THE PULMONARY INTERSTITIUM IN CAPILLARY EXCHANGE

Aubrey E. Taylor, James C. Parker, Peter R. Kvietys,* and Michael A. Perry*

Department of Physiology
University of South Alabama
Mobile, Alabama 36688

INTRODUCTION

Fluid movement across the microcirculation of the lung (J_v) is a function of capillary pressure (P_c), tissue pressure (P_t), and the colloid osmotic pressure of the plasma (π_p) and interstitial (π_t) fluids. Average values for these forces have been used in the modified Starling equation[1,2] to describe fluid movement across the pulmonary exchange vessels, i.e.,

$$J_v = K_{f,c}[P_c - P_t - \sigma_d\{\pi_p - \pi_t\}] \quad (1)$$

where $K_{f,c}$ is the filtration coefficient of the microvessels (capillaries) and σ_d is the osmotic reflection coefficient for the plasma proteins at the capillary wall. σ_d is equal to 1 if the membrane is impermeable to the solute, and σ_d is equal to 0 if the membrane is freely permeable to the plasma proteins. When the pulmonary tissue volume is not changing, J_v equals pulmonary lymph flow.

Equation 1 is certainly an oversimplification of the actual forces responsible for fluid movement in lung tissue, since P_c, P_t, π_t, lymph flow, and fluid accumulation may be quite different in apical and basal regions of the lung. Also, the forces and flows may vary between alveolar septal regions and interstitial spaces surrounding large airways and blood vessels at the same vertical height. Since this symposium's major objective is to describe lung microvascular injury in terms of alterations in tissue fluid accumulation and capillary permeability, it is important to understand how the tissue forces, π_t, P_t, and lymph flow affect fluid transudation into pulmonary tissues. In order to understand the complexities associated with lung interstitial fluid accumulation, this paper presents the biochemical makeup of the interstitium and the compartmentalization of tissue forces as they relate to pulmonary capillary pressure, tissue pressure, tissue compliance, lymph flow, tissue colloidal osmotic pressure, and the concept of macromolecule exclusion.

This paper will present a general overview of tissue forces, but it also provides a data base for interpreting the nature of pulmonary tissue forces and their importance in the regulation of lung fluid volume. Many investigators are now measuring forces, especially tissue pressure, within the pulmonary interstitium, and during the course of this conference we will hear presentations devoted to a more detailed analysis of π_t, P_t, and lymph flow.

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Lung Interstitium

When fluid leaves the pulmonary circulation, it can move into the potential spaces surrounding large blood vessels and bronchial structures, leave the lung via the lymphatics, or enter the airways.[3,4] FIGURE 1 shows diagrammatically the possible routes that fluid may take in the pulmonary interstitium. Fluid must move through lengthy interstitial pathways to reach the initial lymphatics at the terminal bronchioles. As greater amounts of filtration occur, tissue fluid pressure will increase and the resistance to fluid movement in the interstitium decreases. As more and more fluid enters the interstitium, the interstitial pressure continues to increase until the alveolar membrane ruptures. Fluid must traverse the capillary wall and interstitium to gain access to the lymphatics in interstitial edema, and traverse both structures plus the alveolar membrane when intra-alveolar edema is formed.

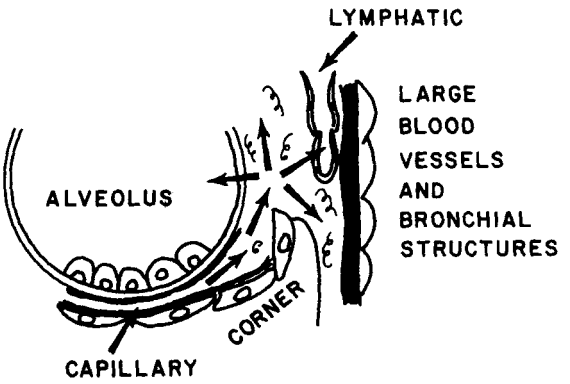

FIGURE 1. A schematic representation of the pulmonary interstitium. The fluid most likely filters in the vicinity of the alveoli and must traverse the interstitial spaces to reach the lymphatics. During edema, fluid fills the potential spaces surrounding larger blood vessels and bronchial structures and finally will fill the alveoli.[3,18]

The pulmonary interstitium is a complex meshwork of types I, II, III, IV, and V collagen, elastic fibers, proteoglycans, and glycosaminoglycans (TABLE 1). Collagen does not swell greatly when the tissues are hydrated, but the proteoglycans and glycosaminoglycans have tremendous swelling potentials. Although these "mucopolysaccharides" do not comprise a large amount of lung tissue, it is now generally thought that the swelling characteristics of *all* tissues are a function of the physical behavior of these macromolecules.[6,7] Because of the difference in structural components within lung tissue, it is possible for pressure gradients to exist between different interstitial compartments. In addition, protein molecules may not be able to penetrate certain portions of the interstitial matrix. The major glycosaminoglycan of the interstitium is hyaluronic acid, and at the present time it is not clear how the physical characteristics of this molecule change in lung injury. The swelling of glycosaminoglycans with tissue hydration has been clearly established, but the changes in their characteristics associated with lung injury have not been investigated.

TABLE 1

CONNECTIVE TISSUE AND INTERSTITIAL MATRIX COMPONENTS*

Macromolecule	Fraction of Total Connective Tissue	Fraction of Dry Weight	Location	Function
Collagen, type I	0.50	0.10	alveolar interstitium, pleura external to basement membranes of vessels and bronchi	thick support fibers
Collagen, type II	0.03	0.01	airway cartilage	support fibrils for cartilage matrix
Collagen, type III	0.20	0.04	alveolar interstitium, vessels, bronchi, pleura	fine, reticular fibers for interstitial matrix
Collagen, type IV	0.02	0.01	basement membranes	support for basement membrane
Collagen, type V	0.02	0.01	basement membranes	support for basement membrane
Elastic fiber	0.21	0.05	alveolar interstitium, vessel walls, airways, pleura	elasticity and support for parenchymal structures
Proteoglycans	0.01	<0.01	interstitial ground substance, basement membrane, cartilage	cell adhesion, cell spacing?
Glycosaminoglycans	0.01	<0.01 0.003	interstitial ground substance	fluid immobilization, interstitial matrix function

*Data from Reference 5.

