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SPECIAL ARTICLE

THE LYMPHATIC EDEMA SAFETY FACTOR: THE ROLE OF EDEMA DEPENDENT LYMPHATIC FACTORS (EDLF)*

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When I first became interested in the dynamics of lymph flow, the previous works were well chronicled by Rusznyak, Földi and Szabo (1), and Yoffey and Courtice (2) in their classic books indicating that experimental conditions which increased capillary pressure or damaged the capillary walls (such as histamine) caused lymph flow to increase. However, little was known of the factors that regulate lymph flow, the forces that drive the interstitial fluid into the lymphatics, and what tissue forces or lymphatic stimulation factors control the lymphatic removal of capillary filtrate. As this article develops, it will become clear that we still do not know the factors that regulate lymph flow, but newly gathered information yields some clues as to what experiments need to be done to improve our understanding of the complexities of lymphatic function in regard to removing fluid from normal and edematous tissues.

Starling's hypothesis of transcapillary fluid movement

Ludwig (1), Starling (3), and Heidenhain (4) in the late 19th century were the first to postulate how lymph formed. Their major disagreement was a very basic one: was lymph formed by active or passive processes operating at the microvascular barrier? Heidenhain observed that lymph flow would increase after placing different substances into the circulation and hypothesized that the lymphatic flow stimulating substances caused the capillary walls to "actively secrete" a plasma-like fluid into the tissues using some "vital force." Heidenhain named these substances which augmented lymph flow "lymphagogues" and thought that edema was a result of the capillaries actively secreting more fluid by this "vital process" into the interstitium than could be removed by the lymphatic system.

Starling, in his classical work, estimated the osmotic pressure of plasma using a simple, but ingenious, experimental approach. He measured the height attained by a column of fluid connected to a plasma filled sausage bag when surrounded by isotonic saline, which was Van't Hoff's definition of the protein osmotic pressure of plasma (π_P). Starling also measured lymph flow (J_L) from the gastrointestinal tract and hind limb and found that the lymph from these tissues also contained plasma proteins (π_T). He

Based on a lecture given at a time the author received the first Cecil B. Drinker Award from the North American Society of Lymphology (October 1988).

hypothesized that capillary pressure (P_C) was similar in magnitude to π_P-π_T which acted to absorb tissue fluids and that tissue fluid pressure (P_T) should increase to oppose increases in capillary pressure, although his P_T data was less convincing than the π_P and π_T data.

Starling also thought that lymph drainage was present in all tissues but, because lymph flow was small, ignored lymph formation as an important force in regulating capillary filtration. Interestingly, Starling anatomically described the lymphatic anchoring filaments in this classical paper to postulate why lymphatic capillaries do not collapse as P_T becomes more positive with edema.

The Starling hypothesis that determines capillary filtration is written in the following fashion in which the hydrostatic filtration pressure (P_C-P_T) is set equal to the protein osmotic absorptive pressure (π_P-π_T):

$$P_C\text{-}P_T = \pi_P\text{-}\pi_T$$

Starling's equation simply states that the capillary fluid exchange system is "self regulating", i.e., if P_C changed then π_T and P_T would change in a direction to oppose the increased capillary filtration, i.e., when P_C increases, π_T and P_T will decrease and increase, respectively, which decreases the filtration pressure and increases the absorptive pressure. When P_C decreases, π_T and P_T will increase and decrease, respectively, which increases the filtration pressure and decreases the absorptive pressure (3).

Heidenhain lost this debate concerning the formation of lymph; however, he argued that the Starling capillary filtration hypothesis would not describe the absorption of fluid from the small intestine because plasma placed into a loop of small bowel was absorbed against the net Starling force balance, i.e., intestinal transport was against the physical gradient and was therefore an active not a passive transport system, truly a "vital force" (4).

Eugene Landis' contributions

For several years, Starling's hypothesis was the accepted theory to describe capillary fluid exchange, and the lymphatic system was thought to drain the excess capillary filtrate if P_T and π_T did not readjust sufficiently to oppose capillary filtration. In the 1920s, a very bright young physiologist from the United States named Eugene Landis studied in Augustus Krogh's famous laboratory in Copenhagen, Denmark. Krogh had developed an argument against Starling's hypothesis of capillary filtration. He postulated that the increased filtration out of capillaries following an elevation of capillary pressure, was due to the increased capillary surface area, not to the increased capillary hydrostatic pressure (5,6). During Landis' postdoctoral training, he measured, for the first time, the filtration properties of individual frog capillaries and discovered that the rate of capillary filtration to be linearly related to the change in capillary pressure (7). From the slope of this relationship, he defined the filtration coefficient for the capillary wall (K_{fc}). Krogh and Landis, in another study, confirmed Starling's original hypothesis, finding that P_C could be changed over a fairly wide range of capillary pressures (up to 25mmHg) without any evidence of edema formation (6). Landis defined this ability of the tissues to prevent edema formation when capillary pressure was increased as the tissues' "margin of safety" against edema formation (8). Guyton many years later redefined this phenomena as the "tissue edema safety factor," which also incorporated lymph flow as another component of the tissues' overall ability to regulate interstitial volume, in addition to π_T and P_T (9).

