STARLING (1894, 1896) described the basic forces responsible for producing fluid shifts between the circulating blood and the surrounding tissue spaces. On page 324 of his classical article entitled "On the absorption of fluids from the connective tissue spaces," Starling described how capillary pressure determines transudation into the tissues and the osmotic pressure of the proteins determines absorption from the tissues. The paper also investigated how tissue pressure affects absorption, and Starling came to the correct conclusion that tissue pressure would not cause fluid to be absorbed from the tissue unless this pressure was not transmitted to the veins. Starling also recognized that a small amount of fluid was lost continually from the circulation ("frictional resistance of the capillary wall") and formed lymph, but believed that this was small and that the forces tending to move fluid out of and into the circulation were almost balanced. Finally, Starling postulated that tissue colloidal osmotic pressure decreased following elevation of capillary pressure and provided the opposing forces to limit transudation of fluid into interstitial spaces. Thus, Starling defined the basic forces responsible for maintaining fluid balance between the microcirculation and interstitium, and physiologists have termed tissue pressure (P_t), capillary pressure (P_c), plasma colloidal osmotic (\pi_p) pressure, and tissue colloidal osmotic (\pi_t) pressure as Starling forces. However, a mathematical relationship between those forces was not formulated by Starling in his original papers. Staub (1978) presents a delightful discourse concerning the historical development of the mathematical description of the Starling hypothesis:

\[ P_c - P_t = \pi_p - \pi_t. \]

Staub indicates that the equation was written for the first time by Iverson and Johansen in 1929, although Landis (1927, 1928), who measured capillary pressure for the first time, produced a regression equation which related \( P_c - \pi_t \) to capillary filtration rate. Perhaps the most extensive review on this subject was presented by Landis in his classical review of 1934 in which he discussed not only the forces, but also how the tissue forces changed to oppose increases in venous pressure ("margin of safety," Krogh et al., 1932).

Until the more recent work of Guyton and colleagues (Guyton, 1963; Guyton et al., 1966, 1975) and Wiederhielm (1967, 1972), who introduced the concept of a subatmospheric interstitial fluid pressure and the physiochemical nature of the interstitium, respectively, scant attention had been paid to the interstitium and how forces generated within this space affect fluid movement between capillary and interstitial fluids. From the early 1960's until the present, the amount of work in this area has increased severalfold, and several excellent experimental models have been developed in which Starling forces can be estimated at very controlled and defined physiological states (Garlick and Renkin, 1970; Staub, 1971; Gibson, 1974; Drake, 1975; Mortillaro and Taylor, 1976; Chen et al., 1976; Granger et al., 1977; Parker et al., 1978, 1979; Grega et al., 1979).

The objective of this review is not to tabulate the many estimates of tissue pressure, capillary pressure, plasma colloidal osmotic pressure, tissue colloidal osmotic pressure, and lymph flows which have been published over the last twenty years, but to present studies in which most of the variables affecting fluid movement have been measured at well defined steady states within a single preparation at different tissue fluid volumes. As this review develops, it should become increasingly clear that the Starling forces and lymph flow, like all physiological parameters, are dynamic, and it is difficult, if not impossible, to discuss fluid volume movement across cap-
illary walls when only one or two forces responsible for the flows are measured. Because of the nature of Starling forces and lymph flow, it is more relevant physiologically to evaluate how these forces are altered at different states of tissues swelling than to present the various published arguments concerning their normal values in a variety of mammalian tissues. For the interested reader, there are four excellent review sources for these basic arguments originating from the laboratories of Guyton (Guyton et al., 1968, 1971) and Wiederhielm (1972, 1979).

The present review begins with a basic discussion of an idealized capillary-tissue fluid exchange system in which the behavior of each Starling force and lymph flow is described as fluid enters the interstitium. A brief description of how each force is estimated in each tissue bed is later developed to facilitate data interpretation. The review then focuses on how the Starling forces are altered during edema formation in several different tissue beds and what interpretative problems are associated with these published findings. Finally, the review develops possible directions for future research which should lead to an extension of our basic knowledge concerning the control of fluid balance at the capillary-tissue level.

Fluid Balance: Capillary-Tissue-Lymphatic System

Capillary walls are pierced by many types of openings which can serve as conduits for fluid movement between capillary fluid and the surrounding tissues. Most capillary walls are usually described as continuous but having a few openings between endothelial cells (lung, skeletal muscle, etc.). The brain capillaries appear to have no openings and are referred to as "tight junction" capillaries. Other capillaries are described as fenestrated and have very thin diaphragms interspaced between endothelial cells (intestinal, bronchial, glomerular, etc.). Finally, other types of capillary walls are described as being discontinuous with very large openings appearing in their walls (liver, spleen). For the purpose of this presentation, only an idealized capillary wall will be used to describe fluid movement in different organs, but in the real system, fluid can cross the capillary walls through junctions between endothelial cells, through the endothelial cells, or through larger leaks in microvessel walls (Bennet et al., 1959).

The evaluation of Starling forces in any capillary-tissue system requires that tissue volume (or weight), lymph flow, lymph and plasma colloid osmotic pressure, tissue pressure, capillary pressure, and capillary permeability characteristics be measured in a single preparation. More importantly, a complete analysis requires that all forces and flows be in a steady-state and the tissue volume not change with time. At the present time, these parameters can be measured simultaneously only in isolated, perfused organ systems. The reader can easily appreciate that each organ's capillary structure is different, depending on its functional role, and to add more complexity to the problem, most organs contain several distinctly different capillary systems (e.g., intestine: mucosa, submucosa, smooth muscle; lungs: pulmonary-different zones, bronchial, etc.). Therefore, a true description of the actual phenomena which occur at each capillary wall cannot be ascertained using data determined in total organs. The Starling forces and lymph flows presented in this review will necessarily represent average organ values which obviously are gross oversimplifications of the real system. However, the data collected in organ systems are extremely useful for describing the overall fluid balance at a given tissue volume and provide us with the only means presently available for assessing the behavior of the capillary-tissue-lymphatic system in intact organ systems (Melander et al., 1964; Wallentin, 1966; Levine et al., 1967; Mellins et al., 1969; Taylor et al., 1973).

Definition of Starling Forces

Figure 1A represents the idealized capillary, in this case, surrounded by a tissue reservoir with a lymphatic system draining the tissues. In this system, the volume flow occurring across the capillary walls (Jv) can be described by (Pappenheimer and Soto-Rivera, 1948; Kedem and Katchalsky, 1958):

\[ J_v = K_{fc} [(P_c - P_t) - \sigma_0(\pi_p - \pi_i)] \]  

where \( K_{fc} \) is the filtration coefficient of the capillary wall (volume flow/unit time per 100 g tissue per unit pressure), \( P_c \) is the capillary pressure, \( P_t \) is the interstitial fluid pressure, \( \pi_p \) is the colloid osmotic pressure of the tissue fluids, and \( \sigma_0 \) is the osmotic reflection coefficient of all plasma proteins. \( \sigma_0 \) is equal to 1 if the capillary wall is impermeable to the colloid and is equal to zero if the membrane is freely permeable to the colloid.

Equation 1 represents a stationary state equation which requires all forces, \( P_c, P_t, \pi_p, \) and \( \pi_i \), to be at steady state values and \( K_{fc} \) and \( \sigma \) constant for a given condition.