FORCES

Capillary Pressure

FIGURE 2 depicts an estimate of capillary pressure at different lung heights.[8] Note that the estimated capillary pressure (P_c) appears to be located approximately halfway between the arterial (P_{pa}) and venous (P_{pv}) pressures until zone-II conditions exist (when alveolar pressure is less than pulmonary arterial, but greater than venous, pressure). As pulmonary arterial pressure approaches alveolar pressure at upper zone-II levels, the capillary pressure must approach

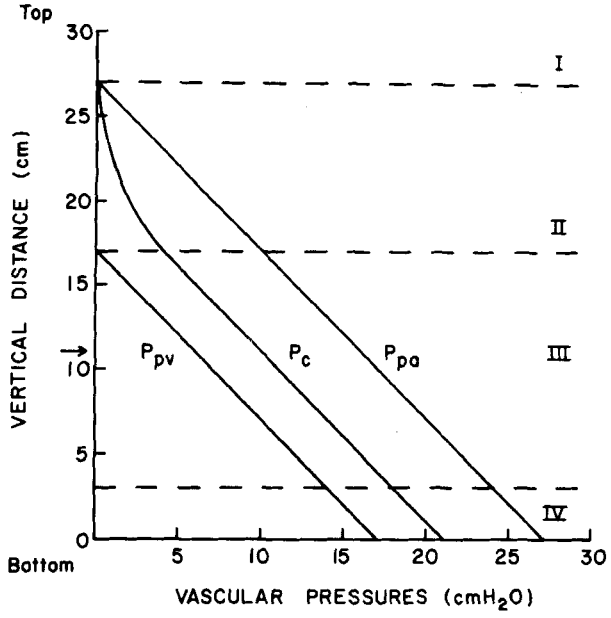

FIGURE 2. *Vertical gradient capillary pressure. Estimations of capillary pressures at* different lung heights. P_{pv}, P_{pa}, and P_c represent pulmonary venous, arterial, and capillary pressures in cm H_2O.[8]

the arterial pressure. In addition to the vertical differences in estimated capillary pressures, the pre- and postcapillary resistances are different in zones II and III. Since the capillary pressures change at each lung level, then we would expect the most dependent portions of the lung to filter more fluid and produce the majority of lung lymph.[9] Therefore, average values for P_l, π_l, and lymph flow may not describe the actual forces responsible for fluid movement into the pulmonary interstitium.

Tissue Pressures in Lung

The vital role of tissue pressure in determining the transcapillary filtration gradient and gradients for fluid movement within the lung tissue has led to considerable research.[3,10-17] TABLE 2 summarizes the current estimates of tissue

TABLE 2

TISSUE PRESSURES*

Species, Anatomic Site, Reference Pressure	P_t (cm H_2O)	P_{TP} (cm H_2O)	P_c (cm H_2O)	Methods	Source (Reference)
Dog, intact, average perimicrovascular ?, P_A	*control hydration* −9 to −12.2	5† to 8	9 to 14	implanted capsules, Starling force balance, fluid absorption	10,11,12
	edema −2 to +4	5†	20 to 40		
Sheep, intact, average perimicrovascular, P_A	0	5†	20	Starling force balance	3,13
Dog, isolated lobe, hilar peribronchial-perivascular, P_{pl}	*control hydration* −3 to −8	5	10‡	wick catheter at hilus	14–17
	increased transpulmonary pressure −11 to −20	25	10 to 15‡		
	increased vascular pressure 0 to −4	5	25 to 30‡		
	edema (30 to 50% weight gain) 0 to −3	5	15 to 30‡		

*P_A = alveolar pressure, assumed to equal atmospheric pressure or average during tidal breathing in intact animals. P_c = capillary pressure at filtration midpoint in perfused vessels, based on the equation: $P_c = 0.4\ (P_{pa} - P_{la}) + P_{la}$. P_{pl} = pleural surface pressure. P_{TP} = transpulmonary pressure. P_t = tissue pressure.

†Estimated transpulmonary pressure for intact, closed-chest animal during tidal breathing.

‡P_{mv} = uniform pressure in all small and large vessels in unperfused vessels filled with fluid or air.

pressure in normal and edematous lungs. Estimates of tissue pressures in intact dog lungs using implanted capsules and intraalveolar absorptive pressures indicate that tissue pressure is between 9–12 cm H_2O negative relative to alveolar pressure at functional residual capacity.[10–12] These pressures increased with capillary filtration and tissue edema.[10–12] Recent studies, using implanted wick catheters and micropipettes, indicate a hilar fluid pressure that is 3 to 8 cm H_2O negative relative to pleural surface pressure.[14–17] These direct interstitial pressure measurements become more negative at increased lung volumes, and less negative or even positive with vascular distention, increased capillary filtration pressure, and increased tissue hydration.

FIGURE 3 indicates the effects of increased transpulmonary pressure, increased vascular pressure, and increased tissue hydration on hilar fluid

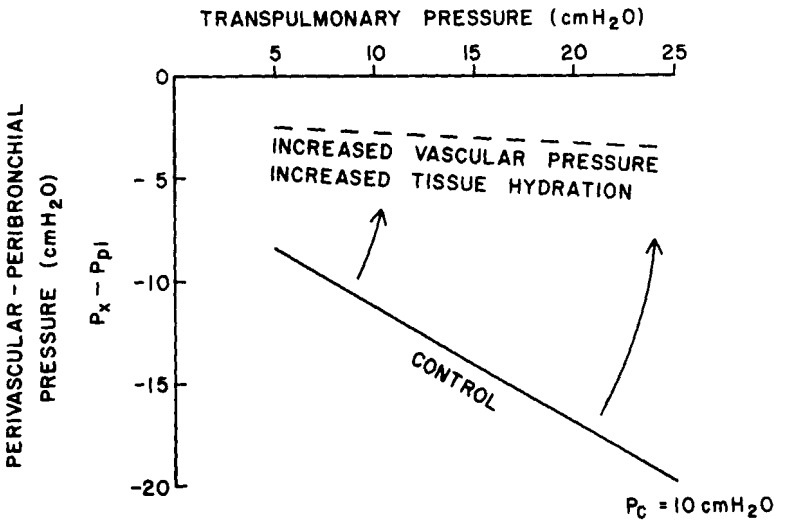

FIGURE 3. Hilar interstitial pressure. A plot of perivascular minus pleural pressures ($P_x - P_{pl}$) as a function of transpulmonary pressure (cm H_2O) for control (solid line) and edematous tissue (dashed line).[16,17]

pressure (P_x) relative to pleural pressure (P_{pl}). In general, the perivascular-peribronchial pressure decreases with increased transpulmonary pressures because of a greater radial traction on the membranes surrounding hilar blood vessels and bronchi (solid line). Distention of the blood vessels or an increase in interstitial volume will reduce the distending stress during lung expansion (dotted line). In fact, $P_x - P_{pl}$ changes by 13 cm H_2O in normal lungs as compared to a change of 3 cm H_2O in edematous lungs.

