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A new look at the Starling equation

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The Starling hypothesis for describing the net volume movement across the semipermeable capillary membrane is seemingly a simple mathematical expression. Certain hydrostatic forces and colloid oncotic pressures interrelate to produce mathematical gradients. It is most important to recognize that the gradients in the Starling equation reflect the difference in similar forces—either hydrostatic forces inside and outside the capillary or oncotic pressure of the serum and interstitial fluids. These gradients are physiological forces which can be mathematically calculated to describe the sum total of all forces acting upon fluid movement.

If the equation is a simple mathematical expression (Fig. 1), why has the interpretation of the equation in different areas of the body given rise to so much controversy? There appears to be a number of reasons: (1) Measurement techniques often produce different values for each of the factors considered. Interpretation of results, therefore, depends upon understanding of the methodology. Different methodologies often measure physical forces that, although loosely considered to be similar, are in fact quite different. (2) Variability in tissues. It would be desirable for simplicity's sake that all tissues have the same operating forces. Thus, if one simple-to-study area could be completely described, such knowledge could be applied to other areas as well. Unfortunately, it seems that the converse is true; tissues such as solid organs, lungs, and the subcutaneous areas are entirely different. To compound the problem, it appears that the capillary membranes themselves have different properties in different areas. For instance, lung capillaries seem to be more permeable to albumin than are tissue capillaries. (3) Species differences. The choice of experimental model appears to be extremely important in studying some of these problems. Unfortunately, the less expensive and readily attainable experimental animals, such as the canine species, do not bear as close a physiological relationship to humans as pylogenetically similar, but expensive animals (subhuman primates). Thus, many experimental results obtained for the sake of expediency must be carefully examined before their relevance to human physiology is accepted. (4) Physiological state. It appears that compensatory mechanisms operating in the interstitial space, particularly in the lung, vary with the current status: for instance, interstitial compliance (Fig. 2) is markedly changed by changes in interstitial pressure (ISP).[1] When ISP is negative with respect to low atmospheric pressure compliance, and ISP rises above zero, compliance increases markedly. Should these changes not be included in the consideration of the Starling equation, tremendous variations will be introduced. In the normal situation, too, most fluid exists in the gel state. When interstitial fluid accumulates (Fig. 3), it accumulates as free fluid and thus, alters the relationship between solid and gel as well as affects total tissue pressures. (5) Many other factors are actually involved in defining the interstitial space status. Merely describing the volume of fluid crossing the capillary membranes may be totally inadequate. For instance, if an increase in hydrostatic pressure caused an increase in net filtration, there still could be no change in interstitial fluid volume if the lymphatic drainage could accommodate such increases. Thus, when the Starling equation is applied to the lung with the intention of, in fact, describing the accumulation of interstitial edema, additional factors must be considered: capillary permeability, the Staverman reflection coefficient, the lymph flow effect, interstitial space geometry, pressures operative in the interstitial space, the dynamics of the interstitial pressure (interstitial fluid volume relationship), and finally, the distribution of fluid between the solid and gel states.

Because Starling's law appears so simple, it is common practice to measure a few of the variables involved, substitute commonly accepted values for the

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$$J_V = K_F\left[(P_C - P_T) - \delta(\pi_C - \pi_T)\right]$$

FIG. 1. A mathematical expression of the Starling equation. J_v = net volume flow; K_f = filtration coefficient; P_c = pulmonary microvascular pressure; P_i = interstitial pressure; δ = Staverman reflection coefficient; π_c = capillary oncotic pressure, π_i = tissue oncotic pressure.

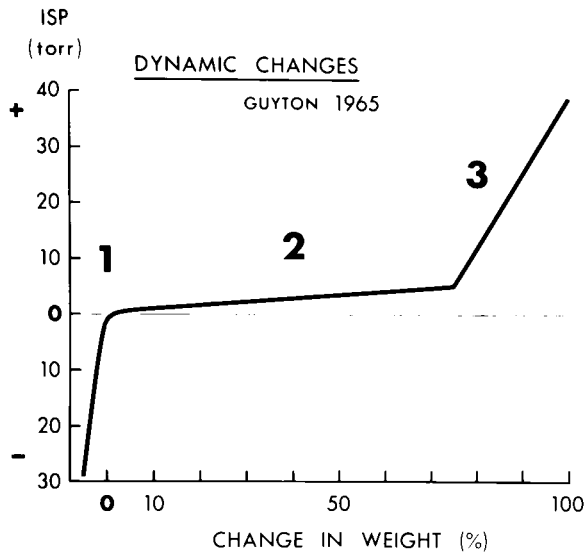

FIG. 2. The dynamic relationship between interstitial volume (estimated by change in leg weight) and interstitial pressure. Redrawn from Guyton et al.[1] Numbers *1*, *2*, and *3* defined in text.

