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Distribution of Interstitial Compliance and Filtration Coefficient in Canine Lung

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Summary

Utilizing a modification of the isogravimetric methodology, we have estimated the perivascular interstitial compliance and filtration coefficient in the canine lung. These values averaged 1.8 g/cm H_2O and 34 (g/h)/cm H_2O, respectively, per 100 g lung wet weight. By studying lungs at both low and high states of inflation (where the alveolar septae are collapsed) we were also able to determine the spatial distribution of both the interstitial compliance and filtration coefficient. We estimate that of the above total interstitial compliance a maximum of 55% is around alveolar septal vessels, 20% around extra-alveolar arteries and 25% around extra-alveolar veins. Of the above total filtration coefficient, 50% represents filtration from alveolar septal vessels, 23% from extra-alveolar arteries, and 27% from extra-alveolar veins. Our results imply that there are finite interstitial compliances communicating with all permeable vessels. Significant pressures can be built up in these spaces, thereby acutely limiting the further formation of interstitial edema.

Introduction

Under conditions where there is fluid filtration into the lung the nature of the interstitial space into which the filtered fluid accumulates must have a direct effect on the rate of fluid filtration. For example, if the interstitial space is relatively stiff, little fluid will accumulate before a significant back pressure opposing filtration is built up. Although there have been estimates of the interstitial compliance in systemic tissues (1), such estimates for the pulmonary interstitium are limited (2, 3). There are several reasons why the lung is a particularly difficult organ in which to obtain this important information. The lung may contain several distinct interstitial compartments, surrounding alveolar septal vessels, small non-septal arteries and veins (including so-called corner vessels), and around the larger extra-alveolar vessels and bronchi. Indeed it is in this latter region where fluid appears to accumulate (4, 5), even though leakage directly from these larger vessels is unlikely. Also complicating the situation is the fact that the lung changes in both size and stiffness as it is inflated, and if the inflation is high enough, the alveolar septal vascular space can be completely collapsed. In the present study, we have devised a method by which we can estimate the pressure-volume relationship of the interstitial space in canine lung lobes under conditions of high (Zone I) and low (Zone III) states of lung inflation. The method allows us to partition the interstitial compliance into regions surrounding alveolar septal vessels and regions surrounding the leaky extra-alveolar arteries and veins. It also yields information regarding perivascular fluid pressures and regional filtration coefficients. Our results suggest that the interstitial compliances surrounding the permeable vessels are sufficiently small to limit fluid build-up in acute conditions by increasing the local interstitial pressure.

Methods

Pentobarbital anesthetized (25–30 mg/kg) dogs were rapidly exanguinated and the thorax opened. The left lower lobe was isolated and

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artery, vein and bronchus were cannulated. With care to avoid introduction of air, the deflated lobe was flushed at low pressure (5 cm H_2O above the top of the lobe) with 300 ml of dog plasma. The plasma-filled artery and vein were both connected to a common plasma-filled reservoir. Two 4 cm diameter foam pads were pasted to the flat posterior surface of the lobe, and the lobe was then suspended from a weight transducer (Grass Model FT-03) by attachment to these pads. The lobe was hung in such a manner with the hilum dependent and was carefully adjusted to minimize the vertical height of the lobe. Hung in this manner the height was kept to 5–6 cm.

Since the artery and vein are connected to the same reservoir there is no flow in these lobes, and thus, at any given vertical height the vascular pressures are everywhere the same. The state of lung inflation was held fixed by connecting the bronchial cannulae to a controlled constant air pressure source. Vascular pressures were measured in both the arterial and venous cannulae via catheters, with the catheter tips placed near the hilum, and connected to Statham strain gauges. Vascular pressures were referenced to the bottom of the lobe, and were recorded along with lobe weight on a Grass polygraph.

Values of interstitial compliance and filtration coefficient reported here are expressed as per 100 g initial wet weight of the lung. The total initial wet weight was determined at the start of each experiment with the vasculature drained to pressure of -5 cm H_2O. At the end of each experiment the net weight of the plasma filled cannulae and tubing was determined, and then subtracted from the total initial wet weight to obtain the initial lung wet weight.