Pressure gradients between interstitial regions may also influence regional fluid filtration and movement of fluid within the interstitial spaces. The early appearance of edema fluid around extraalveolar vessels and bronchi implies that a pressure gradient exists for fluid movement from the alveolar perivascular spaces to spaces surrounding medium and large extraalveolar vessels.[18] Recent micropuncture measurements of alveolar and septal interstitial fluid pressures indicate a gradient between these pressures and hilar pressures of approximately

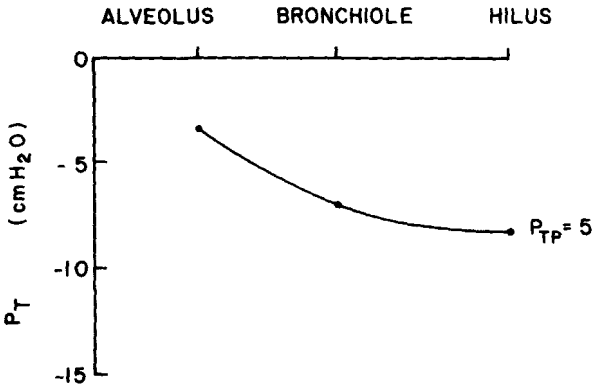

FIGURE 4. Horizontal gradient tissue pressure. Pressure gradients measured between alveolus and hilus using wicks and small pipettes.[15-17,19,20]

5 cm H_2O[19-20] (FIGURE 4). Such a gradient would be useful in removing excess fluid from interstitial spaces in the gas-exchange portions of lung parenchyma to the less vital regions of lung interstitium surrounding larger blood vessels and bronchi.

In addition, a vertical gradient in fluid pressures has been observed using chronically implanted capsules and intraalveolar absorptive pressures.[21] These gradients are shown in FIGURE 5, and were 0.60 cm H_2O/cm vertical distance

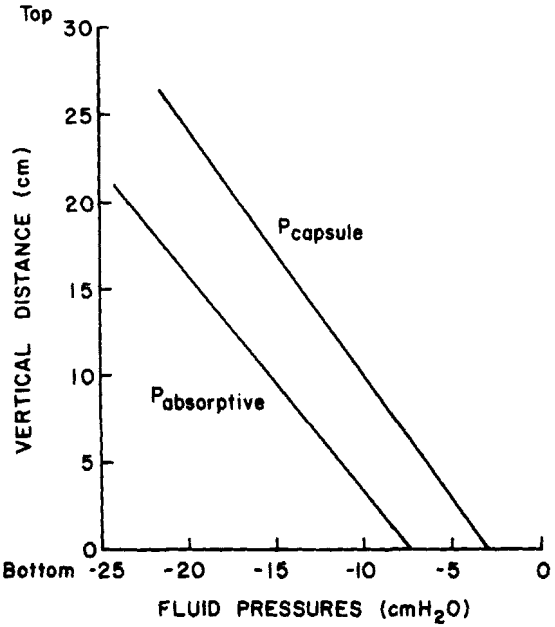

FIGURE 5. Vertical gradient in pulmonary interstitial pressure estimated using chronically implanted capsules ($P_{capsule}$) and alveolar absorption ($P_{absorptive}$) pressures.[21]

TABLE 3

TISSUE COMPLIANCE IN THE LUNG

Species, Anatomic Site, Reference Pressure	Compliance Phases (g/cm H_2O/ 100 g wet wt.) Low	High	Transition Pressure (cm H_2O)	Transpulmonary Pressure (cm H_2O)	Method	Source (Reference)
(1) Dog, intact, perimicrovascular, P_A	0.7	9.0	−1	5*	absorption pressure of alveolar fluid, gravimetric lung water	12
(2) Dog, isolated lobe, average perimicrovascular, P_{pl}	2.2	13	0	2	calculated tissue pressure change between isogravimetric states, lobe weight gain	24,25
(3) Dog, isolated lobe, hilar peri-bronchial-peri-vascular, P_{pl}	10	60	−2	6	wick fluid pressure, lobe weight gain, P_{mv} = 10–25 cm H_2O	14
(4) Dog, isolated lobe, average perimicrovascular, P_{pl}	0.7	10	—	5	pressure change between isogravimetric states	26

*Estimated transpulmonary pressure for intact, closed-chest animal during tidal breathing.

using capsules, and 0.78 cm H_2O/cm vertical distance using the intraalveolar fluid pressure measurement. A large portion of the gradient could be a result of the regional differences in transpulmonary pressures up and down the lungs of intact animals.[22] This observed gradient, obtained using implanted capsules, is approximately equal to values predicted using regional differences in capillary pressures.[23] Such a vertical gradient in perivascular fluid pressure would partially compensate for the differences in capillary pressure between the top and bottom of the lung relative to fluid filtration.

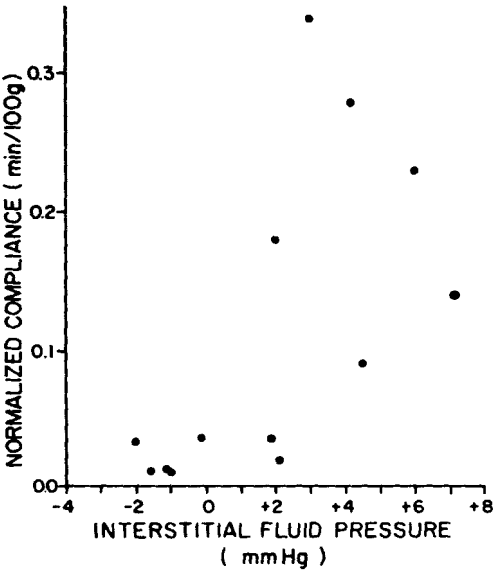

FIGURE 6. Estimation of tissue compliance changes in isolated dog lungs. The compliance was normalized by dividing $\Delta V/\Delta P$ by the blood flow per 100 g lung.[24,25]

Pressure-Volume Characteristics of the Interstitial Spaces (Interstitial Compliance)

TABLE 3 summarizes the estimates of compliance calculations for the interstitial spaces using several different experimental methods.[12,14,24-26] In general, lung tissue has a relatively low interstitial compliance during the early phase of interstitial edema formation, but a higher compliance during more severe edema. In intact dogs and isolated dog lungs, the low-compliance phase ranged from 0.7 to 2.2 g per cm H_2O per 100 g wet weight.[12,24-26] This compliance increased manyfold in the high-compliance phase of fluid accumulation. The transition point in compliance occurs when tissue pressure approaches alveolar pressure. This transition point may represent the onset of alveolar flooding, but it may also represent movement of fluid into more compliant portions of the interstitial space. Measurements of wick pressures in the hilar perivascular space suggest a much more compliant interstitial compartment than is calculated for the average perimicrovascular space.[14]