unmeasured variable, pick a physiological state, and balance the equation in such a manner to prove the point at issue. Thus, if one wishes to describe the normal state in which there is a small lymph flow, but no interstitial fluid accumulation, one would commonly balance the equation to produce a 1–2 torr positive pressure gradient. However, if one wished to "create" pulmonary edema, one would have to create a positive pressure gradient which exceeded the "edema safety factors" of 18 torr and so forth. Let us take a look at the "commonly accepted" values and use similar mathematical calculations to arrive at the limitations of such an approach. The pressure component reflects capillary pressure minus interstitial pressure. In Table 1, reported minimal and maximal values for each are displayed. The pressure gradient could conceivably reflect the pressure differential between the minimal capillary pressure (2) and the maximum interstitial value (1). Thus, the minimal gradient could be as low as 1 torr. If one subtracted the minimal value for interstitial pressure (−7) from the maximal value for capillary pressure (12), the maximal gradient could be as high as 19 torr.

Similarly, the oncotic forces are displayed in Table 2. Minimal gradient (minimal serum minus maximal ISP) gradient would be equal to 2, whereas the maximal gradient (maximal serum minus minimal ISP) would be 30 torr. Combining the pressure and oncotic gradients in all possible fashions would lead to a number of different solutions: −29, −1, 11, or 17 torr (Fig. 4)! Thus, should you have a particular point to illustrate, by careful scrutiny of all variables and commonly reported ranges, one would have approximately 46 torr leeway to use to "balance the equation." Because measurements of intracapillary pressure and serum oncotic pressure are the most readily available and frequently performed, if disagreements occur among investigators as to the significance of

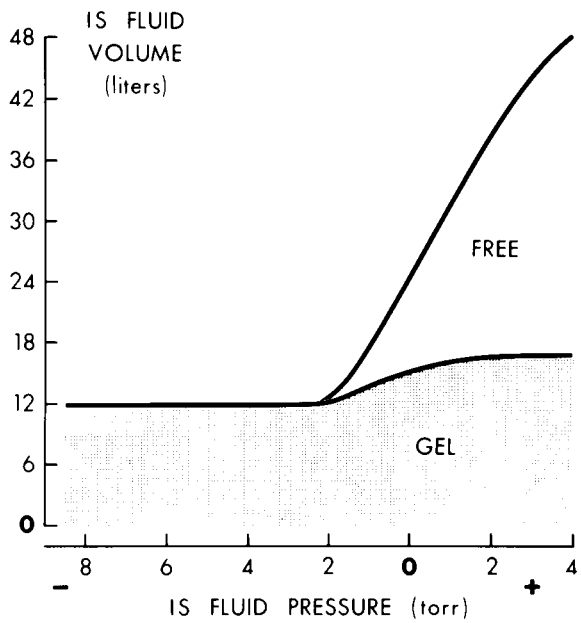

FIG. 3. The distribution of interstitial fluid volume between the solid and gel states. Redrawn from Guyton et al.[1]

TABLE 1. Pressure factors

	Minimum	Maximum
Capillary	2	12
Interstitial	−7	1

Potential gradients
Minimum capillary − maximum interstitial = 2 − 1 or 1
Maximum capillary − minimum interstitial = 12 − (−7) or 19

TABLE 2. Oncotic forces

	Minimum	Maximum
Capillary	20	35
Interstitial	5	18

Potential gradients
Minimum capillary − maximum interstitial = 20 − 18 or 2
Maximum capillary − minimum interstitial = 35 − 5 or 30

$$(P_C - P_I) - (\pi_P - \pi_I)$$

COULD BE

-29, -1, 11, 17

OR

ANYTHING IN BETWEEN !!