Drinker's lymph flow studies

Cecil Drinker, in the late 1920s, conducted many quantitative lymph flow studies. *Fig. 1* shows the results of one of his studies conducted on dog lungs (10). The upper curve shows the protein concentration of lymph (labeled P in gm %),

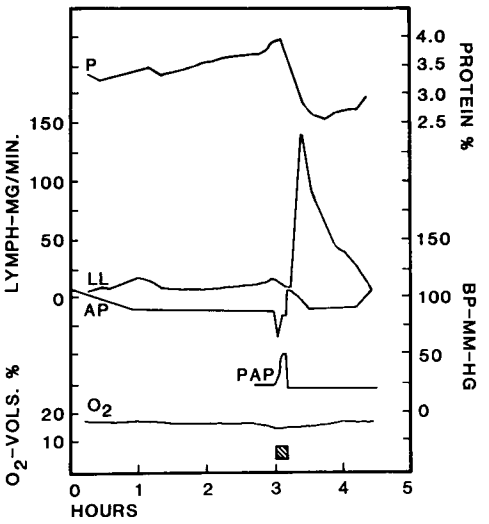


Fig. 1. Lymph plasma protein concentration (P, grams/100ml, %), lung lymph flow (LL in mg/min), arterial pressure (AP, mmHg), pulmonary arterial pressure (PAP), and arterial oxygen content (volume %). At three hours (designated by square), pulmonary veins were partially collapsed. Note the 10-fold increase in lymph flow and the dramatic decrease in protein concentration of the lymph from approximately 4 to about 2.5gm%. (Redrawn from MF Warren and CK Drinker: Am. J. Physiol. 136 (1942), 207-221.)

the LL curve refers to the flow of lung lymph in mg/min, PAP refers to the pulmonary arterial pressure (mmHg), A.P. refers to the arterial pressure (mmHg), and the lowest curve shows the O_2 content of arterial blood (vol %). After 3 hours of control measurements, the pulmonary veins were compressed to increase PAP (denoted as solid square), and the same parameters were measured. Note two things, 1) the lymph flow increased dramatically from about 10mg/min to 150mg/min, almost a 15-fold increase, and lymph protein concentration decreased from 3.8 to approximately 2.5gm/100ml. He postulated that lymph protein decreased as Starling had predicted to oppose the pulmonary capillary pressure increase and a large amount of the increased capillary filtration was also carried away from the tissues by the increased lymph flow.

In another portion of this same study, Drinker noted that lymph flow increased; yet the lymph protein concentration actually increased slightly as animals breathed a low O_2 mixture, as shown in *Fig. 2.* He concluded from these stud-

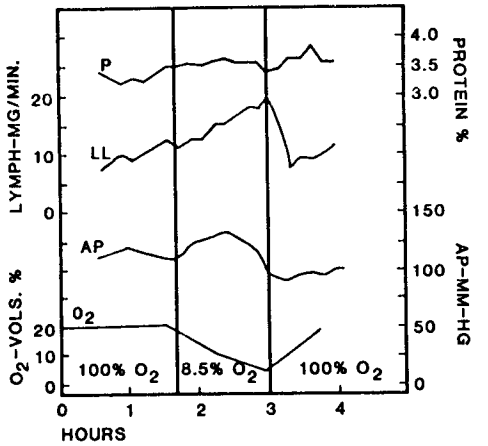


Fig. 2. Protein concentration in lymph (P, gm%), lung lymph flow (LL, mg/min), arterial pressure (AP, mmHg), and arterial O_2 concentration (volume %). The animal was ventilated with 100% O_2 until 1.75 hours at which time the inspired gas mixture was switched to 8.5% O_2. At the end of three hours, the animal was again ventilated with 100% O_2. Note that lung lymph flow increased from 10 to 20mg/min and plasma protein concentration did not change significantly; in fact, it increased by a small amount. This was interpreted by Drinker as indicating that low alveolar PO_2 caused a reversible damage to the pulmonary capillaries. (Redrawn from MF Warren and CK Drinker: Am. J. Physiol. 136 (1942), 207-221.)

ies, that low O_2 reversibly damaged the pulmonary endothelium. Although the lungs of some species are not damaged by low O_2, Drinker's original findings were confirmed in isolated dog lungs by Richard Parker (11) and in *in situ* dog lungs by Martin and Grimbert (12). Drinker was the first to analyze lymph flow and its protein content to describe the integrity of the capillary wall. He hypothesized that when lymph protein did not increase (or increased) with increasing lymph flow that the endothelium was damaged. This same experimental approach and method of analysis was successfully used by Courtice's (2) and Rusznyak's (1) groups.