FIGURE 6 indicates the biphasic nature of tissue compliance calculated for

TABLE 4

LYMPH FLOW AND PROTEIN COMPOSITION*

Species, Conditions	State	P_c (cm H_2O)	$\dot{Q}_L$ (μl/minute)	Lymph (g/dL)		Plasma (g/dL)		L/P		Source (Reference)
				TP	A	TP	A	TP	A	
Sheep, intact unanesthetized, CMN, increased left atrial pressure.	control	19.9	95.0	4.51	2.43	6.59	2.76	0.69	0.88	13
	↑LAP	39.1	246	2.26	1.43	6.45	2.82	0.35	0.51	
Sheep, intact unanesthetized, CMN, increased left atrial pressure and infusion of *P. aeruginosa*.	control	19.2	138	4.69	2.43	6.73	2.71	0.70	0.89	27
	↑LAP	33.6	250	3.66	2.06	6.94	2.78	0.53	0.74	
	P. aeruginosa	23.6	895	3.43	1.83	5.74	2.41	0.60	0.76	
Sheep, intact unanesthetized, CMN, infusion of 4 μg/kg per minute serotonin.	control	11.0	90	4.45	1.97	5.92	2.51	0.75	0.78	28
	serotonin	14.0	138	3.86	1.70	6.19	2.35	0.62	0.72	
Sheep, intact anesthetized, CMN, embolization with 100-μ glass beads.	control	12.5	118	—	—	—	—	0.62	0.78	29
	embolization	22.6	278	—	—	—	—	0.71	0.89	
Dog, intact, open chest, anesthetized, TBN, increased left atrial pressure.	control	9.6	19.4	4.20	1.34	6.20	1.66	0.68	0.81	30
	↑LAP	26.6	82.9	2.8	0.93	5.90	1.61	0.47	0.58	
Dog, intact, open chest, anesthetized, increased left atrial pressure, TBN.	control	11.1	19.6	4.23	1.84	6.20	2.26	0.68	0.81	31
	↑LAP	47.7	198	2.39	1.02	6.25	2.11	0.38	0.48	
Dog, intact, open chest, anesthetized, ANTU infusion, TBN.	control	11.9	32.2	4.35	—	6.00	—	0.73	—	32
		16.0	118.2	3.33	—	5.67	—	0.59	—	

*CMN = caudal mediastinal lymph node, postnodal cannulation. TP and A refer to total protein and albumin concentrations, respectively. TBN = left tracheobronchial afferent, prenodal cannulation. ↑LAP = increased left atrial pressure. P_c = pulmonary capillary pressure.

isolated dog lungs.[24] These compliance values were calculated using the calculated tissue pressure changes between isogravimetric states, and have been normalized for blood flow. A transpulmonary pressure of 2 mm Hg was used in these lobes, and represented the approximate transition pressure between the two compliance phases.

Lymph Flow

When left atrial pressures are elevated above normal values, lung lymph flow always increases above baseline.[13,27,30,31] If vascular permeability increases, lymph flow also increases without any change occurring in pulmonary vascular pressures[27,32] (TABLE 4). FIGURE 7 shows how dog lung lymph flow ($\dot{Q}_L$) increases when capillary pressure is elevated from 10 to 50 cm H_2O.[31] The maximal increase in lymph flow appears to be approximately 10 times control. When the capillaries are more permeable to plasma proteins, a greater increase in lymph flow is observed for similar increases in capillary pressure.[32] The reason for this difference is not clear at the present time, but could be explained by the higher π_t and P_t associated with increased permeability of plasma proteins, which decreases the edema safety factor.[33]

The curves in FIGURE 8 represent lymph flow changes as a function of interstitial volume when filtration is altered by either increasing capillary pressure (●) or by volume expansion (×).[30,34] The lymph flow response in this set of experiments is greater for capillary pressure elevation than for plasma dilution at all interstitial volumes. This most likely results because interstitial compliance is decreased with vascular distention and the larger P_t serves to either increase the filling pressure at the initial lymphatic wall or provides a greater driving force between the septal capillaries and the more distant initial lymphatics.

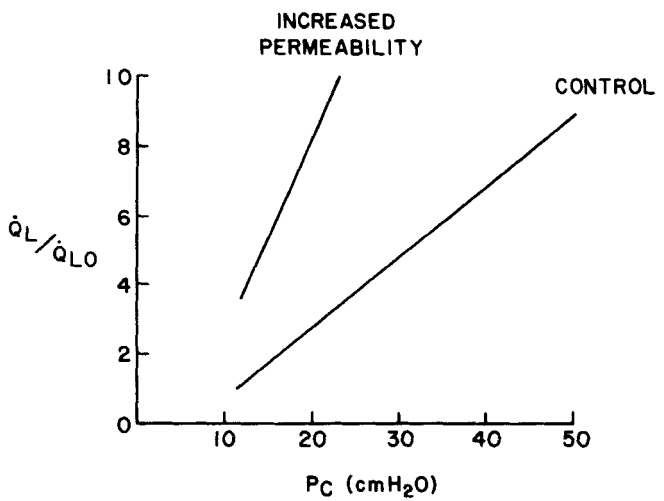

FIGURE 7. Plot of relative lymph flow ($\dot{Q}_L/\dot{Q}_{LO}$) changes as a function of calculated capillary pressure for control and leaky lungs (ANTU). $\dot{Q}_L$ refers to experimental lymph flow, and $\dot{Q}_{LO}$ refers to control values.[32]

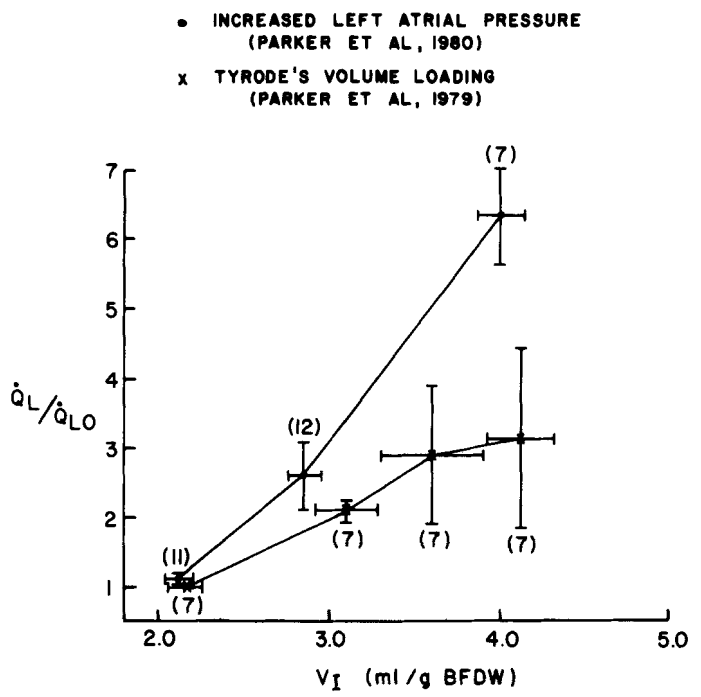

FIGURE 8. Plot of relative lymph flow changes ($\dot{Q}_L/\dot{Q}_{LO}$) as a function of interstitial volume following increases of capillary pressure (●) or volume expansion using Tyrode's solution (×).[30,31]