Capillary Pressure (Pc)

In Figure 1A, the pre- and postcapillary resistances are depicted as inflow and outflow resistances because these parameters determine capillary pressure. Capillary pressure has been measured experimentally by using direct cannulation procedures (Landis, 1927; Wiederhielm, 1967; Zweifach and Taglietta, 1958) and estimated indirectly by measuring gravimetric pressures in isolated organs (Pappenheimer and Soto-Rivera, 1948; Johnson and Hanson, 1966; Gaar et al., 1967; Diana and Laughlin, 1974). Obviously, many hormones, drugs, etc. affect vascular resistance, so capillary pressure is variable from moment to moment in all capillary beds. For the remainder of this discussion, we will allow cap-
ILLUSTRATION: A. CAPILLARY + TISSUE + LYMPHATIC SYSTEM

VOLUME FLOW ACROSS CAPILLARY WALL

LYMPH FLOW

EXAMPLES: MUSCLE, SKIN, JOINTS

B. CAPILLARY + TISSUE + LYMPHATIC + OVERFLOW SYSTEM

VOLUME FLOW ACROSS CAPILLARY WALL

LYMPH FLOW + OVERFLOW SYSTEM

EXAMPLES: LUNI - ALVEOLI, INTESTINE - LUMEN

KIDNEY - URINE, LIVER - ASCITES

Figure 1 A schematic representation of a capillary-tissue-lymphatic system (A) and a capillary-tissue-lymphatic overflow system (B). The Starling forces, capillary pressure ($P_c$), tissue fluid pressure ($P_t$), plasma colloid osmotic pressure ($\pi_p$), and tissue colloid osmotic pressure ($\pi_t$) are schematically represented in the capillary and the surrounding tissue compartment. The lymphatic flow is represented by an overflow pipe and collector and the overflow system is depicted as an arrow. Dots represent plasma proteins in plasma, tissue fluid, and lymph.

ILLUSTRATION: STARLING FORCES/Taylor

pressures at the two ends of the capillary system. Wiederhielm (1979) recently has presented a model incorporating this hypothesis which indicates that the average capillary pressure as presented in this article represents an average capillary pressure weighted by the volume conductance of the arterial and venular portions of the fluid exchange system.

Tissue Fluid Pressure ($P_t$)

$P_t$ has been estimated in several different fashions: by implanting porous devices into tissues (Guyton, 1963, 1966; Prather et al., 1971; Calnan et al., 1972), by using cotton wicks inserted into tissue (Scholander et al., 1968; Snashall et al., 1971; Har-gens et al., 1978), or by inserting needles into tissue spaces (McMaster, 1946; Wiederhielm, 1967; Brace et al., 1975; Nicoll and Hogan, 1978). Using most techniques, the tissue pressure responds to fluid entering or leaving the tissues. The importance of tissue pressure as a Starling force is related to how efficiently it responds to changes in tissue volume; i.e., do small changes in tissue volume cause only small or large changes in tissue pressure?

Wiederhielm (1972) has described the interstitium in terms of its mucopolysaccharide-collagen make-up and describes the tissue spaces as being composed mainly of hyaluronate, chondroitin sulfate, and collagen. These macromolecules provide a meshlike network through which fluid must percolate to reach the lymphatics. The swelling characteristics of many tissues behave similarly to hyaluronate swelling, and it is now well accepted that the swelling characteristics of tissue is determined by these macromolecules and surrounding structures such as muscle sheaths, skin, or capsules.

Colloid Osmotic Pressure of Tissue ($\pi_t$) and Plasma ($\pi_p$)

The colloid osmotic pressure ($\pi_p$) of plasma can be measured by using the simple osmometer of Prather et al. (1968) and also can be calculated using the equations developed empirically by Landis and Pappenheimer (1963) when the concentration of the different protein fractions in the plasma is known. The calculations based on empirical equations are affected greatly by alterations in the various protein fractions in plasma (Navar and Navar, 1977; Gabel et al., 1980), and $\pi_p$ should be measured at body temperature rather than calculated whenever possible. The value of $\pi_t$ has been estimated by sampling lymph and by analyzing the fluid collected from wicks and within implanted devices (Aukland and Fandes, 1973; Taylor and Gibson, 1975; Reed and Aukland, 1977). For most organs, tissue fluid and lymph collected before entering a node appear to be very similar (Taylor and Gibson, 1975; Rutili and Arfors, 1977; Renkin, 1979); however, some tissues, such as lung, are problematic relative to this assumption of equivalency between lymph and tissue fluids. The basic problem inherent in lung tissue is that the contents of the larger...
perivascular and peribronchial spaces do not seem to be well mixed. At high lymph flows, this does not constitute any real problem, but at normal and slightly elevated lymph flows, the mixing effect could cause a substantial problem (Nicolaysen et al., 1975; Guyton et al., 1976; Gee and Havill, 1980).

Lymph Flow (LF)

When the tissue is neither gaining nor losing weight, the amount of fluid leaving the capillary is exactly equal to lymph flow. Lymph flow has been measured in several organs by simply measuring the flow from a lymph vessel draining the organ utilizing either calibrated pipettes or lymph weighing procedures. From estimates of lymph flows at different tissue steady states, the Starling forces' balance can be estimated (Johnson and Richardson, 1974; Erdmann et al., 1975; Chen et al., 1976; Taylor and Drake, 1977; Mortillaro et al., 1978; Laine et al., 1979; Richardson et al., 1979). It is well appreciated that lymphatics remove proteins from the tissue spaces, yet their capability to oppose tissue volume expansion following increases in capillary filtration is variable among tissues.

Volume Overflow Systems

In several organs, another system serves as a means of removing excess tissue fluids and perhaps preventing excessive interstitial swelling—an overflow system which is depicted schematically in Figure 1B. When excessive fluid enters the interstitium in organs such as lung, intestine, and liver, fluid can begin to enter the alveoli, intestinal lumen, and peritoneal cavity, respectively (Guyton and Lindsay, 1959; Staub, 1974; Yablonski and Lison, 1976; Granger et al., 1977; Laine et al., 1979). However, at least two fluid systems, the brain and eye, do not possess lymphatics and their normal drainage systems are best described as an overflow system. The arachnoid granulations and the canal of Schlemm represent the only means by which fluids and tissue protein can be removed from the brain and eye, respectively (Davson, 1960; Rapoport, 1976; Bradbury, 1979).

Filtration Coefficient (Kf,c)

There are two coefficients used to describe the Starling relationship: the filtration coefficient (Kf,c) and the reflection coefficient (σ). Kf,c is equal to the product of the hydraulic conductance of the membrane (Lp) and the surface area of the organ (S). The hydraulic conductance of the capillary membrane is equal to: NCr'/AΔX; where N is the number of pores per cm², C is a constant, τ is the radius of the filtering pores, ΔX is the thickness of the capillary wall, and n is the viscosity of the filtering fluid. Lp is a membrane parameter and is independent of exchange surface area; however, the Kf,c estimated for capillary beds is a function of available surface area. Since different organs possess different capillary densities, then Kf,c may be quite different among organs, yet their Lp's may be similar. Also, within the same organ, Kf,c may increase or decrease because of closure or opening of more capillaries with similar conductance characteristics.

Kf,c has been shown to change 4-fold in some organs (Johnson and Hanson, 1968; Mortillaro and Taylor, 1976). Although usually a 2-fold change in Kf,c represents the maximal change associated with this parameter (Granger et al., 1976; Richardson et al., 1979; Granger et al., 1979a), there is little doubt that changes in effective surface area can greatly alter fluid movement into the tissue spaces, independent of alteration in Starling forces (Haglund and Lundgren, 1972). The methods for measuring Kf,c in organs rely on weighing isolated organs and analyzing their weight transients after imposing a capillary pressure. The range of Kf,c estimates from several laboratories are: 0.07-0.25 for lung, 0.08-0.24 for intestine, 0.010-0.015 for skeletal muscle, and 0.2-0.3 for colon in units of ml/min per mm Hg per 100 g.