Protocol

Low Lung Inflation

The experimental protocol is based on the following observation. We find that if we initially set the transpulmonary pressure, Ptp, at 4 cm H_2O and the common intravascular pressure, Piv, at 10 cm H_2O, within 10–20 min the lobe reaches a stable weight or isogravimetric condition. From this state we now increase the Piv to 25 cm H_2O as shown in the left side of Fig. 1. We observe the typical bi-phasic response in the lobe weight, where it is assumed that the initial rapid transient is intravascular volume change and the slower change in weight is fluid filtration into the interstitial space. The slow change in weight is not quite linear, but as the first approximation we draw a line which represents the average filtration rate between 20 sec to 1 min following the step change in vascular pressure. This separation of vascular and interstitial volume change is central to our method, and to the extent that intravascular volume changes occur after 20 sec our technique will overestimate filtration coefficients and interstitial compliances. We chose to limit our periods of filtration to 1 min in order to limit the amount of volume filtered. In this way we can increase the interstitial fluid volume in small discreet steps rather than by continuous filtration. This allows us to examine the changes associated with the acute filtration

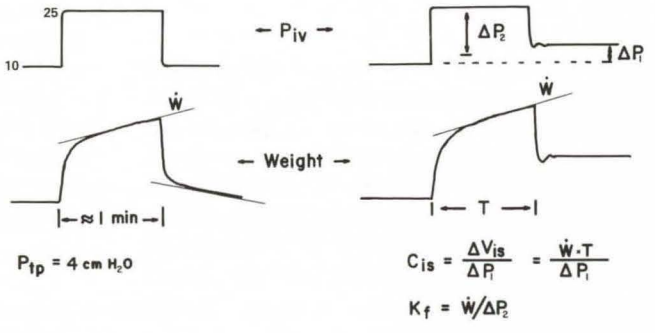

Fig. 1 Sample chart record illustrating the observations on which the method is based. Piv = intravascular pressure in cm H_2O, Cis = interstitial compliance, Kf = membrane filtration coefficient, $\dot{W}$ = rate of weight gain used to estimate rate of filtration, ΔVis = change in interstitial volume, T = filtration time interval, ΔP_1 = change in intravascular isogravimetric pressure, ΔP_2 = average filtration pressure gradient during interval T

process in more detail. Although this technique for estimating rates of fluid filtration has been widely utilized in numerous organs including the lung (6, 7, 8), its legitimacy has recently been challenged (9, 10, 11). We shall discuss this matter in more detail later.

Having determined the filtration as mentioned, we now lower the Piv back to the control value of 10 cm H_2O and observe a similar weight response in the opposite direction. This observation has been made by others (12, 13), but attention has not been focused on its significance. Why does fluid continue to filter back out of the lung? During the period of inward filtration there must have been either an alteration in the colloid osmotic gradient or an increase in interstitial fluid pressure. Assuming the latter to be the case, we were able to evaluate the change in this interstitial back pressure by a slight modification of this procedure.

Instead of returning the Piv to control, we manually adjust it to a level which re-establishes the constant weight condition. This is illustrated in the right half of Fig. 1. We found this new isogravimetric pressure to be always above the control value. From the change in isogravimetric Piv we then can estimate an interstitial compliance and filtration coefficient as follows. We calculate the interstitial volume change (ΔVis) simply by multiplying the average filtration rate by the time interval over which the filtration occurs. Dividing this by the change in isogravimetric Piv (ΔPisog) gives us a minimal estimate of interstitial compliance (i.e., Cis = ΔVis/ΔPisog). It is a minimal estimate because we assumed a relatively constant colloid osmotic gradient.