Tissue Colloid Osmotic Pressure (π_i)

When pulmonary hydrostatic pressure is increased, the total protein concentration of lymph decreases. This decrease in lymph protein concentrations in a steady state must reflect tissue protein concentrations.[35] Gee has recently shown a very slow rate of lung interstitial protein turnover,[36] which complicates the interpretation of lymph protein data collected for only short time intervals. FIGURE 9 represents a replot of data from R. Parker and K. Brigham's laboratory,[37] for which the lymph-to-plasma ratios of total plasma proteins (L/P) were obtained from sheep lymphatics and plotted as a function of lymph flow. Note that L/P equals 0.25 for high lymph flow rates and is insensitive to further increases (filtration independence).[38] This L/P represents the maximum decrease in tissue colloid osmotic pressure that can act as a force to retard fluid accumulation in the tissues following elevation of capillary pressure. For normal values of plasma proteins (7 gm%), this represents a maximal possible change in tissue colloid osmotic pressure of approximately 11 mm Hg. In most cases of severe intraalveolar edema, the edema fluid contains plasma proteins at concentrations approximately one-half that contained in plasma. This corresponds to a change in tissue colloidal osmotic pressure of only 5.2 mm Hg, indicating that the pulmonary exchange vessels are more leaky to plasma proteins than in the normal case. Whether this represents a "stretched pore effect" due to the

increased vascular pressures or only the opening of large leaks is not clear at the present time, but it appears that large leaks do open in the capillary wall since edema fluid contains red blood cells.[11]

FIGURE 9 also indicates the behavior of L/P when lymph flow increases and the capillary barrier is more permeable to the plasma proteins. L/P approaches a higher value at high lymph flows, and π_l will be greater than that observed for normal capillaries at each increased filtration state. Thus, the tissue's ability to buffer changes in capillary hydrostatic pressure is lessened when the exchange vessels are abnormally leaky to plasma proteins.

A vertical gradient of colloid osmotic pressure in lung tissue has been proposed by Staub.[3] Such a vertical gradient would exist if lung lymph flow and capillary filtration were greater in the more dependent regions of the lung. FIGURE 10 shows the work of Molsted, in which lymph protein concentrations were measured in small lymphatics draining the top and bottom portions of isolated, vertical dog lungs.[39] Although this study has many technical problems, i.e., mixing times, drainage patterns of lymphatics sampled at the hilus, etc., it does indicate that a gradient may exist up and down the lung, with π_l increasing by 0.13 cm H_2O per cm height from apex to base of the lung, although individual experiments may vary as shown in FIGURE 10.

The problem of horizontal gradients existing within lung tissue has not been addressed in a quantitative fashion. However, there is no doubt that perivascular fluid protein exchanges very slowly with other fluid compartments in lung tissue.[36] If lymph is collected over sufficient time intervals and all flows and forces are in a steady state, then π_l should be equivalent to lymph colloid osmotic

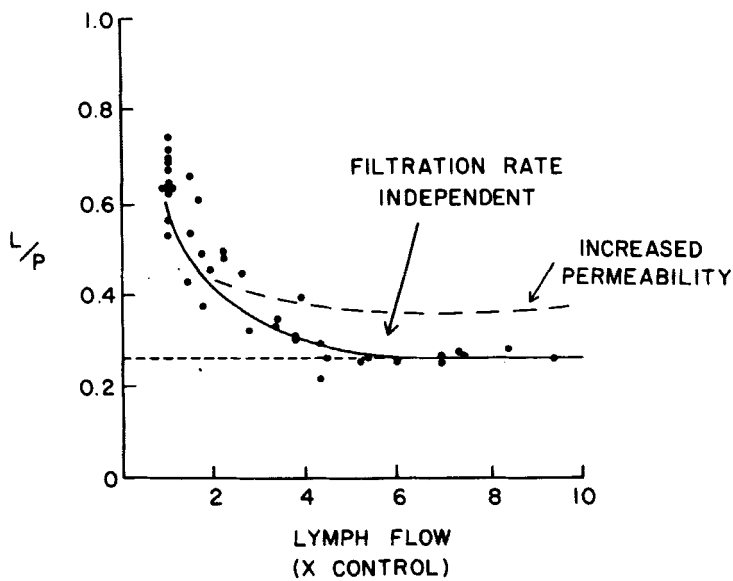

FIGURE 9. Plot of lymph-to-plasma concentration ratios of total plasma proteins (L/P) as a function of lymph flow. The control values are shown as a solid line, and the increased capillary permeability is represented by a dashed line. Note that both curves approach asymptotic values at high lymph flows (filtration-rate independence).[37]

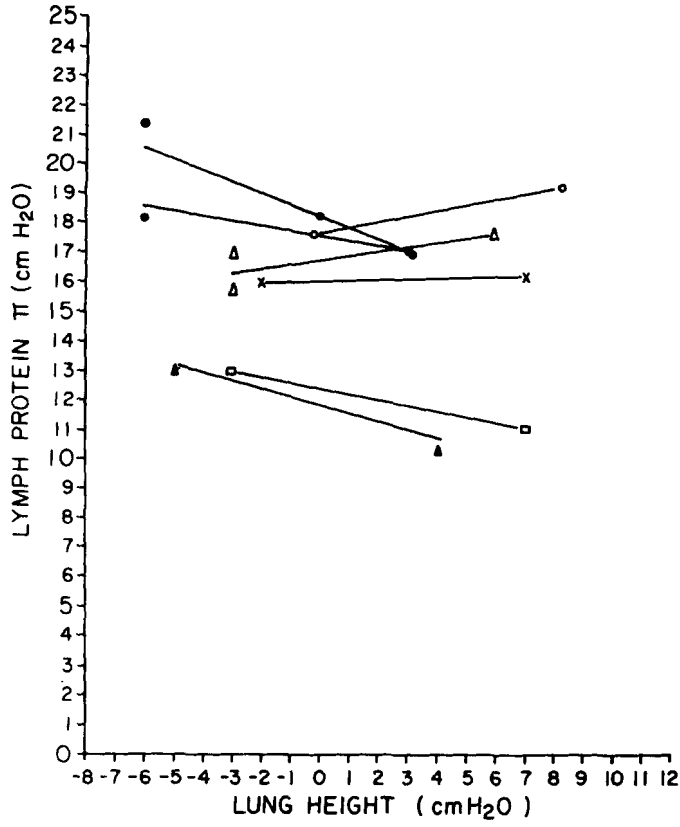

FIGURE 10. Plot of lymph protein colloid osmotic pressure obtained from small lymphatics in isolated dog lungs that were placed in an upright position. Zero is the reference level, and negative and positive values refer to distances (in cm) above or below, respectively.[39]

pressure. However, again it should be emphasized that a short sampling period may yield erroneous estimates of π_t when using π_L.