FIG. 4. The possibilities available from the values accessible in the literature. The variations seem to encompass all possible interpretations!

these measured variables, in reality, changes in the unmeasured variables may well account for the differences. I shall concentrate, therefore, on a perhaps oversimplistic overview of the less common measurements and the resulting greater disparity of interpretation.

In considering the physiologically important gradients, let us establish the underlying principle that these reflect what should be subtracted as described in the original equation, not what can be because they are simple clinical measurements. Thus, the intracapillary pressure-serum oncotic pressure gradient may be misleading[2] if changes in these measured variables are accompanied by any change in either interstitial oncotic pressure or interstitial fluid pressure. Let us concentrate on these latter two variables. Pressure relationships in the interstitial space are themselves capable of a simple mathematical expression: total tissue pressure equals solid tissue pressure plus interstitial tissue pressure.[1] Solid tissue pressure (Fig. 5) represents the sum of three forces exerted by collagen fibers, pressures exerted by the gel in the interstitial space, and pressures generated by cells abutting against other cells. ISP (Fig. 6) is generated by fluids passing into the capillaries as well as the evacuation of interstitial fluid by lymph flow. Solid tissue pressures are usually positive with respect to the atmospheric pressure and interstitial fluid pressures are negative, their sum or total tissue pressure is usually near atmospheric pressure or 0. Measurement of ISP has been the goal of many experimental efforts. Methodology here is crucial because technique can measure either total tissue or interstitial fluid pressure. The tremendous variability in results probably reflects the interpretation of total tissue pressure as interstitial fluid pressure. Experiments using a small balloon, a piece of isolated vein, or an excised vessel all have produced results in the range of +1–+3 torr.[3-5] However, this technique uses sensors so large that they contact both the interstitial fluid and the solid elements; therefore, they measure total tissue pressure.

Another measurement technique used capillary tubes or needles.[6, 7] Again, results varied from +1–+3 torr. Free fluid spaces, however, are only 0.05 μ in diameter. By necessity, then, a needle must distort the anatomy and result in measurement of total tissue pressure. Capillary tubes have been used to measure the pressures in interstitial "lakes." With this technique there are no solid tissue elements and, therefore, "interstitial pressure" measured equals total tissue pressure. Again, a positive result would be expected if the measurement technique is understood.

Fluid equilibrium techniques[8-10] have also been used to measure ISP. Here the variation according to technique can be as great as +1—13 torr. However, most results using implanted spheres or wicks report values in the range of −5—7 torr. Unfortunately, for the purposes of this discussion, Guyton et al.[1] have stated that "implantations in lung have not been satisfactory enough for one to feel confident of the pressures measured." In summary, ISP in the lung seems to be in the negative range, perhaps −5—7 torr. The experiments reporting positive values probably represent measurements of total tissue pressure.

INTERSTITIAL PRESSURE AND VOLUME RELATIONSHIPS

Of even greater importance, however, is the relationship between ISP and interstitial fluid volume. Three distinct and important relationships actually can be described (Fig. 2). When ISP is negative, very slight increases in interstitial volume cause rapid increases in ISP. In other words, compliance is slight (0.4 ml/torr per 100 g of tissue). Thus, the addition of a very small amount of fluid in the interstitial space increases ISP to 0.

Once atmospheric pressure is reached, however, large increases in interstitial volume are necessary to create any further increases in ISP. Compliance can be described as suddenly increasing 24-fold. This change in compliance can be interpreted as a safety valve that permits accumulation of large volumes of interstitial fluid in order to prevent increases in intravascular pressures. Once filtration increases to the point that interstitial volume expansion has caused ISP to reach atmospheric pressure, tremendous volumes can be accommodated in the interstitial fluid

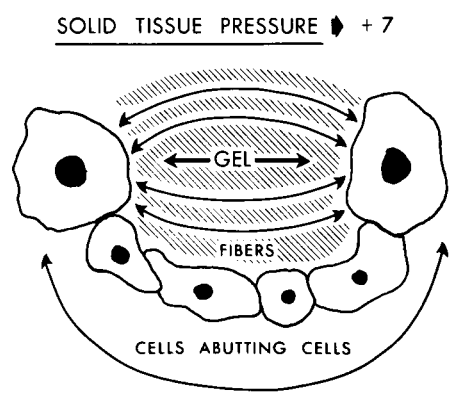

FIG. 5. A diagrammatic representation of the forces resulting in total tissue pressure.