To the extent that intravascular protein is concentrated or interstitial protein is diluted, then the true change in interstitial fluid pressure will be less than the change in isogravimetric pressure. The limitation of this estimate will be discussed later. The filtration coefficient is calculated by dividing the filtration rate by the pressure gradient which causes the filtration. In this case the gradient is 15 cm H_2O immediately after increasing the Piv from 10 to 25, but the gradient falls to 25 minus the new isogravimetric pressure after the period of filtration. Since we have estimated the average filtration rate, we utilize the average of the initial and final filtration pressure gradients. These calculations are illustrated in Fig. 1.

This entire procedure is then repeated several times. That is, from the new isogravimetric pressure level, we again increase the Piv to 25, allowing additional fluid to be filtered, and then lower the Piv back to that value required to establish isogravimetric conditions. Fig. 2 shows an actual chart record of one such sequence. Note that following each increment of filtration caused by the elevation of Piv to 25, the Piv required for isogravimetric conditions increases progressively, up to 22 cm H_2O in this case. Note also that with each positive increment in isogravimetric Piv, the filtration rate which occurs with the Piv at 25 is progressively reduced. This is clearly shown by the progressively decreasing slope of the weight response. Following this sequence of increasing pressure increments, the procedure is then reversed and we examine decreasing pressure changes.

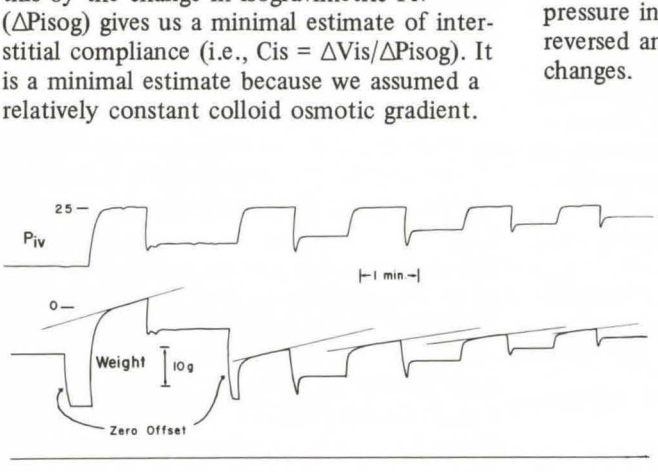

Fig. 2 Chart record showing progressive increments in the isogravimetric intravascular pressure following repeated periods of filtration. Note also the progressively decreasing filtration rate (see text)

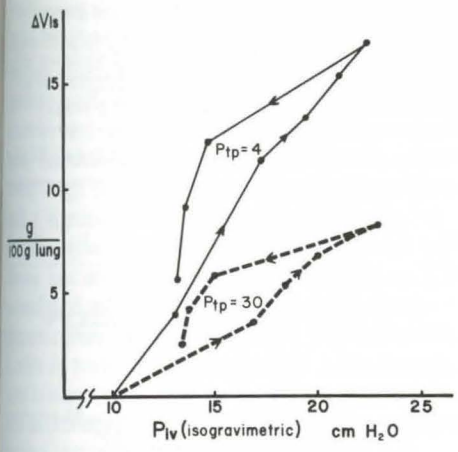

Fig. 3 Graph of isogravimetric intravascular pressure vs. the change in interstitial volume for the same lung as in fig. 2. Shown are the curves for both low and high lung inflation (transpulmonary pressure, Ptp = 4 and 30 cm H_2O, respectively). Arrows indicate direction of pressure changes

By determining the change in interstitial volume at each increment in isogravimetric pressure, we can thereby plot part of the interstitial pressure volume curve. Fig. 3 shows this for the same lobe as in Fig. 2. Since we do not know the absolute level of the interstitial fluid volume in our control state, we can only plot relative changes in interstitial volume. We plot these volume changes against changes in the isogravimetric Piv. As will be discussed later these pressures should approximate the interstitial fluid pressures.