The importance of Kf,c as it relates to fluid balance is as follows: if the total lymph flow draining an organ is known as well as the filtration coefficient, then the imbalance in Starling forces (ΔPf) can be estimated when the tissues are not changing volume by the following equation:

$$\Delta P_f = \frac{\text{total lymph flow}}{K_{f,c}}$$

where \(\Delta P_f = (P_e - P_t) - \sigma_l (\sigma_p - \sigma_t)\). Some investigators have also used Equation 2 to estimate Kf,c. By measuring or calculating all the Starling forces and collecting total organ lymph flow, Kf,c can be solved for in Equation 2 provided that the organ is not losing or gaining weight (Erdmann et al., 1975). Equation 2 points out a very important relationship between lymph flow and its ability to buffer changes in capillary pressure. If Kf,c is small, then small lymph flows may be important in preventing excessive build-up of tissue fluids; however, if Kf,c is large, then even large lymph flows may not represent important volume overflow systems. The point to remember concerning the importance of lymph flow in fluid balance regulation is not the absolute magnitude of lymph flow but the lymph flow relative to Kf,c. The relationship described by Equation 2 determines the lymphatic's ability to remove filtered fluid following changes in capillary pressure rather than the absolute magnitude of lymph flow (Nicoll and Taylor, 1977; Taylor and Drake, 1977).

For the case of an overflow system (Figure 1B), the AP operating across the capillary wall must be related to the sum of total organ lymph flow plus the volume flow escaping the tissues via the overflow system (Vof)

$$\Delta P = \frac{Lp + V_{OF}}{K_{f,c}}$$
For tissues such as intestine and liver, $V_{OF}$ may be considerable following elevations of tissue pressure (Laine et al., 1979), and $V_{OF}$ can be a considerable portion of the lymphatic safety factor relative to interstitial swelling.

**Reflection Coefficient ($\sigma_d$)**

Until very recently, neither the mathematical approach nor the experimental data were available for estimating the reflection coefficient in any capillary system. In the last 3 years, the correct mathematical approach and empirical methods have been developed to estimate $\sigma_d$ in several organs using lymph protein fluxes (Patlak et al., 1963; Taylor et al., 1977; Brace et al., 1977a; Brace et al., 1978; Granger and Taylor, 1980). The basic approach for assessing the reflection coefficient is derived from the equation relating the lymph to plasma ratios of a particular plasma protein at different lymph flow states:

$$CL/CP = \frac{1 - \sigma_d}{1 - \sigma_d e^{-x}}$$

where $x = (1 - \sigma_d) \frac{J_l}{PS}$ (Granger and Taylor, 1980) and where $C_L$ and $C_P$ refer to the concentrations in lymph and plasma of the particular protein, $J_l$ refers to the lymph flow, and $PS$ refers to the permeability coefficient surface area product. Equation 3 states that the lymph to plasma ratio will approach $1 - \sigma_d$ at high volume flow states when the denominator approaches one. Using this theoretical approach, $\sigma_d$ has been obtained for total plasma proteins and several protein fractions in a number of organ systems by increasing lymph flow until $C_L/C_P$ is essentially constant. When $C_L/C_P$ is constant, the reflection coefficient can be estimated by:

$$\sigma_d = 1 - CL/CP$$

For total plasma proteins, $\sigma_d$ appears to be 0.7 - 0.95 for intestine (Granger and Taylor, 1980), lung (Parker et al., 1980), hindpaw (Rutillà et al., 1979), and colon (Richardson et al., 1980). However, $\sigma_d$ is close to 0 for liver sinusoids (Granger et al., 1979b) and has not been evaluated in other capillary beds. For the basic Starling equation to correctly predict volume flow, the measured $\Delta\pi$ acting across the capillary wall should be multiplied by the appropriate value of $\sigma_d$. However, caution should be used when applying this simple logic because the capillary permeability may be altered by different experimental procedures. For example, in the small intestine histamine reduced $\sigma_d$ from 0.93 to 0.6 (Mortillaro et al., 1979). Therefore, $\sigma_d$ must be measured in each preparation before the effective $\Delta\pi$ across the capillary wall can be evaluated relative to fluid volume regulation.

**Changes in Starling Forces Following Elevation in Capillary Pressure**

Figure 2A is a schematic representation of events that occur in an idealized capillary bed when capillary pressure is elevated. Tissue pressure increases, lymph flow increases, and tissue colloid osmotic pressure decreases, but tissue volume does not change greatly. These forces change to accommodate the increased capillary pressure, and the ability of these forces to change and offset alterations in capillary pressure has been described as the "edema safety factor" (Guyton and Coleman, 1968; Taylor et al., 1973) and the "margin of safety" (Krogh et al., 1932). When the forces can no longer change, a great amount of fluid will enter the tissues for only small changes in capillary pressure; i.e., the edema safety factors are overwhelmed.

Figure 2B represents an overflow tissue system in which $P_t$, $\pi_t$, and lymph flow change to some degree following elevation of capillary pressure and then the overflow system becomes operative. Ob-
viously in lung, fluid-filled alveoli are detrimental to blood oxygenation; in intestine, fluid entering the lumen opposes the active absorption process and increases in ascitic fluid formation cause large losses of solute and water from the plasma. However, it may well be necessary to protect the liver interstitium against excessive tissue swelling because of its metabolic functions. Although ascitic fluid formation is abnormal, it may serve as a safety factor as far as the liver-tissue volume is concerned (Laine et al., 1979).

**Tissue Pressure**

When tissue pressure is measured, by whatever means, it has been found to behave as shown in Figure 3. At low capillary pressure changes, tissue fluid pressure changes markedly for only small changes in tissue volume. However, when the tissues begin to swell excessively, tissue pressure does not change greatly in most beds even when large amounts of fluid accumulate in the tissues (Guyton, 1965; Guyton et al., 1975; Mortillaro and Taylor, 1976; Chen et al., 1976; Parker et al., 1978). This behavior has been observed in many tissue beds and is related to the swelling characteristics of the interstitium (Wiederhielm, 1972). As volume begins to enter the interstitium, only small volume changes are necessary to raise tissue pressure (low tissue compliance; compliance = ΔV/ΔP). However, as the tissues expand, tissue elements expand more easily and large amounts of fluid enter the interstitium (high compliance) (Guyton, 1965). In capillary beds with overflow systems, such as the alveoli in lung, the amounts of fluid which can accumulate in these potential spaces are tremendous. Conversely, organs which do not possess overflow systems may respond by producing very high tissue fluid pressures. This condition is seen in skin before some stress relaxation occurs in the tissue. As fluid first beings to accumulate in the leg, the skin is very taut and high tissue pressures oppose further filtration. However, with time, the pressure causes the skin to become more elastic and the tissue pressure decreases, which results in greater tissue fluid accumulation.

**Tissue Oncotic Pressure**

Figure 4 demonstrates how tissue colloid osmotic pressure behaves as capillary pressure is increased across an idealized capillary wall. As filtration proceeds, tissue oncotic pressure will decrease until it finally attains values associated with a true capillary filtrate. This behavior has been observed in all capillary beds studied, with the exception of the liver. The decrease in Ψt increases the magnitude of the second term in the Starling equation [Δ(Ψt - Ψp)] and thus buffers the change in capillary pressure. The liver is an interesting organ in regard to changes in Ψt, with filtration because the changes are opposite to those observed in other tissues (i.e., Ψt actually increases with increasing filtration). This finding has been interpreted as indicating that the liver tissue limits the movement of proteins between lymph and capillaries at normal tissue hydration states. When the tissues swell, the interstitial matrix no longer restricts protein movement and the fluid entering the lymphatics approaches the concentration in plasma (Granger et al., 1979b; Laine et al., 1979). If capillaries become "leaky," then Ψt will not change to the same extent as observed in normal capillaries when filtration is increased (dotted lines). This phenomenon has been demonstrated in lung (Brigham et al., 1974; Brigham and Owen, 1975a; Brigham et al., 1976), hindpaw (Rutili et al., 1979), and intestine (Granger et al., 1980) following administration of histamine, *Pseudomonas*, and in most cases, *Escherichia coli* endotoxin. In most capillaries, Ψt decreases when filtering forces are increased; however, any factor which tends to increase capillary permeability to plasma proteins will certainly affect this phenomenon and decrease the effectiveness of Ψt in opposing capillary filtration. Moreover, the importance of the second term in the Starling equation will be diminished even further when the capillary wall becomes leakier to
plasma proteins because, not only will \( \pi \) be larger, but \( \pi_t \) will be smaller; i.e., the effect is not simply additive, but amplified.