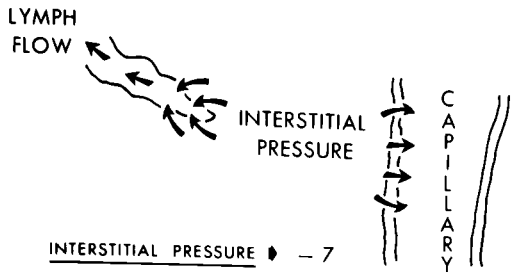

FIG. 6. The factors that create a negative interstitial pressure, diagrammatically represented.

space without further increasing either ISP or intravascular pressure.

Finally, after pitting edema occurs in the peripheral tissues, ISP begins to rise again as skin tension increases. The latter decrease in compliance then represents increasing skin tension. This dynamic relationship between ISP and interstitial volume must be further considered in terms of interstitial anatomy and the solid/gel distribution. If one views the alveolar septum in terms of function, there are two distinct portions; the alveolar capillary interface and the "thick portions of the septum." It is extremely important to avoid accumulation of fluid in the alveolar capillary septum because this would interfere with gas exchange. It appears, however, that the presence of the collagen fibers in the thick portion serves to attract interstitial fluid to this area where these fluids can be accommodated without affecting gas exchange. A number of experimental models has shown that extravascular lung water can be significantly increased without affecting gas exchange.[12] In fact, an x-ray diagnosis of pulmonary edema can occur without altered arterial oxygenation. This would seem to underscore the importance of defining the exact anatomic location of interstitial edema before assuming that any interstitial volume will deleteriously affect the movement of oxygen from the alveolus to the pulmonary capillary.

SOLID AND GEL STATE CONSIDERATIONS

Reconsideration of the distribution of this interstitial fluid in terms of the sol and gel states should serve at least to emphasize the importance of considering all factors operative in this very complex area. Approximately 99% of all the fluid interstitial space exists in gel form (Fig. 3). In a society in which so much emphasis is placed on certain contours and shape, this is an obvious advantage. If interstitial fluid was, in fact, free, its anatomical distribution would change according to the pull of gravity, we would all tend to look like plastic bags partially filled with water. Gels do have other desirable properties:[13] when exposed to free fluid, swelling will occur which will incorporate additional fluids; gels will impair bulk flow 10-millionfold compared to free fluid. However, diffusion is permitted to occur in unrestricted fashion. Thus, shape is maintained and distribution of various solids is not impeded.

Pressures exerted by the gel contribute to solid tissue pressure. These pressures result from the presence of the fluid inside the gel, surface tension, and, finally, a contribution caused by the Donnan effect of the charged particles. The gel possesses an abundance of negative charges which attract positive ions. These positive charges act to increase total osmotic pressure. This increase in osmotic pressure attracts free fluid into the gel.

The relationship between the interstitial fluid volume and interstitial fluid pressure can also be examined in terms of the distribution of fluid between the gel and free states. There is relatively little change in the interstitial fluid volume until interstitial fluid pressure approaches atmospheric pressure. Again, rapid accumulation of interstitial fluid volume occurs without any major changes in interstitial fluid pressure. This increase in interstitial fluid volume represents accumulation of free fluid. Only small amounts of increased interstitial fluid volume can be accommodated by changes in gel state volume. Accumulations of large amounts of free interstitial fluid, then, will result in changes in the distribution of interstital fluid volume according to the pull of gravity. This results in an accumulation of peripheral edema. Thus, once the safety factors are exhausted, free interstitial fluid accumulates, rather than further increases, in intravascular pressures. However, the cosmetic disturbances of peripheral edema can be changed to the physiological disturbance of pulmonary edema, paroxysmal nocturnal dyspnea by altering body habitus because the excess fluid cannot be accommodated by the gel state and is redistributed according to the forces of gravity imposed by the supine position.