Staub and his workers (13,14) used this same approach to analyze lymph from the lungs of awake sheep to greatly expand our knowledge of the formation of lung lymph and the exchange of plasma proteins across the pulmonary capillary wall.

Effect of tissue fluid pressure on lymph flow

I was first introduced to the art of lymphatic cannulation by a surgeon from Argentina, Dr. Carlos Chavez, and my first study was designed to evaluate the effects of tissue fluid pressure, as measured with implanted capsules, on lymph flow and protein concentrations of tissue fluid and lymph. These studies were conducted with Drs. Kermit Gaar, Harry Gibson, and Arthur Guyton in the physiology department in Jackson, Mississippi. The lower solid curve in *Fig. 3* shows the

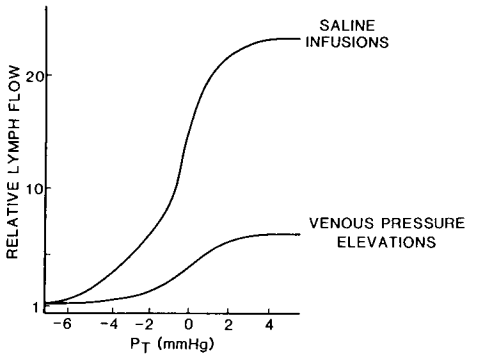


Fig. 3. Lymph flow from the dog paw (times normal) for increased venous pressure (50mmHg) and saline infusion. Note the tremendous difference in lymph flow for the same tissue fluid pressure. (Redrawn from Taylor, Gibson, and Guyton: Lymphology 6 (1973), 192-208.)

lymph flow increase (times normal) measured in a dog paw preparation when venous pressure was increased by placing a cuff inflated to 50mmHg around the upper leg. The upper curve shows the lymph flow measured in the same paw lymphatic following rapid intravenous volume expansion using isotonic saline. Two important findings are seen in these data: 1) lymph flow from the paw preparation plateaus for both experimental conditions at tissue pressures exceeding about +2mmHg and 2) the lymph flow response for fluid volume expansion is 3 to 4 times greater than that measured with increased venous pressure. The plateau in lymph flow is thought to be caused by a "waterfall effect" of tissue pressure acting at the lymphatic walls, i.e., as the tissue fluid pressure becomes positive, the pressure pushes down on the collapsible initial lymphatics and raises their internal pressures to equal the surrounding pressure causing the lymphatic filling pressure (P_T—pressure in the lymphatics) to remain constant. However, there is no apparent reason why saline infusions should produce greater lymph flows since the capillary force changes associated with saline infusion should not have exceeded that for the elevated venous pressure study (50mmHg)! As this paper develops, I will again return to this concept of greater than predicted lymph flows when discussing the edema safety factors under different experimental conditions especially in regard to the large increase in lymph flow that is associated with damaged capillary endothelium (14,15).

Edema safety factors

After this initial lymph flow and tissue fluid pressure study, I became interested in determining how capillary filtration was regulated and turned to the more rigorous equation of Kedem and Katchalsky (16), which was taught to me by Dr. Peter Curran and described transcapillary fluid movement as:

$$J_V = K_{fc}[(P_C - P_T) - \sigma_d(\pi_P - \pi_T)]$$

P_C, P_T, π_P, and π_T have the same definitions used by Starling but two coefficients are needed to describe net capillary filtration (J_V): The filtration coefficient (K_{fc}) as defined by Landis (7) determines how rapidly fluid will filter across the capillary walls when an imbalance in the Starling forces is present. The coefficient in front of the protein osmotic pressure gradient,

σ_d, was defined by Staverman (17) as the reflection coefficient for the capillary wall to total plasma proteins. If the protein is freely permeable across the capillary wall (not reflected) then $\sigma_d = 0$ and absolutely no osmotic pressure will be exerted by the plasma proteins. If the capillary wall is impermeable to plasma proteins (totally reflected), then $\sigma_d = 1$ and the total protein osmotic pressure gradient, $(\pi_P - \pi_T)$, will be exerted across the capillary wall. In reality, a $\sigma_{di}(\pi_{Pi} - \pi_{Ti})$ for each plasma protein should be used in the volume flux equation, but, for simplicity sake, I will use only the total protein osmotic pressure, i.e., the total plasma protein osmotic pressure, which is sometimes designated as plasma oncotic pressure or plasma colloid osmotic pressure. But, the reader should realize that this constitutes an error in determining the effective osmotic pressure exerted by the plasma proteins across a capillary wall because of the variable amounts of different sized proteins in different plasma samples.