Why does \( \pi \) decrease when filtration is increased above normal values? There are several mechanisms responsible for the decreased tissue colloid osmotic pressure: (1) a simple dilution of tissue proteins occurs due to the filtration of a relatively protein-poor fluid into the tissues, (2) a bulk removal of tissue proteins by the lymphatics occurs when fluid enters the tissues, and (3) a change in the volume of distribution of tissue proteins occurs at higher tissue volumes. All three mechanisms are operative in different capillary beds, and their specific contribution to the overall decrease in \( \pi \) is variable (Drake, 1975; Chen et al., 1976; Granger, 1979; Parker et al., 1980).

**Lymph Flow**

In most organs, lymph flow increases when capillary pressure is elevated, but the magnitude of change varies greatly from tissue to tissue. Figure 5 schematically represents the experimental findings from several different capillary beds. Lymph flow appears to increase linearly with increased capillary filtration in most organs, reaches a plateau at high filtration rates (subcutaneous tissue, muscle), or actually decreases at high tissue volume states (intestine, lung). Since lymph flow is propelled by either tissue motion or intrinsic lymphatic pumping ability and filled by the tissue pressure-lymphatic pressure gradient, it is evident that the lymphatic system can respond differently at different hydration states (Casley-Smith, 1977). Basically, the lymphatics finally must reach their maximum flow rate, but this may not be attainable in some organs. However, the lymphatics do attain a maximum flow rate in subcutaneous tissue (hind-paw) unless the observed effect is due simply to the increased tissue pressure somehow retarding lymph flow.

The decrease observed in lymph flow at high tissue hydration states occurs in intestine (Granger et al., 1977) and lung (Parker et al., 1979) and is somehow related to opening of mucosal and alveolar membranes, respectively, with a concomitant decrease in tissue pressure which decreases the lymphatic filling pressure. The possibility exists that opening of an overflow system causes the resulting interstitial spaces to behave like a balloon. The effect is described mathematically by the Laplace relationship between radius and wall tension. Basically, if the tissues behaved as a balloon, then initially, a large change in pressure would result from only small changes in tissue volume; then the pressure may well decrease as the volume increases (a negative compliance) until a critical volume is reached at which the pressure again rises. This effect has been described in detail as it applies to alveolar stability and explains how a small volume balloon can empty into a larger volume balloon. The possibility does exist that a negative compliance portion of the interstitium exists, especially if the organ demonstrates a Laplace effect. This possibility has not been examined specifically but, if operative, could explain why lymphatic flow decreases at high tissue volume states in some overflow systems.

Finally, it should be emphasized that lymph flow can increase to tremendous values [90 times control in right duct lymph] following decreases in plasma proteins (Gee and Spath, 1980). Yet, when capillary pressure is increased in steps and lymph flow measured at each steady state, the high values which are associated with the non-steady state measurements never are attained by the system. In fact, Chen et al. (1977) have published a very interesting article along these lines. Chen’s study revealed that lymph flow increased immediately after elevations of capillary pressure, but that lymph flow decreased to values roughly two-thirds of the maximal value after a few minutes. This effect was even more pronounced at high capillary pressures. They interpreted these findings as indicating that lymph flow increases in response to the rate of change in tissue pressure, not in response to its absolute value. Since tissue compliance usually increases with hydration, more volume must be filtered to change the tissue pressure, and this would explain the lower lymph flows relative to those obtained when tissue pressure was changing greatly in the low compliance range. However, the failure of lymph flow to maintain its highest possible flow rates when the tissues are in an edematous state is a very puzzling observation relative to fluid volume regulation. Why does lymph flow not maintain its maximal value to provide the tissues with a better volume overflow mechanism as predicted by theory rather than decreasing to lower values? Perhaps future research relative to how tissue forces affect the behavior of the lymphatic system will provide the necessary information to answer this important physiological question.
Changes in Starling Forces Associated with Increased Capillary Pressure

The following examples of Starling force analysis in various tissue beds represent portions of studies in which rather large changes in capillary forces (≥20 mm Hg) were imposed on the organ by altering capillary pressure. These selected studies will emphasize primarily the maximal change which can occur in tissue pressure, tissue colloidal osmotic pressure, and lymph flow before excessive tissue edema occurs. However, in most analyses presented in this section, other tissue hydration states also were studied which demonstrated that the contribution of each Starling force to the total opposing force may be different at lower tissue hydration states. In each organ, tissue volume, lymph flow, and lymph and plasma colloidal osmotic pressure were measured when the organ neither lost nor gained weight, lymph flow was constant, and lymph protein was unchanging for a defined period of time (usually 30-50 minutes). In some instances, capillary pressure, tissue pressure, the filtration coefficient, and the reflection coefficient were also measured. Once these parameters were considered to be in a steady state, the venous pressure was elevated to increase capillary pressure and the parameters were again measured after the system had attained a new steady state. The contribution of \( P_t \), \( \sigma_e \) (\( \pi_e - \pi_t \)), and lymph flow to the overall ability of the tissues to oppose changes in capillary pressure and prevent excessive edema, the total edema safety factory, can then be evaluated from the data.

Small Intestine

Figure 6, A and B, represents estimates of the changes observed in lymph flow (LF, dotted histogram), colloid osmotic pressure gradient (\( \pi_e - \pi_t \), striped histogram), and tissue pressure (\( P_t \), clear histogram) relative to the total increase in capillary pressure imposed on two different intestinal preparations. In both experimental models, the Starling forces increased sufficiently to provide a buffering capacity (or edema safety factor) equal to the imposed change in capillary pressure. The percent of the total change in Starling forces is shown for each parameter on the ordinate, and the pressure equivalent of each force change is shown under each histogram.

In the work of Mortillaro and Taylor (1976) (Fig. 6A), capillary pressure was increased by 20 mm Hg in a cat ileal preparation. The change in tissue colloids provided 50% of the tissue force change opposing filtration, whereas increased lymph flow and tissue pressure provided 20 and 30% of the counterbalancing force, respectively. Figure 6B represents the findings from Johnson and Richardson's (1974) study, which was conducted on an isolated dog ileal preparation. Capillary pressure was increased by 9 mm Hg, and the major portion of the capillary pressure change was buffered by the increased colloid osmotic pressure gradient acting across the capillary wall. Lymph flow can be estimated to provide approximately 20% of the tissue's ability to buffer the increased capillary pressure in this study.

The reason that different tissue pressures are obtained in two similar studies of intestine is not clear at the present time, but it could be the result of several different factors. (1) \( P_t \) was estimated in Mortillaro's study using the Starling equation (\( \Pi_t \) and \( \sigma_e \) were the only parameters in the Starling equation not measured in this study). If the reflection coefficient differed from unity, then the calculated \( P_t \) would be in error. It now is well known that fat absorption increases capillary permeability in the small intestine. In fact, \( \sigma_e \) decreased from 0.9 to 0.7 during fat absorption (Granger and Taylor, 1978). If permeability was changing during the course of the experiment, then the \( P_t \) calculation...
would be in error. (2) $P_t$ was measured in Johnson and Richardson’s study using a needle. Brace et al. (1975) have shown recently that a needle will not follow tissue pressure changes except under very controlled conditions. Therefore, the actual tissue pressure may have been different from that measured using the needle method. (3) The possibility always exists that different species have different means of providing fluid balance control. However, Granger and Taylor (1980) have demonstrated recently that the lymphatic protein concentration decreases to 10% of plasma levels when venous pressure is elevated to 30 mm Hg in the cat intestine, and this is similar to the colloid osmotic pressure changes observed in Johnson and Richardson’s study. (4) The magnitude of volume absorption in the small intestine greatly affects $P_c$ and $\pi_t$. For instance, if the tissues were absorbing in either study, then $\pi_t$ would be expected to behave in a different fashion since absorption will increase the tissue volume and also dilute tissue proteins. Increasing capillary pressure in an absorbing or volume expanded state will result in different behavior of $\pi_t$ (Granger and Taylor, 1978). (5) The increase in capillary pressures was quite different between the two studies: 9 vs. 20 mm Hg. However, Mortillaro also estimated Starling forces at other hydration states and at the same capillary pressure range as studied by Johnson and Richardson, and the tissue proteins did not decrease to the same extent. Thus, it appears that the differences observed between these two studies could be explained by different capillary permeabilities and tissue hydration states existing in the preparations, but a more complete description of how the intestine behaves during edema formation requires further study. The most important finding in these investigations is that studies from different laboratories, using similar tissues, demonstrate that the Starling forces do change to oppose increased filtration, although different mechanisms ultimately may be responsible for the final force balance.