INSTERSTITIAL ONCOTIC PRESSURE

The oncotic pressure gradient has been designated as playing a major role in determining net volume movement in normal tissues. Because plasma oncotic pressure is easily measured, uncertainty about the magnitude of the gradient depends upon the value of interstitial oncotic pressure (IOP). In the lung, IOP is probably 70–80% of the serum value.[14, 15] This is quite different from the 15–20% of serum level usually ascribed to peripheral tissues. If normal oncotic pressure is 20–25 torr, then the true gradient across the lung would be merely 4–6 torr. If one used a gradient of perhaps 15–20 torr in the Starling equation, the importance of oncotically active forces, in determining volume movement, would be greatly overestimated. The implication of the markedly elevated IOP is related to the permeability of the pulmonary capillary

to albumin that is the major constituent of oncotic pressure.

The Staverman reflection coefficient is a mathematical expression of he permeability of a membrane to any particular substance.[16] For instance, if a membrane is impermeable for a particular substance, its reflection coefficient would be described as 1. Thus, whatever gradient did exist would act in full force as a determinant of fluid movement. However, if the membrane was completely permeable, its reflection coefficient would be represented as 0. Because the effect of permeability is obtained by multiplying the coefficient times the gradient involved, a coefficient of 0 would eliminate any effect of that particular oncotic force. Recent experiments suggest that the pulmonary capillary is not as impermeable to albumin as commonly assumed in the past. Numerous techniques including histochemical, radioimmune assays, and anatomical studies have confirmed that the pulmonary capillaries are reasonbly permeable to albumin. The reflection coefficient may be in the range of 0.7 ± 0.1. Thus, the permeability of the pulmonary capillary to albumin results in a higher level of IOP and an overall decrease in the importance of any established gradient to affect fluid movement. The importance of IOP, however, should not be underestimated because it forms a major safety valve to prevent edema formation. As pulmonary microvascular pressure increases, a simultaneous decrease in IOP will occur (Fig. 7). This "interstitial protein washout" acts as an important safety mechanism because increases in the pressure gradient will be offset by an increase in the oncotic gradient; plasma oncotic pressure would remain the same, IOP would decrease; thus, the total gradient would increase.

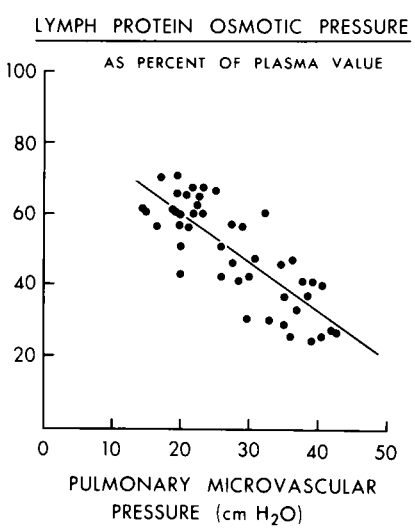

FIG. 7. The relationship between microvascular pressure and its resultant effect upon the plasma osmotic pressure, actually oncotic pressure because it is linearly related to albumin concentration.

However, if changes in capillary permeability also occur, such a selective decrease in oncotic pressure would not be expected. Under these circumstances, the oncotic gradient would be lessened because the pulmonary capillary would permit free passage of all oncotically active substances in the serum and one might expect that IOP would approach serum oncotic pressure. In fact, in certain experimental preparations such as the capillary injury induced by alloxan,[18] this hypothesis is confirmed.

Finally, if serum oncotic pressure is decreased, a concomitant reduction in the oncotic pressure gradient must not be assumed unless one can show unequivocally that IOP was maintained at its previous level. The available evidence would suggest that this, indeed, is not the case and that interstitial washout of oncotically active substances occurs at the same rate as serum oncotic pressure falls.[15] The gradient, however slight, is maintained despite the fact that serum oncotic pressure can be decreased markedly (Fig. 8).

LYMPHATICS

The role of the pulmonary lymphatic system deserves special attention. Not only does the ability to increase lymph flow provide a great margin of safety to accommodate increases in net fluid flow from the capillary into the interstitial space, but the creation of a negative interstitial pressure in the interstitial space is largely affected by the lymphatic system. A number of special features of the lymphatic system have been discovered over the last 40 years. In some respects, the lymphatic system may be relegated to a "Cinderella" role: lack of appreciation for the many functions encompassed in its dynamic minute-to-minute activities.

