using these values, the volumes of lung L and lung H can be calculated. The ratio of the surface areas of the two lungs can then be derived by equation 5. Although we have probably overestimated the volume of lung H at very high lung volumes and lung L at very low lung volumes because of the sigmoid shape of the pressure-volume curve of the lung, this would have only a very small effect on the calculated ratios of the surface areas of the two lungs because this ratio is derived...
INTERSTITIAL PRESSURE OF THE LUNG

from the one-sixth power of the ratio of lung volumes.

When the rate of fluid accumulation in lung H is corrected for the increase in capillary surface area due to lung inflation by dividing it by the ratio of surface area of lung H to lung L, there is no significant difference in the rate of fluid accumulation of the two lungs (Fig. 5) \( P > 0.05 \).

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References


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