Colon and Liver

Figure 6, C and D, represents Starling force analyses conducted on colon and liver preparations when capillary pressure was altered by 12 and 24 mm Hg, respectively. In the colon preparation used by Richardson et al. (1980) (Fig. 6C), lymph flow did not provide a substantial safety factor and only the increases in the colloid osmotic pressure gradient and tissue pressure changed to provide the opposing forces. Since the liver sinusoids are extremely permeable to plasma proteins, $\pi_c - \pi_t$ was not changed when capillary pressure was altered in the study of Laine et al. (1979) (Fig. 6D). In liver, lymph flow and/or ascites formation provides 40% of the tissue’s response to increase capillary filtration. Surprisingly, tissue pressure increases to levels which provide 60% of the retarding force.

Thus, no generalizations can be made from the studies presented in this section, except to point out that $\pi_c - \pi_t$ appears to be the most important change in the Starling forces occurring in the gastrointestinal tract following elevations of capillary pressure. However, it must be emphasized that $\sigma_d$ must be measured for each tissue at each hydration state before inferences can be made concerning the actual osmotic effect of decreasing tissue protein concentrations. Tissue pressure changes provide a major portion of the safety factor in the data presented in Figure 6, A, C, and D, and it is unclear at the present time why this was not demonstrated in the data from Johnson and Richardson’s study. Lymph flow appears to provide some buffering ability in all tissues, with the exception of the colon where it is quite clear that the lymphatic system does not provide any force relative to volume removal.

Lung

Figure 7, A and B, represents Starling force analyses performed on lung tissue. Figure 7A shows data replotted from the study of Erdmann et al. (1975) which was conducted in the intact sheep model developed by Staub (1971, 1978).

In this study, lymph flow and lymph and plasma colloid osmotic pressures were measured and capillary pressure was calculated using the equation developed empirically by Gaar et al. (1967, 1968). Using these measurements, the only two forces which changed to oppose the capillary filtration were the increased lymph flow and colloid osmotic pressure gradient.

Figure 7B is a representation of the data from the work of Drake (1975) who estimated the Starling forces in isolated dog lungs. Lymph flow, lymph and plasma colloid osmotic pressure, the filtration coefficient, and isogravimetric capillary pressure were measured in each preparation. Using these values and assuming that the reflection coefficient $\epsilon = 1$, $P_t$ could be calculated using Equation 1. Again, it is evident that the major force which changes to oppose capillary filtration is the decrease in tissue
colloids (50%) while lymph flow and tissue pressure increases provide approximately 25% each to the tissue's ability to buffer changes in capillary pressure.

There is excellent agreement between Erdmann's and Drake's studies relative to the changes observed in tissue colloid osmotic pressure. Drake's study indicates that both lymph flow and tissue pressure play a role in opposing capillary pressure changes, whereas only the former appeared to be important in the intact sheep lung studies. Several other investigators have employed the sheep model to evaluate changes in capillary permeability, and an analysis of these data indicates that lymph flow and the osmotic pressure changes are important factors opposing edema formation in that model (Brigham et al., 1974; Brigham and Owens, 1975b; Bland et al., 1977; Malik, 1977). It appears that the differences observed between the studies conducted in sheep and dog lungs can only be resolved when all Starling forces are measured in a single preparation. To accomplish this in intact animals is difficult at the present time; yet, new techniques should make this type of study possible in the very near future.

Nordin et al. (1978) recently measured vascular pressures, tissue pressure, and tissue and plasma colloidal osmotic pressure in bronchial tissues using microtechniques. From this study the authors built an interesting fluid balance model for bronchial tissue. The model predicts how the capillaries provide the fluid which accompanies the Cl transport occurring across the bronchial epithelium to form the bronchial fluid layer. Moreover, these investigators also were able to analyze the effects of lung height on interstitial fluid accumulation in bronchial tissue as it related to capillary filtration. Although some measurements reported in this study are open to serious arguments, they do indicate the magnitude of the Starling force changes and provide a great deal of information with which to describe the physiology of a very complex capillary-tissue-lymphatic system. Studies of this type are needed for all organ systems in order that the exact mechanism of fluid exchange can be assessed at the microcirculatory level. However, many technical limitations exist, and experimental designs must be improved before assessments of fluid volume control can be accomplished at the microcirculatory level in lung tissue.

It also is important to point out that different investigators recently have applied Starling force analyses as a means of evaluating the effects of various pathophysiological states on lung fluid dynamics (Bland et al., 1977; Malik, 1977; Demling, 1978). This approach certainly indicates the directional changes of the forces and constitutes an important experimental method to study lung fluid balance. Although qualitative in nature, this approach does provide a great deal of insight into the mechanisms associated with lung fluid balance and will serve as the basis for the design of more complete Starling force balance studies in intact lung models.

Finally, Drake et al. (1980) have developed means to determine the total edema safety factor in intact dog lungs. They have defined a "critical capillary pressure" by extending the observations made by Guyton and Lindsey (1959) that left atrial pressure must be increased to approximately 25 mm Hg before the lung gains weight at a continuous rate. In the experimental model used by Drake et al., an intact dog lung is weighed continuously, and left atrial pressure is elevated until the lung gains weight at a constant rate. The pressure at which the lung gains weight in a continuous fashion has been termed the "critical capillary pressure." This "critical pressure" then can be used to interpret how efficiently the Starling forces can change in different pathological and physiological conditions since the "critical pressure" represents the total edema safety factor. If the lung capillaries are leaky to plasma proteins, then the "critical capillary pressure" will decrease. By measuring the "critical pressure," lymph flow, and lymph colloids, the contribution of these forces in opposing filtration forces has been established by the investigators in several pathological conditions (Gabel et al., 1978).

### Hindlimb and Hindpaw

Figure 8, A and B, represents the data obtained by Brace et al. (1975) and Chen et al. (1976) for hindlimb and hindpaw preparations, respectively. Brace measured lymph and plasma colloid osmotic pressure and tissue pressure using implanted capsules when capillary pressure was increased by 7 mm Hg. From these measurements, they deduced that changes in Starling forces were confined to tissue pressure (70%) and osmotic gradient (30%) effects. Obviously, without a measurement of lymph flow and capillary permeability (both and ) it is difficult to assess the importance of each Starling factor and lymph flow in this particular study.

![Figure 8](image.png)
The study of Chen et al. represents the only complete study published to date relative to describing all Starling forces and lymph flow at several different tissue hydration states. They measured lymph flow, the filtration coefficient, tissue pressure, lymph and plasma colloidal osmotic pressure, and the capillary pressure at three different states of fluid hydration. Chen's findings are very similar to those observed by Bracey et al. over the same capillary pressure range. But Chen's data obtained at higher capillary pressures indicates two very important mechanisms relative to fluid volume regulation in subcutaneous tissue. First, the Starling forces are low in both hindpaw and hindlimb; therefore, this factor cannot change as greatly as has been observed in other tissues which contain high concentrations of tissue proteins. Secondly, since the Starling forces change by only 5-6 mm Hg, tissue pressure must absorb most of the change in capillary pressure in organs for which tissue proteins cannot change greatly, especially at high capillary pressures. Lymph flow also may provide a substantial buffering capacity in these types of organs provided that the Starling forces are small. It is of interest to note that tissue pressure changes 15 mm Hg as capillary pressure is increased from 12.8 to 38.0 mm Hg. Since the hindpaw is a dependent region, it appears that the low compliance of the tissues provides an additional safety factor which is not present in many tissues; i.e., the lower compliance characteristics of the hindpaw at relatively high tissue volume states prevents excessive fluid from entering the tissues even at rather high capillary pressures, which is not the case for most organs.