The interrelationships between lymphatic function and the interstitial pressure-fluid relationships are most important and difficult to interpret independently. The lymphatic system creates the negative ISP as shown by Allen[19] in 1938. This static function was enhanced by the findings of Guyton[20] in 1965 showing that, in peripheral tissues, physical motion was also important to contribute to this negative pressure. While no direct correlation to the nonmuscular pulmonary parenchyma can be inferred, breathing does induce similar motion changes in interstitial anatomy. Furthermore, the impact of pulsatile blood flow upon the motion of fluid into lymphatics was noted over 30 years ago.[21] The existence of lymphatic valves and lymphatic contractions has also been substantiated in numerous experimental procedures.[22]

How does one effectively synthesize these experimental results into a foundation for discussion and further interpretation? Certain tested hypotheses can be formed: lymphatics can pump fluid out of the interstitial space even at negative interstitial fluid

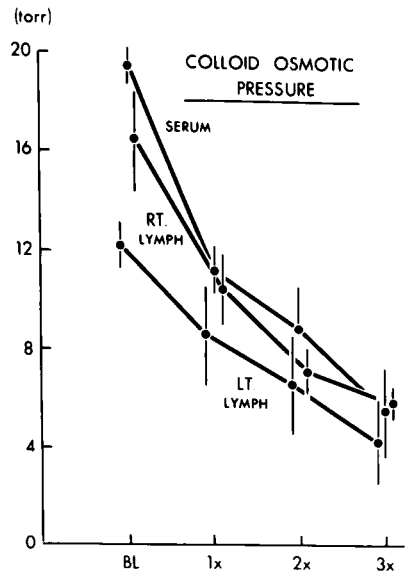

FIG. 8. The relation between colloid osmotic (again, basically albumin concentration) and interstitial osmotic pressure in right lymph (pulmonary lymph) and left lymph (total body lymph). Note that decreases in serum proves all are related in a linear fashion to both lymph values; the gradient remains the same!

pressures. However, this cannot completely account for the negative interstitial pressure encountered.

The relationship between ISP and lymph flow depends on initial ISP. (Formed at negative ISP, the lymph flow cannot pump with enough suction to totally create the ISP, but it can evacuate a space so that fluid accumulation does not occur.) Envision a boat with a 6-foot hold. If a small leak developed, it would be possible to pump out the fluid accumulation without ever approaching the limits of the pump of the hold. This is analogous to a small increase in filtration pressure and net flow in the lung.

If fluid accumulation increases to a point that ISP reaches 0 (atmospheric pressure is attained), lymph flow can increase a maximum of 20-fold (Fig. 9)[23], clearly an extremely important safety factor.

Finally, at markedly increased ISP, the total tissue pressure outside lymphatics will "balance" the hypothetical intralymphatic pressure. This may reduce overall lymphatic flow. The fact that 20-fold increase in lymph flow occurs with relatively small ISP changes (0–4 torr) emphasizes the dynamic aspects of lymphatic function.

Interpretation of the Starling equation clearly rests on pulmonary microvascular pressure, oncotic pressure gradient, normal capillary membrane function, and an appreciation of the limits of lymphatic function and interstitial anatomy and geometry. A restatement of physiologically important goals is that the interstitial fluid system tends to prevent edema and yet serves as a safety valve for the cardiovascular system.

If pulmonary gas exchange is a crucial function, the gas exchange interface should be protected; in fact, edema collects in the thick portion of the alveolar septum (defined by the collagen fibrils). Furthermore, an increase in ISP uses up "the initial compliance factor" resulting in a rapid accumulation of interstitial volume without an increase in ISP. This results in peripheral edema which effects cosmetic and nonphysiological changes. If beauty is in the eye of the beholder, remember that an edematous ankle may be preserving a functional lung!

A 300% increase in pulmonary capillary pressure (4–12 torr) can occur without any increase in interstitial fluid volume, due to changes in compliance and increased fluid entry into the lymphatics. If the cardiovascular system can be compared to a major city subject to flood water variations in its river system, the entire flood control system is based on the premise that, should flood waters rise, these waters will be diverted without affecting the down-river function. The interstitial space actually performs a similar function. If there is an increase in intravascular volume, it may either serve to increase intravascular pressures and decompensate the cardiovascular system or it may "spill over" into the interstitial space (Fig. 10). If the interstitial space was unable to accommodate such an increase in volume, this would be an etiologically unhappy turn of events. However, the increase in compliance seen at 0 ISP results in an easy accommodation of massive quantities of extra fluid to prevent an increase in intravascular pressure which would increase the workload of the heart according to the law of Laplace. Increased ventricular radius, induced by an increased intraventricular pressure,