The non-linear shape shown in Fig. 3 is typical of all lobes studied. That is, the curves are reasonably linear for increasing pressure increments, but reproduceably non-linear for decreasing pressure increments. This non-linearity may reflect the non-linearity in lung parenchymal pressure-volume characteristics. A similar hysteresis and non-linearity has also been shown for the systemic interstitial spaces (24). The compliance values for interstitial compliance which we report are averages taken only for increasing pressure increments. For consistency this was also done for the filtration coefficients.

High Lung Inflation

Following the above pressure-volume cycle the lobes were all brought back to a Piv of 10, and the transpulmonary pressure increased to 30 cm H_2O in order to collapse the alveolar septae and isolate the arterial and venous beds. After a stabilization period to re-establish the isogravimetric state the entire sequence of vascular pressure changes was repeated. In 7 of the 12 lobes (Group I) the vascular pressure was increased equally in both the arterial and venous sides. In the remaining 5 (Group II) one side was clamped off after completing the protocol at low lung inflation. The sequence of pressure changes was then done on the other vasculature which was still connected to the reservoir. In this manner the arterial and venous vasculatures were studied separately in five lobes.

Under the conditions of high lung inflation we insured that the alveolar septal capillaries were completely collapsed by examining the pressure records obtained for each vasculature. If there was no change in pressure in one side when the pressure in the opposite side was increased, we concluded that there was no significant communication between the arterial and venous regions. In some lobes, lung inflation could not eliminate all arterial-venous communication, and these lobes were not included in the analysis.

Having thus determined the total extra-alveolar and venous interstitial compliance and filtration coefficients (either together, Group I, or separately, Group II), we could then estimate the alveolar septal fraction simply by subtracting these values from the total value found at low inflation. This subtraction is valid only if lung inflation has little direct effect on the measured parameters (see discussion).

Results

Inflating the lung to 30 cm H_2O always resulted in a significant reduction in interstitial compliance. As can be seen in Fig. 3 the general shape of the pressure-volume curves are similar; that is, there is a relatively linear portion for increasing pressures and a non-linear portion for decreasing pressures. Although the results shown in Fig. 3 are from a Group I lung, the curve shape was still similar (though further reduced in slope) when arterial

Tab. 1 Average (± s.e.m.) data of group II and groups I and II combined for total vasculature interstitial compliance and filtration coefficient, $Cis,_T$, $Kf,_T$: combined extra-alveolar interstitial compliance and filtration coefficient, $Cis,_{EA}$, $Kf,_{EA}$; and separate extra-alveolar arterial and venous interstitial compliance and filtration coefficient, $Cis,_{EAA}$, $Kf,_{EAA}$ and $Cis,_{EAV}$, $Kf,_{EAV}$, respectively. Units for all compliances are g/cm H_2O per 100 g lung, and units for all filtration coefficients are (g/h)/cm H_2O per 100 g lung

Group	$Cis,_T$	$Cis,_{EA}$	$Cis,_{EAA}$	$Cis,_{EAV}$	$Kf,_T$	$Kf,_{EA}$	$Kf,_{EAA}$	$Kf,_{EAV}$
I & II	1.8 ± 0.3	0.9 ± 0.2			34 ± 8	16 ± 4		
II	1.7 ± 0.5	0.75 ± 0.2	0.3 ± 0.1	0.45 ± 0.15	36 ± 9	18 ± 5	8 ± 3	10 ± 3

or venous regions were examined separately (Group II).

The average results are summarized in Table 1. Values for both groups I and II are averaged together for the total compliance and filtration coefficient at low lung inflation, and for the combined extra-alveolar compartment found at high lung inflation. Values for the 5 lobes in Group II are listed separately.

We found that the total extra-alveolar region comprises about half of the total filtration coefficient and slightly less than half of the total interstitial compliance. Of this extra-alveolar fraction, 23% of the filtration coefficient and 20% of the compliance was from the arterial side. The venous side contributed 27% of the filtration coefficient and 25% of the compliance. Statistical analysis (t-test) showed no significant difference ($p > 0.05$) difference between the arterial and venous compartments of the total extra-alveolar fraction. However, the total extra-alveolar fraction in each case was statistically different ($p < .01$) from the values for the entire lobe.