The reflection coefficient of albumin is 0.90-0.95 in many capillary beds and the reflection coefficients of the larger plasma proteins are near to, but not quite equal to, 1: i.e., 0.97-0.99. Thus, normally about 95% of the total protein osmotic pressure gradient $(\pi_P - \pi_T)$ is effectively exerted across the capillary walls of most organs (18).

In order to more easily and accurately measure the transcapillary volume movement in different organs, my coworkers have developed quantitative ways to measure each and every Starling force, and both membrane parameters, K_{fc} and σ_d, for lung, the gastrointestinal tract, subcutaneous tissue, heart muscle, skeletal muscle, and even in brain capillaries and the following section presents only a small fraction of these many excellent studies (19-24).

Figs. 4A, 4B, and 4C show diagrammatically how each Starling force changes when capillary pressure is increased from 8 to 28mmHg in lungs. Tissue fluid pressure changes from -4 to +1mmHg with only a small increase occurring in tissue volume (a net change in P_T of 5mmHg). As the capillaries filter *(Fig. 4B)*, the lower protein concentration contained in the capillary filtrate decreases the tissues' protein concentration which increases the protein osmotic pressure gradient acting across the capillary wall $(\sigma_d(\pi_P - \pi_T))$ from its normal value of 10mmHg to 20mmHg (a net change in the absorbing pressure of 10mmHg). *Fig. 4C* shows a calculation of the edema safety factor that is determined by the amount of capillary filtrate that can be removed by the lymphatic system. This estimation of the lymphatic's ability to remove volume is based on Starling's original definition of the "capillary pressure drop." Starling understood that the transfer of fluid across the capillary wall was described by a coefficient which determined the amount of capillary filtration occurring for a given change in capillary pressure, i.e., Landis' capillary filtration coefficient. If the tissues were neither shrinking nor swelling, then the capillary filtrate (J_V) will be exactly equal to total lymph flow (J_L) draining an organ:

$$J_L = J_V = K_{fc}[(P_C - P_T) - \sigma_d(\pi_P - \pi_T)];$$

if ΔP equals the pressure drop across the capillary wall associated with lymph formation, then

$$J_L = K_{fc}(\Delta P_C)$$

and,

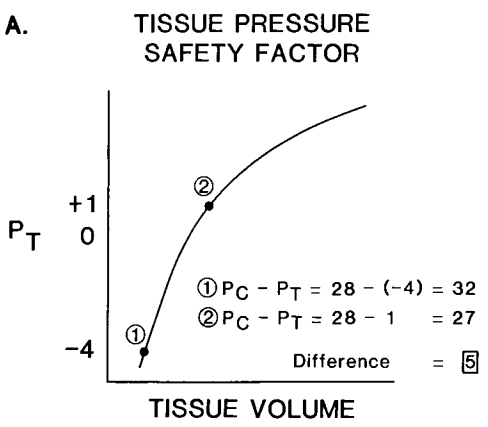
$$\Delta P_C = J_L / K_{fc}$$

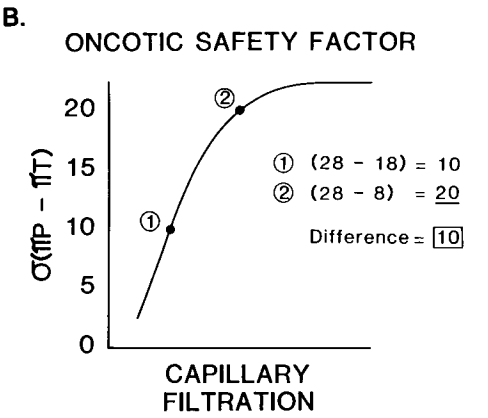
For the control Starling forces measured in *Fig. 3*,

$$\Delta P_C = \frac{J_L}{K_{fc}} = 0.8 mmHg$$

Since J_V increased 6 fold after increasing capillary pressure, then the ΔP producing the higher lymph flow is equal to:

$$6 \times 0.8 = 5 mmHg$$





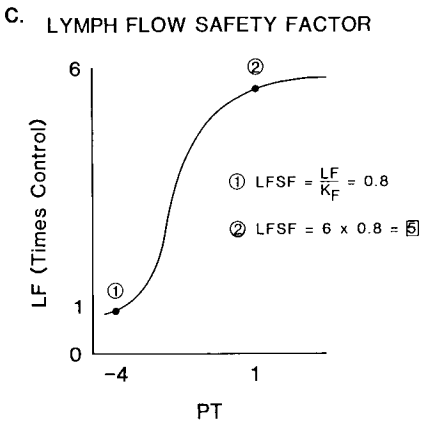


*Fig. 4. (AT LEFT) (**A**) Effect of tissue volume on interstitial fluid pressure (P_T) as capillary pressure was changed from 8 to 28mmHg. The filtration pressure (P_C-P_T) was calculated for the instantaneous effect ① and after P_T had increased ② (**B**) Change in the absorptive force ($\sigma(\pi_P - \pi_T)$) after increasing capillary pressure to 28mmHg. ① refers to the initial absorptive force while ② refers to the absorptive force at the maximal washdown of tissue proteins. (**C**) A plot of lymph flow vs interstitial pressure showing the initial lymphatic flow safety factor [LFSF ①] and the lymphatic flow safety factor after capillary pressure was increased from 8 to 28mmHg [LFSF ②].*