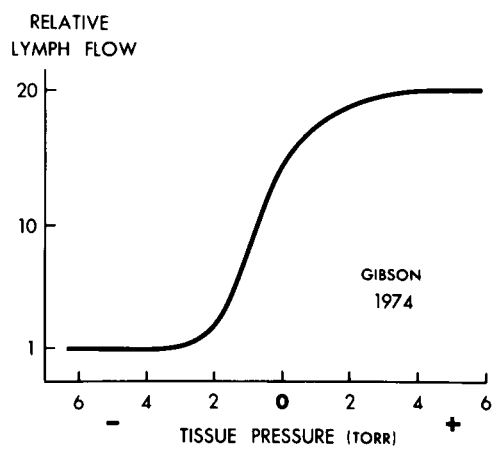

FIG. 9. Lymph flow is a function of interstitial pressure. Note that minor changes in ISP (2–4 torr) occurring near atmospheric pressures result in major (20-fold) increases in lymph flow. The implications of this relationship can be interpreted as a potent safety valve to accommodate major changes in ISP without resulting in interstitial edema because lymphatic function can "cope" with major increases in filtered fluids.

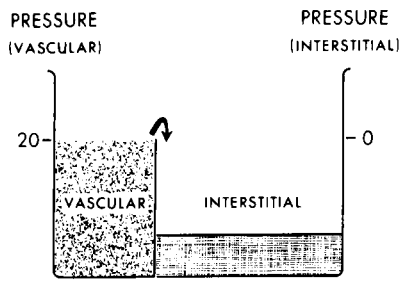

FIG. 10. The "spillover-safety valve concept," to prevent overdistention, ventricular filling pressure > 20 torr, the "system" provides for an increase in interstitial volume without significant change (i.e., approaching atmospheric pressure) in interstitial pressure.

would result in a concomitant increase in myocardial work.[24] If the heart is initially failing, any increase in diameter would further stress the heart. Therefore, this safety valve acts as a spill over for a failing myocardium. The function of the interstitial fluid system can be conceived as the safety valve to prevent excessive increases in intraventricular pressure while the heart continues to pump an adequate amount of oxygenated blood.

Expressions of hydrostatic and oncotic pressures are only partial solutions to the problem that Starling originally addressed. Physiologically important gradients reflect the difference between similar physiological variables! Thus, if one wishes to discuss the "pressure gradient," one needs to measure pulmonary microvascular pressure (neither wedge pressure, pulmonary artery pressure, or left atrial pressure) and pulmonary interstitial pressure. If one wishes to discuss oncotic gradients, one must measure both plasma and interstitial oncotic pressure. Convenient gradients such as the difference between colloid oncotic pressure and pulmonary capillary pressure cannot serve any useful function (Fig. 11)[27] unless the situation encompassed can be explicitly determined to be free of any changes in interstitial oncotic pressure or interstitial fluid pressure. As yet, no experimental or clinical situation has been shown free of such concomitant changes.

What controversies rest on the interpretation of the Starling equation? It appears that the relationship of albumin solutions and albumin concentration on the formation and resolution of pulmonary interstitial edema occupies an obvious focal point. The role of oncotically active albumin solutions[25] is presupposed to increase the oncotic pressure gradient; this, in turn, supposedly "tips" the Starling equation toward fluid resorption and (with subsequent elimination in the urine) permits a gradual, but effective, "drying of the lungs." This is an attractive hypothesis! Does it bear scrutiny?

First, can one establish an oncotic pressure gradient across the lung? The available evidence would suggest that this is not possible. The pulmonary capillaries are normally semipermeable to albumin and, in many disease states, are completely permeable. Second, if one increases plasma oncotic pressure, does this increase the gradient? If the membrane were totally impermeable to albumin, this might be a reasonable expectation. Again, one must consider that even a normal capillary is permeable to albumin and certainly that the damaged capillary is totally permeable. Therefore, we must conclude that a gradient cannot be established.