The fractional distribution of filtration coefficient and interstitial compliance are more clearly shown in the schematic diagram of Fig. 4.

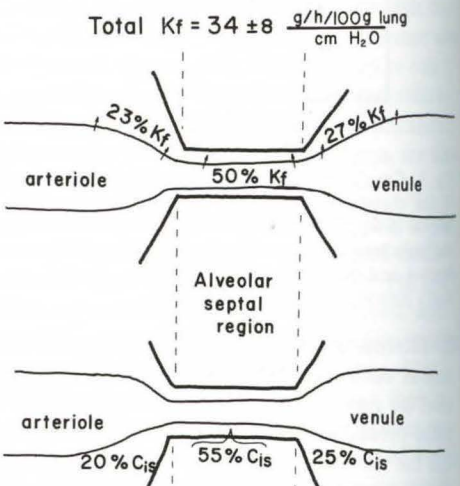

Fig. 4 Schematic diagram summarizing the fractional distribution of filtration coefficient and interstitial compliance between alveolar septal and extra-alveolar arterial and venous regions

Discussion

The information reported in this study may help to provide a more thorough understanding of the dynamics of pulmonary filtration and interstitial edema. However, our results and conclusions are based on several assumptions which must be examined more closely.

As a first approximation we have ignored the effects of potential osmotic buffering. To the extent that the interstitial protein concentration is decreased or intravascular protein is concentrated as fluid is filtered, then the true change in interstitial fluid pressure will be less than the change in isogravimetric pressure. This follows since part of the change in isogravimetric pressure will be accounted for by a change in the colloid osmotic pressure. Thus our estimate of the interstitial compliance will be a minimal estimate. It is difficult to determine the magnitude of our overestimate, but we think that it is small. Indeed this error will become negligible under two conditions: 1. where the interstitial protein is low and the membrane is impermeable to protein; 2. when

the interstitial protein is high and the membrane is highly permeable to protein. Although there is considerable controversy regarding both the concentration of interstitial protein and membrane permeability to protein, the consensus seems to indicate a relatively high interstitial protein concentration and a significant membrane permeability to albumin (i.e. $\sigma < 1$) (2, 7, 14). Recent evidence has also been presented indicating that in isolated perfused dog lobes, the colloid osmotic pressure gradient is very small (15). If this is true then we may also draw certain conclusions regarding the relation between the interstitial fluid pressure and the isogravimetric intravascular pressure (see below).

Our experimental method also requires that we can adequately separate intravascular volume change from the interstitial fluid filtration. Since we did not use any intravascular marker we were unable to know precisely when intravascular volume was no longer changing, but we assumed that beyond 20 sec we were measuring the change in interstitial volume. Evidence on this point is controversial. *Waaler* and *Aarseth* have recently stated that the intravascular volume changes occur mainly in the first 30 sec (16). Also *Kern* and *Wangensteen* recently re-examined this question with Cr^{51} labelled red blood cells (17). They found no detectable change in intravascular volume after the initial 10 sec. In our laboratory we have also studied the elastic properties of extra-alveolar blood vessels in situ by inflating them with air (18). Under these conditions where there is clearly no filtration the vascular stress relaxation is effectively finished in 15–20 sec. However, the validity of the gravimetric methodology has been questioned (9, 10, 11), and there has been some suggestion that even when the lung is not gaining weight, fluid filtration is occurring at the expense of intravascular fluid contraction (9, 10). Nevertheless we presently believe that the application of the method is useful for our purposes of estimating pulmonary interstitial compliance. To the extent that some of our fluid filtration is actually intravascular volume change, then our calculation of interstitial compliance will be an overestimate of the true value.