Other Organs

I will not review the extensive literature concerning the Starling force estimates made in the kidney. There are several excellent reviews on this subject (Brenner et al., 1976; Brenner and Humes, 1977; Essig and Caplan, 1979; Robertson, 1980), but the kidney poses some very interesting and physiologically important questions: How do the Starling forces behave in postglomerular capillaries? What differences exist between upper cortical vs. lower cortical capillaries? What types of capillary dynamics are present in the vasa recta? These are all very important questions and presently are under extensive investigation in several laboratories throughout the world.

The evaluation of Starling forces in the nervous system also has seen new and exciting experimental approaches. A simple model presented 4 years ago indicated that essentially no Starling forces had been measured in the brain at that time (Taylor and Granger, 1976). The only Starling force known with any certainty at that time was the colloid osmotic pressure of brain interstitial fluid, which is essentially zero. The article pointed out that: (1) a few interstitial fluid pressures had been measured in brain tissue, but the results ranged from -7 mm Hg to the positive cerebrospinal fluid pressure; (2) the brain fluid is composed of different fluid compartments, i.e., cerebrospinal fluid, white and gray matter, etc., which may have different swelling characteristics; (3) the fluids in various brain interstitial compartments are the results of active processes (choroid plexus), capillary filtration and cell swelling, not just capillary filtration alone, and (4) since the brain parenchymal capillaries are not permeable to most solutes, the crystallloid osmotic pressure gradient across the capillary wall would be an important regulator of tissue fluid volume.

That article stimulated several new studies in the area including two that have shown how tissue pressure, fluid conductance pathways, and crystalloids (as well as colloids) provide safety factors in brain tissue which oppose edema formation (Rapoport, 1978, 1979). Although the brain is an extremely difficult organ with which to work, several investigators are now measuring interstitial pressures and fluid conductance pathways during various phases of brain edema (Marmarou et al., 1975; Marmarou and Shulman, 1976; Bruce, 1978; Marmarou et al., 1978). Future studies using techniques developed in other organ systems should provide estimates of brain Starling forces, fluid drainage patterns, tissue fluid formation, and osmotic effects, not only within the vascular system, but also relative to how crystalloids in the tissues buffer increases in capillary pressure (Rapoport, 1979).

Complete Starling force and lymph flow analyses have not been conducted in other tissues. Fluid balance studies usually were confined to measuring one or two Starling forces in a particular organ because of technical limitations. In most instances, the tissue hydration states and capillary permeability estimates were not investigated, and these parameters must be evaluated before a complete fluid balance study can be interpreted in any organ system. As can be seen from this section, interpretations of data using only a few of the four Starling parameters are extremely difficult. In some instances a particular force may not change during edema formation and the force can rightly be ignored in an overall fluid balance analysis. However, each force must be evaluated experimentally in each organ system before eliminating it as a component of the tissue's edema safety factor.

Functional Studies

Very recently, a few studies have appeared which indicate the responsiveness of the Starling forces and lymph flow in different functional states. For example, the data from Granger and Taylor's (1978) study indicate that the absorptive force increases across the capillary wall when the ileum is absorbing fluid, since the transported volume contains no protein and Starling forces decrease. This $\Delta \pi$ change provides the major force allowing the capillaries in the intestine to remove the majority of the absorbed volume. The intestinal capillary permeability to plasma proteins also increased in this study. Therefore, the
Figure 9: Plot of Starling force analyses from the studies of Granger et al. (1980) conducted in a cat intestinal preparation. The clear histograms refer to $P_t$, $LF$, and $\sigma_d(\pi_p - \pi_l)$ for controls and the striped histograms refer to the same parameters measured after the infusion of glucagon into the intestinal circulation. The ordinate represents the value of each parameter (mm Hg). Note that tissue pressure increased from negative to positive values and lymph flow was not greatly changed. $\sigma_d(\pi_p - \pi_l)$ actually decreased, which indicates an increased capillary permeability to plasma proteins and reflects both a decreased $\sigma_d$ and an increased $\pi_l$ following glucagon infusions.

The effect of changing $\Delta \tau$ on capillary fluid exchange was not as great as would be predicted using normal values for the protein reflection coefficient.

Figure 9 represents another recent functional study by Granger et al. (1980). In this study, lymph flow and all Starling forces (with the exception of $P_t$) were measured, and in addition, both the filtration and reflection coefficients were measured at each tissue hydration state. The control values of $P_t$, $LF$, and $\sigma_d(\pi_p - \pi_l)$ shown as clear histograms, then were compared to those measured following infusions of glucagon, shown as striped histograms. Tissue pressure increased by 6 mm Hg, lymph flow increased but not significantly, and $\sigma_d(\pi_p - \pi_l)$ actually decreased, indicating that glucagon increased the capillary permeability to plasma proteins. In fact, in these studies, the intestine was "secreting" rather than absorbing during the glucagon infusions. Therefore, this study indicates that glucagon, a physiological hormone, affects the Starling forces and indirectly affects net volume transport across the intestinal mucosa.

The use of Starling force analysis for evaluating functional states of organs represents an important new area of research, and only by designing studies of this nature can the fluid balance in different organs be related to its physiological function. For example, in the two studies cited above, the change in $\sigma_d$ allows the investigator to more fully interpret the change associated with $\Delta \tau$. It is now becoming more apparent that Starling forces may behave quite differently when both functional and pathological conditions have changed within any particular organ system. Therefore, future studies along functional lines should greatly enhance our knowledge concerning the interaction of Starling forces, not only in opposing edema formation but also as they relate to altered functional roles in different physiological and pathological conditions.

**Interpretation of Starling Force Studies**

For the purpose of placing the preceding Starling force analyses into their proper perspectives, it is important to consider how the Starling forces behave at both normal and expanded tissue volume states. The study conducted by Chen et al. (1976) in dog hindpaw contains sufficient data to begin this discussion. Using values obtained for $P_t$, $P_c$, $\pi_p$, $\pi_l$, and lymph flow and assuming $\sigma_d = 1$, the following Starling relations are obtained:

**Force imbalance**

$$J_v = \frac{P_c - P_t}{K_f_c}$$

**Force imbalance**

$$= \frac{12.8 - (-4.7)}{(20.9 - 3.8)}$$

$$= 0.4 \text{ mm Hg;}$$

(Normal tissue volume, normal lymph flow)

**Force imbalance**

$$= \frac{24.8 - (-0.1)}{(20.9 - 1.6)}$$

$$= 5.6 \text{ mm Hg;}$$

($\Delta V = 1.7 \text{ ml/100 g; } LF = 10 \times \text{ control}$)

**Force imbalance**

$$= \frac{37.9 - (+10)}{(20.9 - 0.5)}$$

$$= 7.5 \text{ mm Hg;}$$

($\Delta V = 17.5 \text{ ml/100 g; } LF = 13 \times \text{ control}$)

At normal tissue hydration states, the forces are near a balance point. Only a small driving force exists across the capillary wall, which represents the normal lymph flow factor. The tissue volume is expanded only slightly when capillary pressure is altered by 12 mm Hg; the change in tissue pressure (4.6 mm Hg) and the decreased tissue colloids (2.2 mm Hg) compensate to oppose the increased filtration tendency of the capillary. The imbalance in forces at this hydration state is 5.6 mm Hg, which represents the lymph flow safety factor. At this level of capillary pressure, no visible edema was present; in fact, the tissues had only gained 1.7 ml/
100 g, which represents approximately a 10% change in interstitial volume. Thus, the tissue Starling forces and lymph flow can absorb a change in capillary pressure of 12 mm Hg in such a fashion that very little enters the interstitium.