Thus, the sum of all safety factors, i.e., the increased tissue fluid pressure, the increased protein osmotic absorbing pressure, and lymph flow equals 20mmHg. The safety factors change sufficiently to prevent the build-up of any edema even when the capillary pressure is considerably increased. For this example, the lymph flow factor is only about 25% of the total safety factor. Although this is an appropriate physical way of evaluating the lymphatic flow edema safety factor, it is based on several assumptions which are difficult to assess in a capillary-tissue-lymphatic system: 1) total lymph flow must be measured or estimated to some degree of accuracy; 2) tissue volume must not be increasing nor decreasing, i.e., lymph flow must be equal to the total capillary filtrate which occurs when the tissues are neither swelling nor shrinking; and 3) the pressure drop across the capillary wall, the tissue spaces, and the lymphatic system can be approximated by the lymph flow divided by the capillary filtration coefficient which requires that the capillary wall has a larger resistance than the combined resistances of the tissue and lymphatic systems.

Since the total lymphatic pathway filtration coefficient contains the capillary filtration coefficient, the filtration coefficient of the interstitial pathway and the filtration coefficient of the lymphatic drainage system, then the lymphatic safety factor can only be calculated using the

$K_{f,c}$ when the combined filtration coefficient of the tissues ($K_{f,t}$) and the lymphatic system is very large (20-30 times the $K_{f,c}$ as shown on the last row of *Table 1*).

Table 1
Effect of Varying the Interstitial Filtration Coefficient ($K_{f,t}$) on the Total Capillary - Tissue - Lymphatic Pathway Filtration Coefficient ($K_{f,T}$)

$K_{f,c}$	$K_{f,t}$	$K_{f,T}$	$K_{f,c}/K_{f,t}$
0.30	0.01	0.01	30
0.30	0.10	0.075	3
0.30	0.30	0.15	1
0.30	1.00	0.23	0.3
0.30	10.00	0.30	0.03

$$K_{f,T} = \frac{K_{f,c}K_{f,t}}{K_{f,c}+K_{f,t}}$$

Revised from Taylor et al (22,23)

If the K_f's of the capillary wall and interstitial pathway are equal (as shown in the middle row of *Table 1*), then the filtration coefficient of the total lymphatic pathway ($K_{f,T}$) will be 1/2 the K_f of either pathway (22,23). So, the lymphatic safety factor will be in error if the K_{fc} of the capillary wall is used since

$$\Delta P_C = \frac{J_L}{K_{f,T}} \quad (4)$$

when $K_{f,c} = K_{f,t}$, then the actual ΔP_C that incorporates the interstitial and lymphatic system resistance would be twice that calculated using the capillary filtration coefficient to estimate the lymphatic safety factor. When the $K_{f,c}$ is 20-30 times the $K_{f,t}$ then only the tissue resistance determines the formation of lymph as shown by the first line in *Table 1*. We recently used this relationship between $K_{f,T}$, $K_{f,c}$ and $K_{f,t}$ to develop a model of fluid exchange in which the $K_{f,t}$ was small and ΔP_C high at low lymph flows because the high tissue resistance constituted the major barrier to fluid entering the lymphatic system. However, ΔP decreased to lower values as the tissues expanded with edema (i.e., $K_{f,t}$ greatly increased), and lymph formation became only a function of the resistance of the capillary wall. Therefore, lung lymph flow may provide the major safety factor against edema at low capillary pressures, but as the tissues begin to expand, the lymphatic factor decreases and other Starling forces would become the more predominant edema safety factors (22-24).

Table 2 shows Starling forces measured in several organs following increasing capillary pressure by 20mmHg where these tissues gained only a slight amount of edema. *Fig. 5* shows graphically the relationship between capillary pressure and tissue fluid volume based on these data from *Table 2*. Note, the curve is almost flat at low capillary pressures indicating that the capillary fluid exchange system is a self-regulating system as originally defined by Starling. However, the amount of fluid entering the tissues increases abruptly when tissue pressure, lymph flow and the protein osmotic gradient can no longer change to oppose the increased capillary pressure (24). It is now certain that Starling forces and lymph flow can change to prevent the

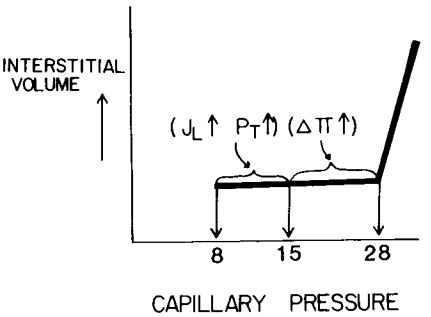


Fig. 5. The edema safety factor. Note that as capillary pressure increases from 8 to 28mmHg, that the interstitial volume does not increase by a measurable amount because lymph flow (J_L) increases, P_T increases, and the absorptive force $\sigma_d(\pi_P - \pi_T)) = \Delta\pi$ increases to oppose the increase in capillary pressure. After these safety factors have been exhausted, edema begins to form at a very rapid rate (reproduced from Taylor: Circ. Res. 49 (1981), 557-595).