In determining the alveolar fractional distribution of both compliance and filtration coefficient, we have assumed that the magnitude of the extra-alveolar compartment is the same in both high and low states of lung inflation. We intuitively feel that the interstitial compliance around the extra-alveolar vessels ought to be reduced when the lung itself is stiffened by inflation. Indeed the extra-alveolar vessels demonstrate a decreased compliance as the lung is inflated (18). At the present time we have no way to estimate the direct effect of lung inflation on the extra-alveolar interstitial space and vascular membrane. If the effect of lung inflation is indeed to decrease the interstitial compliance, then our calculation of the alveolar fraction by subtraction of the extra-alveolar compartment from the total will result in an overestimation. This gives us a maximal upper limit for the alveolar septal interstitial compliance fraction.

In plotting the interstitial pressure-volume curve (fig. 3), the pressure which we used on the abscissa was the isogravimetric intravascular pressure. If we knew the relationship between this pressure and the interstitial pressure we could then plot the interstitial volume change against the actual interstitial hydrostatic pressure. One can argue that, under isogravimetric conditions, if the protein reflection coefficient is less than 1, then the isogravimetric intravascular pressure must equal the interstitial fluid pressure. This follows since if σ is less than 1 and the lung is constant weight, the colloid osmotic pressure difference across the permeable membrane must be 0. Thus, the fluid pressure difference must also be 0. If this is the case then under our control condition, the interstitial fluid pressure is 10 cm H_2O (relative to pleural pressure) and under our experimental protocol increased to as high as 23 cm H_2O.

This situation presents a conceptual problem. How can the lung maintain a 20 cm H_2O gradient between the interstitial space and pleural surface? There must be continuity between these regions since lymph can flow out of the lung, and even if the lymphatics are not pumping the lymphatic valves are in the wrong direction to sustain this pressure gradient.

One possible mechanism by which this interstitial pressure could be maintained is to assume a two compartment interstitial space. One compartment (i.e., the compartment which we are studying) consists of the space in the immediate vicinity of the permeable vessels (13, 16), and the other consists of the space around the larger extra-alveolar blood vessels and bronchi. It is here where fluid can be seen to accumulate; this space also contains the lymphatic vessels (4, 5). Communication between these two interstitial spaces is through an interstitial gel matrix which normally has a very high resistance to fluid movement (19, 20). For this situation to obtain, we must have in the lung a gel matrix which is considerably different from other tissue gels, which tend to separate at high positive pressures (19). Either this or else the resistance between compartments consists of something other than a true gel. A similar 2 compartment model has been described by *Taylor* et al. (14), but they locate the resistance between compartments at the initial lymphatic membrane rather than through the interstitial matrix. In either case such a system would provide the lung with a safety factor against acute edema. Only when the perivascular interstitium exceeded a critical pressure or volume would the space around the large vessels and bronchi begin to fill. In our experiments this critical condition occurred when the interstitial pressure was 20–25 cm H_2O and when we had increased lung weight by about 22%.

This critical condition was ascertained by the failure to reach an isogravimetric state. This 2 compartment model is supported by another observation made during isogravimetric conditions. If, after establishing the isogravimetric state, we attempted to maintain this state for periods up to 1/2 h, we found it necessary to decrease very slightly the intravascular pressure (0–2 cm H_2O over the 1/2 h). This would be required if the local interstitial pressure were to decrease as fluid moved through the gel into the downstream compartment.

Recognizing the importance of knowing the pulmonary interstitial compliance, *Staub* has attempted to estimate the normal interstitial compliance (2). He arrived at a maximal estimate of 70 ml/cm H_2O for normal man. For a 500 g lung wet weight, this equals 14 ml/cm H_2O/100 g, and is about 8 times our average value in the dog. However, our value is only for the interstitial space in the immediate vicinity of the vasculature, and the capacity of the entire interstitium may indeed be this large.

Our estimate of interstitial compliance agrees with the recent estimates reported by *Taylor* and *Drake* (3), although we differ considerably with their estimate of perimicrovascular pressure. They obtain much higher estimates of compliance at high perimicrovascular pressures, and we feel that under these conditions, they have exceeded the critical conditions mentioned above, and are looking at both interstitial spaces. They find a critical perimicrovascular pressure of about 3 cm H_2O, whereas ours was 20 cm H_2O higher. We cannot presently reconcile this difference. However, since they also used isogravimetric conditions to determine compliance, they must deal with the considerations discussed above regarding the equality of colloid osmotic and fluid pressure differences under isogravimetric conditions. Their calculated perimicrovascular pressures between –2 and 6 mmHg must be considerably less than the isogravimetric intravascular pressure.