What, then, might be anticipated from the administration of concentrated albumin solutions? If, indeed, any oncotic effect is established, plasma volume will be increased as a result of albumin administration.[26] This will, of course, increase intravascular pressures, ultimately creating a true increase in pulmonary microvascular pressure. Paradoxically then, administration of albumin solutions will not increase the oncotic pressure gradient but, through its oncotically active properties, will increase plasma volume and concomitantly increase pulmonary microvascular pressures! Oncotically active substances can only serve to increase net filtration and enhance the formation of interstitial edema; this cannot be considered a paradox, but must be subjected to careful scrutiny, term by term, factor by factor, without reference to preconceived notions!!

Microvascular pressure changes are probably the most important variable whether they are caused by increases in left atrial pressure or by increases in serum colloid osmotic pressure. As a matter of fact, oncotic pressures cannot be appreciably changed, in

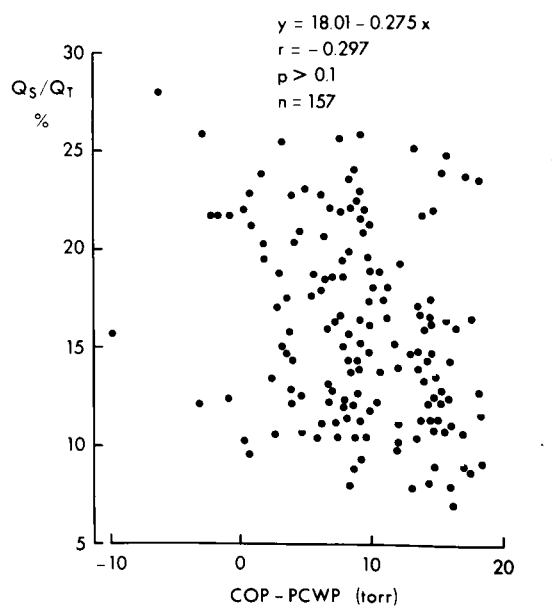

FIG. 11. The independence of the (COP-PCWP) gradient and gas exchange as estimated by intrapulmonary shunt. Redrawn from Virgilio et al.[27] Crystalloid vs colloid resuscitation: is one better? A randomized study. *Surgery* (in press).[27]

terms of the overall gradient, in the normal situation, and certainly cannot in the presence of permeability changes.

Let us focus our attention, then, upon the areas where methodology and evidence have not totally unraveled the mysteries. The alveolocapillary membrane is anatomically distinct from the area where interstitial edema accumulates. This is not happenstance, but a reflection of the fact that collagen fibrils which attract sodium and water are located in the thick portion of the septum.

The dynamics of the interstitial space reflect marked changes according to the physiological state encountered: (1) At negative interstitial pressures, interstitial compliance is quite limited, i.e., small changes in interstitial fluid volume increase interstitial fluid pressure to atmospheric. (2) Once atmospheric pressure is attained, marked increases in interstitial fluid volume will be accommodated without further increases in interstitial pressure, i.e., interstitial compliance increases by a factor of nearly 20-fold! (3) Further increases in interstitial volume are accompanied by increases in interstitial pressure, but this reflects increases in skin tension as tense edema accumulates.

Finally, the gel state preserves our physique. Of our interstitial fluid, 99% is contained in the gel state to enhance our "bodily image." However, once interstitial pressure exceeds the capacity of the interstitial volume to compensate, interstitial fluid accumulates in the free state that ultimately results in gravitationally distributed edema: ankle edema when you are standing, or paroxysmal nocturnal dyspnea when fluid translocates to the lung at night.

A greater appreciation for lymphatic function will be necessary because it can compensate for simple increases in filtration, effect functional evacuation of the interstitial space to create the negative interstitial fluid pressure, and effect interstitial protein washout.

Directions for future endeavors and a framework for interpretation seems to be a reasonable goal. Let us examine future work in terms of the appropriateness of the model and the measurements. Let us try to integrate data from static and dynamic experiments. If we try to include normal and abnormal, we can thus end up with at least 10 independent variables: it is clear that no one can design a particular experiment to encompass all possible situations. Rather than argue relative merits, more productive effort might be the most relevant response.

Remember that the Starling equation approximates fluid flux, not the accumulation of interstitial edema. Thus, "repeal" of Starling's law is not indicated, merely an appreciation of what it does describe, the limitations of methodology, and a challenge to the postulators, experimenters, and clinicians.

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