When capillary pressure is elevated to higher levels (37.9 mm Hg), visible tissue edema results since the tissue volume expands to approximately twice its control value and tissue fluid pressure increases by an additional 10 mm Hg. Lymph flow did not increase significantly above the previous state of tissue hydration (lymphatic safety factor increased by only: 7.5 - 5.6 = 1.9 mm Hg).

The data presented in Figure 9 from an intestinal preparation can also be used to estimate the balance in Starling forces (Granger et al., 1980):

For force imbalance

\[ \frac{J_v}{K_{fe}} = (10.0 - (-2.5) - 12) \]

[Normal interstitial volume]

\[ = 0.5 \text{ mm Hg; } \]

For force imbalance

\[ \frac{J_v}{K_{fe}} = (12 - (+4) - 7) \]

[Gross edema]

\[ = 1 \text{ mm Hg. } \]

At normal hydration states within the small intestine, the Starling force imbalance is only 0.5 mm Hg. This study is not complicated by assuming that \( \sigma_d = 1 \), since it was measured in each preparation. After glucagon infusions, the tissues became grossly edematous, and yet the imbalance in forces was only 1 mm Hg.

There are both important differences and similarities between these two Starling force studies. The two important differences between these two fluid balance studies are: (1) Lymph flow provided a substantial safety factor in the hindpaw at moderately high capillary pressures because \( K_{fe} \) was small. However, in the small intestine, glucagon increased permeability and \( K_{fe} \) increased, and this resulted in almost no lymphatic safety factor, even in the face of gross interstitial edema. (2) Tissue pressure provided a large portion of the edema safety factor at moderate levels of capillary pressure and almost the entire compensating force at high capillary pressures in the hindpaw. Yet in the small intestine, tissue pressure increased to only 4 mm Hg following the glucagon infusions, but could not increase to higher values. This is to be expected since the compliance of the intestinal interstitium increases greatly at tissue pressures between 2 and 2.5 mm Hg and the mucosal membrane is disrupted at tissue pressures exceeding approximately 3 mm Hg (Mortillaro and Taylor, 1976; Yablonski and Lifson, 1976). The two studies demonstrated clearly the differences in the behavior of Starling forces and flows in hydrostatic and permeability edemas.

The important similarities between the tissues are: (1) Interstitial pressure is negative in both intestinal and subcutaneous tissues at normal venous pressures and hydration states. (2) The imbalance in Starling forces is very small at normal capillary pressures. (3) The normal effective colloid osmotic pressure gradient, acting across both types of capillary walls is within 90-95% of the difference in the colloid osmotic pressure of plasma minus the colloid osmotic pressure of the tissue fluid. It appears that lymph represents tissue fluids in both subcutaneous and intestinal tissues, although one organ contains a low protein concentration in its interstitium, whereas the other organ contains a high protein fluid interstitium.

The Starling force analyses conducted in subcutaneous tissue and intestinal tissues appear to be easily interpreted relative to interstitial fluid balance control and represent excellent experimental approaches with which to study functional and pathological fluid balance states in these organs. Complexities could exist within these tissues relative to fluid balance analyses especially in the small intestine, since it contains at least three different vascular systems: smooth muscle, submucosal, and mucosal. But, this does not appear to cause any great difficulties in Starling force interpretation since the behavior of the small intestine in primarily predicated by events which occur in the mucosal region.

It is of interest to note that the recent model of capillary fluid exchange presented by Wiederhielm (1979) predicts behavior of the Starling forces which are similar to those obtained in the study of Chen et al. (1976). Wiederhielm developed a very complex model which incorporated the differences in pressures and volume conductances along the length of the capillary, as well as tissue mucopolysaccharide interactions. However, the Wiederhielm model would not predict the subatmospheric pressures obtained in the Chen study, but would predict the high tissue pressure obtained at the higher tissue volumes. The discrepancies obtained between model predictions and experimental results could be caused by many factors but most probably emphasize the problems associated with extrapolating the behavior of the forces in a particular tissue to another capillary bed. Comparisons are further complicated by the methods used to assess the forces in different experimental models; e.g., capillary pressure is assessed by using either zero flow or zero flow extrapolation procedures in different laboratories which may alter its experimental magnitude. Finally, as more data become available, more complete models can be constructed concerning whole organ predictions as compared to micromeasurements.

Future studies in these organs should certainly
concentrate their efforts toward microtechniques. Gore and his associates are presently measuring $P_c$, $\tau_{im}$, and $K_{fc}$ in the smooth muscle layer of the small intestine (Gore and McDonagh, 1980; Pappenfuss et al., 1980). They have developed experimental and mathematical models which allow estimations of $K_{fc}$ and Starling forces to be made in different segments of the intestinal circulation. Perhaps in the near future, investigations will be conducted on the mucosal capillaries in the intestine which are similar to those reported by Nordin et al. (1978) for bronchial tissue. Microscopic fluid balance studies have been reviewed critically in the past (Intaglietta and Zweifach, 1974; Gore and McDonagh, 1980) and are certainly the direction which should be taken in future fluid balance studies. However, the microscopic studies should be focusing on mechanisms at the microcirculatory level and at least three of the four Starling forces, capillary filtration rate, interstitial volume, and capillary permeability, must be measured in each preparation at defined steady states before any mechanisms can be ascertained concerning the regulation of fluid volume at the microcirculatory level.

Finally, I will apply a Starling force analysis on data collected in lung tissue since it will point out the complexities associated with interpreting average Starling force balance measurements (organ values) when the tissue fluid is compartmentalized. The following Starling force balance was derived using the accepted values for the dog lung capillary Starling forces:

\[
\frac{J}{K_{fc}} = [(7 - (-6)) - (20 - 15)]
\]

\[
= 8 \text{ mm Hg. (Normal)}
\]

From this calculation, it appears that the imbalance in Starling forces is quite large in lung tissue. This large imbalance indicates that the lymphatic safety factor is quite large; i.e., either $K_{fc}$ is small or lymph flow is extremely high or both. In fact, the large Starling force imbalance at normal pressures predicts that the lung should be able to withstand capillary pressure increases of 40–60 mm Hg before edema develops, since lymph flow can easily increase 5- to 7-fold before fluid enters the airways. How can the lymphatic force be this large? The theory predicts a large Starling force imbalance, but it is well known that pulmonary capillary pressure can only be increased to 25–30 mm Hg before gross pulmonary edema ensues. Also, $K_{fc}$'s measured in lung tissue using gravimetric techniques are quite large, indicating only a small lymph flow safety factor, unless lymph flow draining the lung is extremely large. The Starling forces simply do not agree with well established experimental findings, so perhaps the lung cannot be considered as a simple well mixed organ system.

The lung's fluid volume is certainly divided into at least two different compartments: (1) the small, rather rigid septal regions surrounding the alveolar capillaries, and (2) the larger and easily expandable potential spaces which surround the vascular and bronchial systems.

Figure 10 represents a model which describes the lung interstitium as a two-compartment system (Guyton et al., 1976). The septal fluid volume is considered to be the smaller of the two compartments and is connected to the larger perivascular spaces by a high resistance pathway. It has been well documented that perivascular pressures are negative (Lai-Fook, 1980), and because of the curvature of the alveoli and their surface tension, the septal interstitial fluid pressure should also be subatmospheric in that region. The graph in Figure 10 represents the model's prediction when capillary pressure is increased and assuming that: (1) the septal capillaries have a high $K_{fc}$; (2) the resistance to fluid movement between septal and perivascular fluid compartments is high and decreases as the tissues expand; and (3) the lymphatics drain the perivascular region of the lung.