TABLE 2
Contributions of Lymph Flow, Interstitial Fluid Pressure, and Transcapillary Oncotic Pressure Difference in Preventing Interstitial Edema When Capillary Pressure is Elevated by 20mmHg

Normal Organ	Increased Oncotic Pressure Difference, %	Increased Lymph Flow %	Increased Interstitial Fluid Pressure, %
Lung	50	15	25
Hindpaw	15	25	60
Small Intestine	45	20	35
Colon	50	5	45
Liver	0	40	60
Heart	10	10	80

Revised from Taylor, AE and MI Townsley: NIPS 2 (1987), 48-52.

accumulation of fluid in the interstitium of all organs at this level of capillary pressure. However, $\sigma_d(\pi_P-\pi_T)$, P_T, and lymph flow may increase by differing amounts to provide the edema safety factor as shown in *Table 2*, e.g., in liver $\sigma_d(\pi_P-\pi_T)$ is essentially zero because the liver sinuses are freely permeable to plasma proteins. But lymph flow and tissue pressure increase to provide a safety factor of 20mmHg. In fact, it appears that tissue pressure provides the major safety factor in organs with leakier capillaries, since the predominant force in less permeable capillaries, $\sigma_d(\pi_P-\pi_T)$, cannot significantly change. Also, the classical studies of Leeds et al (25) in lung and the Wittes in the liver and GI tract (26) indicate that the lymphatic system can drain much more capillary filtrate when capillary pressure has been elevated chronically. In fact, some patients with chronic heart failure have no visible signs of pulmonary edema even when left atrial pressures are 40-45mmHg, indicating that the edema safety factor has increased either due to a more extensive lymph drainage system or a more efficient lymphatic pump.

A more complete lymphatic safety factor analysis

A recent study from our laboratory by Dr. Masayoshi Ishibashi (27) evaluated lung water and the amount of water removed by the lymphatics following 2 hours at capillary pressure of 10-30cmH_2O. The lung water did not increase, which is not surprising since the safety factors operate with an almost infinite gain over this range of capillary pressures *(See Fig. 5)*. But, the amount of fluid being removed by lymph flow was substantial! At low capillary pressures, lymph flow did not increase greatly but at P_C's of 20-25cmH_2O, lymph flow had increased to levels that removed substantial amounts of fluid. Edema would have resulted at a capillary pressure of 25-30cmH_2O if lymph flow had not been present in these studies. This represents another way to evaluate the lymph flow safety factor by considering how much capillary filtrate can actually be removed by the lymphatic system before significant edema develops. This can be done by simply measuring the lymph flow and the interstitial water in other organs similarly to Ishibashi's studies in order to measure the effect of the lymphatic fluid removal on the development of edema.

Another interesting question to pose concerning the amount of fluid that the lymphatics can remove is: can the lymphatic system increase the amount of fluid it is normally capable of removing after edema develops, to minimize (not

prevent) the amount of edema accumulating in the tissues? This can be done by evaluating the lymphatic removal of volume as compared to the weight gain of an organ over a defined time interval. The following discussion convincingly shows that the lymphatic system can somehow sense that capillaries are damaged (or perhaps edema is present) and increase their removal of capillary filtrate to a significantly higher level than they maximally produce when capillary pressure is elevated to levels that are associated with edema formation.

Lymphatic flow as an overflow system

The lymphatics' ability to prevent edema formation has been considered as the amount of fluid produced by the pressure drop acting across the capillary wall (the imbalance in forces) that can be removed by the lymphatic system before any appreciable edema develops, which was discussed previously relative to the edema safety factors. But we now know that the lymphatic system responds differently to venous pressure elevation and plasma volume expansion by producing more lymph flow with plasma volume expansion. The lymphatic system appears to be capable of removing much more capillary filtrate when conditions are present that predispose the tissues to greater edema formation, such as chronic elevations of capillary pressure or damaged capillary endothelium. Why can't the lymphatic system drain more fluid when the capillary filtrate is increased by only elevating capillary pressure?