The problem of assessing π_t in different lung compartments represents one of the most challenging aspects in lung fluid balance. Perhaps in the future, either micropipettes or wicks inserted into tissues will allow an assessment to be made of this important tissue force at different tissue sites and hydration states.

Exclusion of Interstitial Proteins

TABLE 5 summarizes values obtained in lung tissue for blood and extravascular fluid compartments.[30,34,40-42] The extravascular, extracellular spaces obtained for sucrose and ^{99m}Tc-DTPA (diethylenetriamine pentaacetic acid) ranged from 0.33 to 0.55 of total extravascular lung water. The extravascular lung water per gram blood free dry weight (BFDW) was relatively consistent for normally

TABLE 5

TISSUE FLUID COMPARTMENTS*

Species	Condition	F_B	Q_W (g/g BFDW)	V_I (ml/g BFDW)	V_A (ml/g BFDW)	V_I/Q_W	F_E	Technique	Source (Reference)
Dog, intact, open chest	Control	0.19–0.22	3.83–3.91	2.16–2.18	1.28–1.43	0.55	0.36–0.38	spaces based on pulmonary lymph concentrations, increased left atrial pressure, and volume load edema, ^{51}Cr red-cell blood-volume concentration, V_I = ^{99m}Tc-DTPA space, V_A = ^{125}I-albumin space	30,34
	↑LAP	0.25	4.79	3.41	2.95	0.72	0.14		
	10% BW volume load	0.17	4.91	3.59	2.89	0.73	0.16		
Dog, intact, closed chest	Control	0.37	2.33	1.28	0.95	0.55	0.26	control measurements V_I = ^{14}C-sucrose space V_A = ^{131}I-albumin, residual plasma, volume corrected with ^{125}I-albumin	40
Sheep, intact, closed chest	Control	0.22–0.27	3.95–4.00	1.29–2.08	0.40–0.72	0.33–0.53	0.50–0.81	control measurements V_I = ^{14}C-sucrose space, V_A = ^{125}I-albumin space based on lymph concentration, hemoglobin blood-volume correction	41,42

*F_B = fractional blood weight of tissue; Q_W = extravascular lung water per gram blood free dry weight (BFDW); V_I = extravascular, extracellular space; V_A = albumin space based on lymph concentration; F_E = excluded-volume fraction for albumin.

hydrated lungs, ranging between 3.83–4.00 g/g BFDW. However, the distribution volume for albumin based on its concentration in pulmonary lymph was only about 50 to 74% of the distribution volume measured for molecules the size of sucrose. The most likely explanation for this difference in volumes is an exclusion of albumin from portions of the interstitial water by the macromolecules of the interstitial ground substance. Interstitial collagen, glycosaminoglycans, and proteoglycans form a dense matrix in the interstitium, with many spaces in the interior admitting water and small ions but restricting protein molecules.[6,7] This excluded volume is not located in any particular region of the interstitium, but is dispersed throughout the interstitial matrix.

Interstitial edema tends to expand the hyaluronic acid and proteoglycan molecules and reduce the number of restrictive domains for protein. This leads to a decrease in the excluded water volume for protein during edema formation.

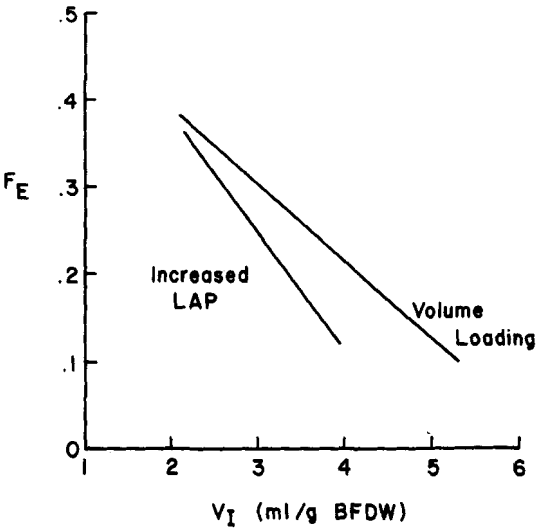

FIGURE 11. Represents a plot of the excluded-volume fraction (F_E) for albumin as a function of the DTPA extravascular space (V_I) in dog lung tissues for increased left atrial pressure and volume loading.

FIGURE 11 indicates the effect of interstitial edema on the albumin excluded-volume fraction (F_E) of the extravascular ^{99m}Tc-DTPA space (V_I). Edema was produced either by increasing left atrial pressures or by volume expansion using Tyrode's solution.[30,34] The slopes of F_E vs. V_I were not statistically different in the two types of edema. This suggests a simple physicochemical relationship between albumin excluded volume and tissue hydration, because tissue and lymph protein concentrations and the transcapillary protein concentration gradients were considerably different between the two edema groups.

Probably more information concerning the exclusion properties of the interstitium is obtained by evaluating the absolute excluded volume (V_E) as a function of tissue hydration[30,34] (FIGURE 12). The excluded volumes decreased significantly in both types of edema, but the relative changes were much smaller than those

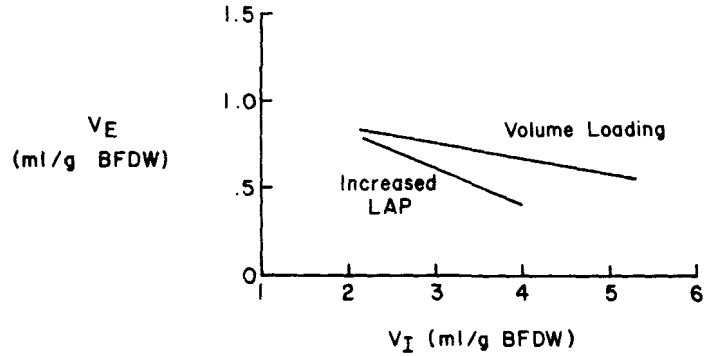

FIGURE 12. Represents the absolute excluded volume (V_E in ml/g blood free dry weight) as a function of V_I (ml/g BFDW) when the tissues were expanded either by volume loading with Tyrode's solution or increasing left atrial pressure (LAP).[30,31]

calculated for the excluded-volume fractions. This indicates that interstitial protein exclusion results from both hyaluronic acid and collagen molecules within the interstitial matrix.