Both our estimate and that of *Taylor* and *Drake* of the total interstitial compliance are consistent with the earlier work of *Gaar* et al. (21). They were looking at changes in isogravimetric capillary pressure in perfused lungs with various degrees of edema, and they found that increases in this pressure were correlated with the amount of lung water. Although they did not calculate any value for interstitial compliance, one can do so from their published data. This value is 1.3 g/cm H_2O per 100 g lung wet weight, and is very close to our average value.

Our methodology has also enabled us to separate the filtration coefficient into alveolar septal, extra-alveolar arterial and venous regions. *Iliff* has made similar measurements in isolated dog lungs, and although we both

concur that extra-alveolar vessels have significant permeability, our results differ quantitatively (22). She found nearly 62% of the filtration coefficient to be from extra-alveolar vessels with the extra-alveolar veins contributing 46%. It is difficult to account for these differences, but differences in methodology may be important. Her estimates were based on total accumulation over 2h periods, whereas our estimates were based on acute weight changes. If there were interstitial channels which allow the perivascular venous fluid to re-distribute over the course of 2h, then her method might overestimate the venous filtration coefficient.

One additional point regarding our filtration coefficient concerns the magnitude of our estimate. Compared to those tabulated in a recent review our value would fall at the upper end of those listed (2). In general, estimates of filtration coefficients for different species, and even within species, are quite variable. Although our estimates are on the high side, there are several reported values which are in the same range (7, 23, 24, 25). One reason why our filtration coefficient are high may relate to our method. The filtration into the immediate perivascular vicinity may indeed be much larger than the filtration coefficient for filtration into the entire interstitial space and lymphatics. These latter estimates, which are based on lung wet/dry weight ratios or steady state lymphatic flow, must include (and would be dominated by) the relatively high fluid resistance of the interstitial gel matrix. This would result in a low effective fluid filtration coefficient.

Implications

The fact that the isogravimetric intravascular pressure increases following a brief elevation of intravascular pressure implies that there has been a change in the balance of forces involved in fluid filtration. Because of the extreme difficulty in measuring the acute changes in intra- and extravascular protein concentration, we have chosen to interpret this phenomenon as resulting solely from fluid pressure changes. As already mentioned this assumption gives an upper limit to the interstitial compliance estimate, but we feel that this model is useful in determining the spatial distribution of interstitial compliance and the safety factor protecting against acute changes in vascular pressure.

Our results support the concept that fluid can leak from vascular regions outside the collapsible capillaries. We estimate that 23% of the total filtration coefficient is from non-septal arteries. An important consideration here is that since the arterial pressure is normally greater than the capillary or venous pressure, leakage from the small extra-alveolar arteries might contribute the largest fraction of the total fluid transudate. This may be particularly important in certain lung pathologies or with positive airway pressure ventilation. The results also offer a simple mechanism to explain the recent results of *Toung* et al (26) who studied the effects of PEEP on lung water accumulation. They showed a poor correlation of accumulated lung water with the level of airway pressure, but the lung water correlated well with the level of pulmonary artery pressure (relative to pleural pressure).

Our results also imply that there are finite interstitial compliances communicating with all permeable vessels. Pressures significantly greater than alveolar pressure can be built up in these spaces, thereby limiting at least acutely the further formation of interstitial edema. Furthermore, the model of a two compartment interstitial space separated by a high resistance gel matrix, which our data support, provides a safety factor to allow the gradual dissipation of accumulated fluid. Fluid in the first compartment around the permeable vessels can slowly seep into a potentially much larger and more compliant second compartment in direct continuity with the lymphatic channels.

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