To illustrate another condition in which this occurs, consider the data in *Fig. 6* showing the effects of an experimental dog paw burn on lymph flow and edema formation (Ferrara, unpublished data). The solid line (filled circles) shows the rate of edema formation in that paw's tissue following the burn (85ml/6hrs). The lymph flow during the same time was 216ml/6hrs. If lymph flow had not been present, the paw would have gained a total of 300ml of edema fluid! These studies were designed to evaluate the

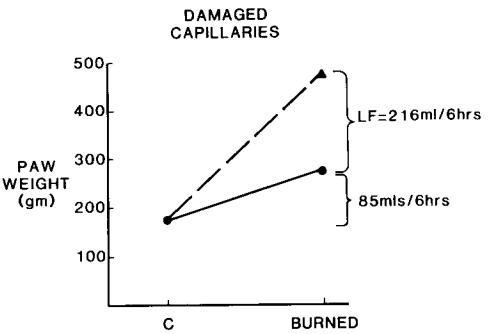


Fig. 6. Effect of burn on the actual fluid accumulation in dog paw (solid line) and weight with predicted lymph flow (dotted line). If lymph flow had not attained such high levels, the paw weight would have increased by almost 300gms! (Redrawn from John Ferrera and Lynn Dyess et al, personal communications.)

amount of capillary damage associated with this burn and capillary pressure had been elevated to 50mmHg prior to the burn. Therefore, one can calculate that lymph flow due to this pressure level would have been only 0.25ml/min (≈90ml in 6 hrs) in the control state; yet, after the burn, lymph flow was more than double this amount! The edema is obviously a result of damaged capillaries, but why did the lymph flow increase to values higher than that associated with only increased capillary pressure?

Figs. 7A and *7B* show another set of data illustrating the ability of damaged capillaries to produce a greater lymph flow than can occur with capillary pressure elevation alone (28). Note that capillary pressure alone increases lymph flow to 10ml/hr whereas endotoxin and pseudomonas both increase lymph flow to 30-35ml/hr. *Fig 7B* shows lymph flow estimated for a 6 hour period of 320ml (lower solid line), and extravascular lung water (EVLW) would have increased by only 20%. This amount of edema fluid can easily be accommodated by the lung tissue without the formation of alveolar edema. If lymph flow had only increased by the amount calculated for a hydrostatic pressure increase of 25-30mmHg, then lymph flow would have increased by only 100ml (upper dashed curve), and exces-

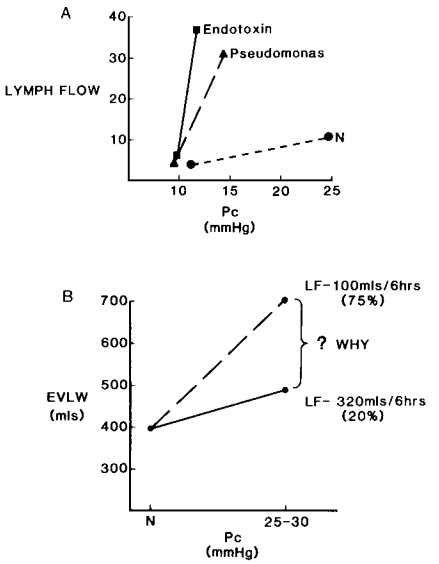


*Fig. 7. (**A**) Lung lymph flow (ml/hr) response (redrawn from the work of Brigham et al: JCI 54 (1974), 792-804) showing the lymph flow response to increased capillary pressure (short dashed line) and after pseudomonas (long dashed line) and endotoxin (solid line). The lymph flow response to these challenges is 3-4 times that seen with pressure elevation alone. (**B**) Estimation of the effects of extravascular lung water (EVLW, mls) using these data. The lower solid line shows the amount of lung water that accumulated with the large increase in lymph flow associated with pseudomonas. Over the same time frame, lymph flow would have increased by only 100ml if only capillary pressure had elevated, and alveolar edema would have resulted since the extravascular lung water would have increased by 75% (dashed triangle line) if the EDLF did not increase.*

sive edema would form because EVLW increased by 75% and the alveoli would have filled with fluid without the augmentation of lymph flow! So, the increased lymph flow produced over and above that occurring with only increasing capillary pressure prevented alveolar edema formation even when the capillaries were damaged and abnormally permeable to plasma proteins.

These experiments were not designed to answer the question they obviously pose: Why does the maximal lymph flow increase more when the capillary wall is damaged (or as seen with saline infusions) than occurs with increased capillary pressure alone? The calculations I presented require many assumptions to represent the data as shown in *Fig. 7A* and *7B*, but the estimations clearly demonstrate that lymph flow can increase over and above the expected amount to provide an additional safety factor, especially when the endothelium is damaged, or when capillary pressure is elevated for long periods of time.