A decrease in excluded volume for protein has physiologic significance, because the effective concentration of tissue proteins is determined by the available volume rather than the total interstitial volume.[6] This can result in increased oncotic buffering for a given degree of interstitial edema. Oncotic buffering refers to the increase in the plasma-to-interstitium colloid osmotic-pressure gradient resulting from the decreased tissue protein colloid osmotic pressure. The effect is shown diagrammatically in FIGURE 13.[6] The exclusion amplification effect on tissue colloid osmotic pressure (π_t) as a function of interstitial volume (V_I) is shown by the dashed line in FIGURE 13. The effect of interstitial volume expansion without any change is excluded-volume fraction is shown by the solid line. For a given interstitial volume, π_t will be less when

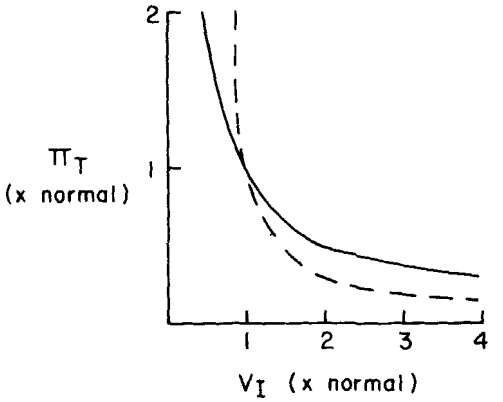

FIGURE 13. Effect of exclusion on changes in relative interstitial colloidal osmotic pressure (π_t) when the relative interstitial volume (V_I) expands. Note that at each increased volume state, π_t is less if exclusion was originally present in the tissues.[6]

exclusion decreases as edema forms. The importance of this mechanism in leaky capillary syndromes has not been evaluated.

Summary and Conclusions

When capillaries filter excessive fluid, tissue fluid pressure increases, tissue colloid osmotic pressure decreases, and lymph flow increases. These changes in tissue forces and flows have been termed edema safety factors since they act to oppose alterations in pulmonary capillary pressure. It is well known that pulmonary capillary pressure can be acutely increased by approximately 20 mm Hg before fluid enters the alveoli, and that the changes in the tissue forces are responsible for this phenomenon.

The decrease in interstitial colloid osmotic pressure appears to account for approximately 50% of the tissue's ability to oppose increases in pulmonary capillary pressure. The tissue colloids change because the capillaries filter a protein-poor fluid, and the exclusion of plasma proteins decreases with increasing interstitial volume. Tissue pressure, at least in the perivascular regions, increases with tissue hydration and provides another major tissue force opposing capillary filtration.

The contribution of lymph flow to the overall edema safety factor is difficult to estimate at the present time. However, it is possible that the pressure drop associated with the flow of interstitial fluid between the alveolar septal interstitium and the larger perivascular spaces could serve as an edema safety factor, rather than the standard lymphatic flow pressure drop across the capillary membrane. To calculate the standard lymph flow contribution to the total edema safety factor, total lymph flow (LF) and the filtration coefficient of the capillaries ($K_{f,c}$) must be known, i.e.,

$$\text{Capillary Wall Drop} = LF/K_{f,c}$$

For normal lung lymph flows and $K_{f,c}$'s, it would appear that this factor is small. However, if the total pressure drop for fluid movement through the entire lung tissue is used to estimate the lymphatic factor, then it may represent a major portion of the edema safety factor, i.e.,

$$\text{Total Pressure Drop} = LF/(K_{f,c}K_{f,t})/(K_{f,c} + K_{f,t})$$

where $K_{f,t}$ is the filtration coefficient of the tissues.

Tissue forces at different sites within the lung tissue are presently under intense investigation in several laboratories. The next years should provide the necessary information to discuss fluid accumulation in lung tissue in terms of local transcapillary forces rather than the average forces that are now the "present state of the art."[33]

References

1. Starling, E. H. 1896. Absorption of fluids from the connective tissue spaces. J. Physiol. London **19:** 312–326.
2. Kedem, O. & A. Katchalsky. 1958. Thermodynamic analysis of the permeability of biological membranes to nonelectrolytes. Biochim. Biophys. Acta **27:** 229–246.
3. Staub, N. C. 1974. Pulmonary edema. Physiol. Rev. **54:** 678–811.