At normal capillary filtration rates, a pressure difference of 6–7 mm Hg is required to overcome the resistance between the septal and perivascular regions and provide the fluid which eventually forms lymph. As capillary pressure is increased to

\[\text{PULMONARY CAPILLARY PRESSURE (mm Hg)}\]

\[\text{SEPTAL} \quad \text{PERIVASCULAR}\]

\[\text{FLOW PATHWAY} \quad \text{LYMPH FLOW}\]

Figure 10 Plot of septal and peribronchial pressures from a lung fluid exchange model developed by Guyton et al. (1976). In this model it was assumed that the fluid compartments of the lung could be represented as septal and perivascular spaces. The spaces are connected by a high resistance pathway, and lymph is drained only from the perivascular spaces.
higher values, the peribronchial pressure begins to increase at a greater rate than septal pressures because the flow resistance between the two compartments is decreasing as the tissues expand. At 20-30 mm Hg, the resistance between the compartments is reduced to essentially zero, and the two pressures become equal. Further capillary filtration will not increase either pressure since fluid now floods the alveoli.

This mathematical model suggests several mechanisms which can be tested experimentally and should help to resolve the apparent discrepancy between the various estimates of Starling forces and physiological observations in the lung. (1) The model predicts that perivascular pressures rises rapidly as compared to septal interstitial fluid pressure, especially at high capillary pressures. This model prediction has been verified experimentally in the recent studies of Lai-Fook (1980) and Hida et al. (1980). These investigators demonstrated that more pressure is reflected from small pulmonary spaces (measured with 2-5 \( \mu \)m pipettes) to the larger perivascular spaces at higher levels of edema. They also have established experimentally that perivascular pressures of -1 to -2 mm Hg are associated with intra-alveolar edema. The model predicts both experimental findings. (2) The model also predicts that the \( K_{f,c} \) estimated by using lymph flow divided by the estimates of Starling forces (an apparent \( K_{f,c} \)) will be much less than the septal capillary filtration coefficient. This results because fluid must flow through a high resistance pathway to reach the perivascular spaces. Recently, Oppenheimer and Goldberg (1980) have demonstrated experimentally that \( K_{f,c} \)'s estimated by gravimetric procedures may seriously underestimate the "true septal \( K_{f,c} \)" because the resistance of fluid movement between the lung fluid compartments is high. (3) Since fluid will take a long time to flow from the small septal volume to the larger perivascular region, there will also be differences between perivascular and septal fluids with respect to plasma protein concentrations in relative short term experiments (1-4 hours) (Parker et al., 1980; Gee and Spath, 1980).

Since the three major assumptions used to build the mathematical model have been experimentally confirmed, model predictions should allow us to explain why a simple Starling force analysis using organ values fails to explain fluid balance in the lung. The model predicts the following Starling force balance, assuming an equivalence between perivascular osmotic pressure and lymph using perivascular interstitial fluid pressures as interstitial pressure and assuming values of 28 mm Hg for plasma colloid osmotic pressure:

\[
\frac{J_v}{K_{f,c}} = \left[ 7 - (-3.3) - (28 - 18) \right] = 9 \text{ mm Hg.} \quad \text{(Normal volume)}
\]

However, if the Starling force balance is calculated using the assumed septal colloid osmotic pressure and septal fluid pressure, the following results:

\[
\text{Force imbalance} = \frac{J_v}{K_{f,c}} = \left[ 7 - (-3.3) - (28 - 18) \right] = 0.3 \text{ mm Hg.} \quad \text{(Normal volume)}
\]

This indicates that the real imbalance in Starling forces is only 0.3 mm Hg at the filtering capillaries, which is similar to that calculated in other capillary beds. The implications of the model are that: (1) the capillary-lymphatic safety factor in lung tissue is not an important factor opposing fluid filtration, even for high lymph flow states; (2) the implanted capsules (Guyton, 1963) must measure a pressure close to that in perivascular regions and do not reflect the pressure responsible for events occurring at the filtering capillaries; (3) the protein content of perivascular spaces is higher than that surrounding the septal capillaries. Gee and Spath (1980), Gee and Havill (1980), and Parker et al. (1980) have presented very convincing data which indicate that the protein concentrations in the perivascular regions are not well mixed and that newly formed capillary filtrate is quite different from fluid within the large perivascular spaces; and (4) a tissue resistance factor may provide a major portion of the total edema safety factor at low tissue hydration states.

Therefore, it appears that the discrepancy observed between measured and calculated values for Starling forces in lung tissue can be resolved partially by using a compartmentalized model approach since the model's predictions have been verified in several different animal experiments. However, the exact value of the septal pressure is not known at the present time, but this value changes relative to the compliance characteristics of the two compartments and the resistance connecting the two fluid volumes.

For tissues such as hindpaw, hindlimb, and intestine, it appears that compartmentalization of fluids does not constitute any appreciable problem when assessing average Starling forces. However, for lung tissues, the compartmentalization of fluids between filtering and nonfiltering regions (Goldberg et al., 1977) poses such a restraint on data interpretation that a Starling force analysis using implanted capsules to estimate \( P_i \), and lymph protein concentration for tissue fluids may yield results which do not explain the basic mechanisms involved in interstitial fluid volume regulation.

In summary, this review has focused on how the tissue Starling forces and lymph flow oppose the formation of interstitial edema, i.e., edema safety factors. When capillary pressure is increased, tissue pressure increases in most tissues, the colloid osmotic pressure gradient acting across the capillary...
wall increases in all tissues with the exception of the liver, and lymph flow is an important component of the edema safety factor in most capillary beds. Some tissues, such as the liver, have overflow systems other than the lymphatic system, which can become operative when filtration is increased to prevent excessive tissue swelling. All capillary and tissue Starling forces are near equilibrium in intestinal and subcutaneous tissues, but a Starling force analysis of lung indicates that the forces measured in several experimental models are far from equilibrium. To explain the differences between the data obtained in different experimental models of lung, a mathematical approach was used in which the lung was represented as a two-compartment system. When fluid accumulation is considered to occur in a septal compartment which is connected by a high resistance pathway to the perivascular spaces, the fluid balance characteristics can be evaluated. Finally, the review indicates that Starling force analyses in whole organs are very useful experimental models with which to study fluid balance in a wide variety of tissues in both functional and pathological states.

However, most published studies concerning fluid balance either measured too few Starling forces or no steady state was defined during the course of the experimental procedures. To describe fluid movement adequately all Starling forces should be measured at steady state conditions, i.e., when lymph flow, lymphatic proteins, and tissue volume are nonchanging with time. Indications are that some tissues may require several hours to attain a true steady state with respect to tissue colloids. Therefore, each experimental model must attain steady state conditions which are clearly defined before any inference can be made concerning the behavior of Starling forces as edema develops.

Future research using microscopic techniques should allow more complete models to be developed concerning the mechanisms responsible for fluid movement at the microcirculatory level. Starling force analyses still provide the major means of assessing an organ’s ability to regulate its interstitial volume, and several organ systems have not been studied. It is hoped that this review will stimulate workers to investigate capillary and tissue Starling forces in other capillary beds, e.g., heart, stomach, muscle, etc., and relate these important determinants of fluid balance not only to edema formation, but also to the functional state of the particular organ. The extension of Starling force analyses to chronic edema states, e.g., myxedema, diabetes, left-sided heart failure, etc., promises to provide physiologists and clinicians with the basic information necessary to explain how interstitial fluid volume is regulated in both healthy and diseased states.

At the present time, investigators can measure tissue pressure, lymph flow, KCS, and tissue volume in human leg and forearm. Although a complete Starling force analysis has not been conducted in human tissues, the techniques are available to estimate P,, p, lymph flow, p, tissue volume, and P,. Perhaps studies will soon be conducted in the human model similar to those presented in this review, using simple maneuvers such as cuffs to elevate venous pressure.

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