Causes of the increased lymph flow observed with damaged capillaries

That lymph flow from damaged organs can increase to much higher levels than can be produced by capillary pressure elevations alone is well documented in the literature. In fact, this finding of an increased lymphatic flow has been used to define damaged capillaries by many investigators. But, how does this phenomena occur? There are several possible explanations which I have named edema-dependent lymphatic factors (EDLF). When capillaries are damaged, lymph flow may increase to higher than predicted values because: 1) the tissue resistance is less and lymphatics fill more easily; 2) the compliance of the tissues is different and interstitial fluid enters the lymphatics more easily without elevating tissue pressure; 3) the lymphatics respond to the greater amount of protein in the tissues by increasing their pumping ability; 4) some compound (or compounds) is released by the damaged endothelium which increases the ability of the lymphatics to remove tissue fluid (this would make EDLF become endothelial-derived lymphatic factor); 5) the inflammatory response associated with lung damage increases the lymphatic pumping ability in order to propel lymphocytes out of nodes and lymphatic vessels into the circulating plasma; 6) the neutrophils entering in the tissues during the inflammatory response

release substances that increase the pumping ability of the lymphatics; 7) when capillaries are damaged, or volume expansion occurs, the plasma volume is usually decreased. This will cause a baroreceptor reflex to occur which could increase lymphatic pumping either directly by a nervous effect (29), or indirectly through circulating catecholamines (30). The release of other substances associated with low vascular pressure, such as prostaglandins, can alter the pressure flow characteristics of the lymphatics as described by Roddie and coworkers. After all, the greater return of fluid to the plasma allows a greater leakage of plasma out of the capillary yet still maintains a stable plasma volume in the process since the fluid merely circulates between the interstitium and the plasma. In fact, this finding shows that the circulating lymphatic fluid is an important component of plasma volume when capillaries are damaged! There are obviously many other explanations that could be used to describe this phenomena such as changes in lymphatic outflow pressures, but regardless of the responsible mechanism, it is now clear that the lymphatics can remove more tissue fluid than can be accommodated by them when capillary pressure is increased (31). Examples of this phenomena have been reported in several different damaged organs, and also with plasma volume expansion using saline. This is a question that needs to be addressed in lymphatic physiology, because either some physical, nervous, or chemical force (EDLF) has the ability to increase the lymphatics' ability to remove capillary filtrate and this additional amount of lymphatic flow is not trivial; in fact, in several instances it is much greater than the amount of accumulated edema fluid.

CONCLUSIONS

My scientific career has been greatly enriched by studies on the lymphatic system, and Dr. Guyton is responsible for introducing me to this exciting field of physiology over 25 years ago. In many cases, I used lymph and the lymphatic system only as a source of the capillary filtrate in order to evaluate the filtration and osmotic reflection coefficients of the capillaries in different organ systems. As we began to study the ability of lymph flow and the Starling forces to change when capillary filtration was increased, it became evident that capillary filtration associated with either damaged capillaries or plasma volume expansion with saline, caused a greater increase in lymph flow than we had measured with increased capillary pressure alone. The difference is substantial, since lymph flow can increase three to five times above normal values when capillaries are damaged by many different experimental maneuvers. *Fig. 8*

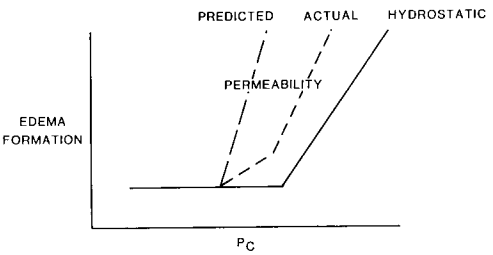


Fig. 8. Comparison of the effects of hydrostatic pressure (solid line), effects on normal capillaries and the predicted change with damaged endothelium (dashed dotted line), and the actual observed change associated with increasing vascular pressure in damaged lungs (small line) on edema formation. Note that some edema occurs in the actual case, but intraalveolar edema (slope of rapid component) is not accelerated because of the large increased lymph flow associated with the increase in permeability and the effects of EDLF.

demonstrates the importance of this additional lymphatic removal of volume in maintaining the tissues in a less edematous state. The solid line represents the build-up of fluid in the tissues when only capillary pressure is increased. When the capillaries are damaged the edema fluid should accumulate at a lower capillary pressure and at a greater rate as shown by the larger dashed line, labeled predicted. Since lymph flow increases to much larger levels when capillaries are damaged, then the edema formation will be described by the curve labeled actual. The higher lymph flow allows the capillary

pressure to be elevated to a higher level before additional edema forms, and the rate at which edema develops will be less than the predicted rate because of the ability of the additional lymph flow to return the filtrate to the plasma volume. I hope in the near future that these phenomena can be evaluated in several organs and coupled with microscopic studies to yield the formation necessary to develop a better understanding of the mechanisms responsible for this important, albeit poorly understood, function of the lymphatic system in order to define the EDLFs which increase the lymphatics ability to remove capillary filtrate.

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