4. GUYTON, A. C., A. E. TAYLOR & H. J. GRANGER. 1975. Circulatory Physiology. II. Dynamics and Control of the Body Fluids. W. B. Saunders Company. Philadelphia, Pa.
5. RENNARD, S. J., V. J. FARRANS, K. H. BRADLEY & R. G. CRYSTAL. 1981. Lung connective tissue. *In* Mechanisms in Respiratory Toxicology. H. P. Witschi, Ed. **2:** 115-153. CRC Reviews. Boca Raton, Fla.
6. GRANGER, H. J. 1981. Physicochemical properties of the extracellular matrix. *In* Tissue Fluid Pressure and Composition. A. R. Hargens, Ed.: 43-62. Williams and Wilkins. Baltimore, Md.
7. COMPER, W. D. & T. C. LAURENT. 1978. Physiological function of connective tissue polysaccharides. Physiol. Rev. **58:** 255-315.
8. PARKER, J. C., R. E. PARKER, D. N. GRANGER & A. E. TAYLOR. 1979. Vertical gradient in regional vascular resistance and pre- and post-capillary resistance ratios in the dog lung. Lymphology **12:** 191-200.
9. BLAKE, L. H. & N. C. STAUB. 1976. Pulmonary vascular transport in sheep. A mathematical model. Microvasc. Res. **19:** 197-220.
10. MEYER, B. J., A. M. MEYER & A. C. GUYTON. 1967. Interstitial fluid pressure: negative pressures in the lungs. Circ. Res. **22:** 263-271.
11. MELLINS, R. B., O. R. LEVINE, R. SKALAK & A. P. FISHMAN. 1969. Interstitial pressure of the lung. Circ. Res. **24:** 197-212.
12. PARKER, J. C., A. C. GUYTON & A. E. TAYLOR. 1978. Pulmonary interstitial and capillary pressures estimated from intraalveolar fluid pressures. J. Appl. Physiol. Respir. Environ. Exercise Physiol. **44:** 267-276.
13. ERDMANN, A. J. III, T. R. VAUGHAN, JR., K. L. BRIGHAM, W. C. WOOLVERTON & N. C. STAUB. 1975. Effect of increased vascular pressure on lung fluid balance in unanesthetized sheep. Circ. Res. **37:** 271-284.
14. LAI-FOOK, S. J. & B. TOPOROFF. 1980. Pressure-volume behavior of perivascular interstitium measured in isolated dog lung. J. Appl. Physiol. Respir. Environ. Exercise Physiol. **48:** 939-946.
15. INOUE, H., C. INOUE & J. HILDERBRANDT. 1979. Interstitial fluid pressure (Px(f)) gradients along bronchi in excised dog lobes. Fed. Proc. **38:** 1265.
16. INOUE, H., C. INOUE & J. HILDERBRANDT. 1980. Vascular and airway pressures, and interstitial edema, affect peribronchial fluid pressure. J. Appl. Physiol. Respir. Environ. Exercise Physiol. **48:** 177-185.
17. GOSHY, M., S. J. LAI-FOOK & R. E. HYATT. 1979. Perivascular pressure measurements by wick-catheter technique in isolated dog lobes. J. Appl. Physiol. Respir. Environ. Exercise Physiol. **46:** 950-955.
18. STAUB, N. C., H. NAGANO & M. L. PEARCE. 1967. Pulmonary edema in dogs: especially the sequence of fluid accumulation in the lungs. J. Appl. Physiol. **22:** 227-240.
19. BHATTACHARYA, J., S. NANJO & N. C. STAUB. 1981. Direct measurement of subpleural interstitial fluid pressure in isolated dog lung. Fed. Proc. **40:** 448.
20. LAI-FOOK, S. & K. C. BECK. 1981. Alveolar liquid pressures measured by micropipettes in isolated dog lung. Fed. Proc. **40:** 448.
21. PARKER, J. C., R. E. PARKER, D. N. GRANGER & A. E. TAYLOR. 1978. Vertical gradient in pulmonary interstitial fluid pressure. Physiologist **21:** 89.
22. AGOSTONI, E. & E. D'ANGELO. 1970/71. Comparative features of the transpulmonary pressure. Respir. Physiol. **11:** 76-83.
23. GUYTON, A. C., A. E. TAYLOR, R. E. DRAKE & J. C. PARKER. 1976. Dynamics of subatmospheric pressure in the pulmonary interstitial fluid. Ciba Symp. **38:** 77-100.
24. DRAKE, R. E. 1975. Changes in the Starling forces during the formation of pulmonary edema. Ph.D. Dissertation. University of Mississippi. University, Miss.
25. TAYLOR, A. E. & R. E. DRAKE. 1978. Fluid and protein movement across the pulmonary microcirculation. *In* Lung Biology in Health and Disease. Lung Water and Solute Exchange. N. Staub, Ed. **7:** 129-182. Marcel Dekker, Inc. New York, N.Y.
26. GOLDBERG, H. S. 1980. Pulmonary interstitial compliance and microvascular filtration coefficient. Am. J. Physiol. Heart Circ. Physiol. **239:** H189-H198.
27. BRIGHAM, K. L., W. C. WOOLVERTON, L. H. BLAKE & N. C. STAUB. 1974. Increased sheep lung vascular permeability caused by Pseudomonas bacteremia. J. Clin. Invest. **54:** 792-804.

28. BRIGHAM, K. L. & P. J. OWEN. 1975. Mechanism of the serotonin effect on lung transvascular fluid and protein movement in awake sheep. Circ. Res. **36:** 761-770.
29. MALIK, A. B. & H. VAN DER ZEE. 1978. Lung vascular permeability following progressive pulmonary embolization. J. Appl. Physiol. **45:** 590-597.
30. PARKER, J. C., H. J. FALGOUT, F. A. GRIMBERT & A. E. TAYLOR. 1980. The effect of increased vascular pressure on albumin excluded volume and lymph flow in the dog lung. Circ. Res. **47:** 866-875.
31. PARKER, J. C., R. E. PARKER, D. N. GRANGER & A. E. TAYLOR. 1981. Vascular permeability and transvascular fluid and protein transport in the dog lung. Circ. Res. **48:** 549-561.
32. RUTILI, G., P. KVIETYS, J. C. PARKER & A. E. TAYLOR. 1980. Studies of lung protein flux and water content in ANTU-induced pulmonary edema. *Microvasc. Res.* **20:** 125.
33. TAYLOR, A. E. 1981. Capillary fluid filtration: Starling forces and lymph flow. Circ. Res. **49:** 557-575.
34. PARKER, J. C., H. J. FALGOUT, R. E. PARKER, D. N. GRANGER & A. E. TAYLOR. 1979. The effect of fluid volume loading on exclusion of interstitial albumin and lymph flow in the dog lung. Circ. Res. **45:** 440-450.
35. RENKIN, E. M. 1979. Lymph as a measure of the composition of interstitial fluid. *In* Pulmonary Edema. A. P. Fishman & E. M. Renkin, Eds.: 145-159. American Physiological Society. Bethesda, Md.
36. GEE, M. H. & A. M. HAVILL. 1980. The relationship between pulmonary perivascular cuff fluid and lung lymph in dogs with edema. Microvasc. Res. **19:** 209-216.
37. PARKER, R. E., R. J. ROSSELI & K. L. BRIGHAM. 1980. *Effects of prolonged left atrial* pressure elevation on lung microvascular protein sieving in unanesthetized sheep. Fed. Proc. **39:** 279.
38. GRANGER, D. N. & A. E. TAYLOR. 1980. Permeability of intestinal capillaries to endogenous macromolecules. Am. J. Physiol. **238:** H457-H464.
39. MOLSTED, L. S. & A. E. TAYLOR. 1976. Effects of hydrostatic height on pulmonary lymph protein concentration. Microvasc. Res. **11:** 124.
40. MEYER, E. C. & R. OTTAVIANO. 1974. Right lymphatic duct distribution volume in dogs. *Circ. Res.* **35:** 197-203.
41. VAUGHAN, T. R., JR., A. J. ERDMANN III & N. C. STAUB. 1971. Subdivisions of lung extravascular water space and calculated interstitial albumin concentration in sheep. Fed. Proc. **30:** 379.
42. BRIGHAM, K. L. & N. C. STAUB. 1975. Lung interstitial protein: studies of lung lymph. *In* Proceedings of Albumin Workshop. J. T. Sgouris & A. Rene, Eds.: 126-132. National Institutes of Health. Bethesda, Md.

DISCUSSION

T. R. HARRIS (*Vanderbilt University, Nashville, Tenn.*): If interstitial fluid pressure changes with lung height, as does microvascular pressure, why do you think there is a regional difference in filtration?

A. E. TAYLOR: If interstitial pressure changes with lung height, as our segmental wedge catheters suggest, it is not necessary to filter more at the bottom of the lung than at the top.

T. R. HARRIS: Our recent work on models of lung fluid exchange also indicates that interstitial fluid pressure must be taken into account in order to explain lymph flow increases with left atrial pressure change.

A. E. TAYLOR: I have no doubt that interstitial fluid pressure in the normal lung is negative, certainly in the peribronchovascular spaces. The important question is, What is the pressure at the filtration site and what pressure is responsible for lymph formation and lymphatic filling?