Published in final edited form as:

Ann N Y Acad Sci. 2010 October ; 1207(Suppl 1): E29–E43. doi:10.1111/j.1749-6632.2010.05709.x.

Role of intestinal lymphatics in interstitial volume regulation and transmucosal water transport

Peter R. Kvietys^a and D. Neil Granger^b

^a Lawson Health Research Institute London, Ontario, Canada

^b Louisiana State University Health Sciences Center-Shreveport, Shreveport, Louisiana

Abstract

Two of the principal functions of intestinal lymphatics are to assist in 1) maintaining interstitial volume within relatively normal limits during alterations in capillary filtration (e.g., acute portal hypertension) and 2) removal of absorbed water and chylomicrons. The contribution of lymphatics to the prevention of interstitial over-hydration or dehydration during alterations in transcapillary filtration is similar in the small intestine and colon. While the lymphatics of the small intestine contribute substantially to the removal of absorbed water (particularly at low and moderate absorption rates), the contribution of colonic lymphatics to the removal of the fluid absorbate is negligible. This difference is attributed to the relative caliber and location of lymphatics in the mucosal layer of the small and large intestines. In the small intestine, large lacteals lie in close proximity to transporting epithelium, while colonic lymph vessels are rather sparse and confined to the basal portion of the mucosa. In the small intestine, the lymphatics assume a more important role in removing absorbed water during lipid absorption than during glucose absorption.

Keywords

small intestine; colon; lymphatics; transcapillary fluid exchange; water absorption; secretion

Introduction

The major function of the intestines is to assimilate ingested nutrients and water. The daily fluid load presented to the intestines is roughly 9,000 ml; 2,000 ml are ingested and 7,000 ml are derived from endogenous secretions of the salivary glands, stomach, liver, pancreas, and intestines proper. Of the 9,000 ml delivered to the intestines, 80% is absorbed by the small intestine and 18% by the colon, with only 2% excreted in the stool.

Water absorption across the intestinal mucosa is linked to the transport of electrolytes and nutrients. Absorbed water is removed from the intestinal mucosal interstitium via the blood and lymph circulations. The blood/lymph microcirculatory unit allows for assimilation of nutrients and water with minimal changes in mucosal interstitial volume. The relative roles of the blood and lymphatic vessels in the removal of absorbed water is dependent on both the type of nutrient absorbed (i.e., sugars vs lipids) and the segment of bowel involved (i.e., small vs large intestine). The intestines can also secrete water into the lumen. The secretion of water can either be an active process linked to solute transport or a passive process that results from over-hydration of the mucosa and/or a weakened epithelial lining (“filtration secretion”). The blood and lymph circulations also participate in a differential manner that is

dependent on whether fluid secretion into the lumen is active or passive, as well as the location of the bowel where secretion is taking place. Although the emphasis of this review is on the role of lymphatics in intestinal transmucosal water transport, the ultimate responses of the lymphatics are intimately linked to events that occur at the level of the blood capillaries. Thus, herein, the pertinent anatomical features and physiological responses of the blood/lymph microvascular unit to water transport will be addressed for the small intestine and, where applicable, for the large intestine.

Anatomic considerations

The blood and lymph microcirculations

The blood and lymph microcirculations of the small and large intestinal mucosae are markedly different, both in terms of their architecture and spatial distribution within the interstitium. In the small intestine, submucosal arterioles enter the villi as a single vessel that passes to the tip and forms a capillary fountain or tuft-like network with numerous anastomoses with the single eccentrically located venule. The villus capillaries are situated within 2 μm of the epithelial cells. The lymphatic system of the small intestinal villi originates as a large centrally located vessel (lacteal) with a “cul-de-sac” endothelium at the apical portion (Fig. 1A). The lacteal is located approximately 50 μm from the epithelium.^{1–3} In the colon, submucosal arterioles ascend along the colonic glands (pits) to form subsurface capillary networks surrounding them; presenting a honeycombed appearance when viewed from the luminal surface.^{4,5} The colonic capillaries are situated closer to the epithelium (1 μm) than their counterparts in the small intestine.⁶ The initial lymphatics of the colon are much smaller in caliber than the central lacteal of the small intestinal villi and sparsely distributed near the base of the glands (Fig. 1B). They are situated 300–400 μm from the surface epithelium.⁵

From an ultrastructural standpoint, the capillaries of the small and large intestine are of the fenestrated type. Approximately half of the fenestrae are closed by a diaphragm and, in general, the fenestrae are preferentially oriented towards the base of the transporting epithelium. The frequency of fenestrae increases from the arterial to the venous end of the capillaries. These capillaries also contain caveolae that can be internalized as vesicles and fuse with other intraendothelial vesicles forming transendothelial channels. The interendothelial junctions can be opened or closed, with the frequency of opened junctions increasing from arterial to venous end of the capillaries. Finally, the luminal aspect of the capillary endothelium is covered by a glycocalyx and the abluminal aspect is surrounded by a basement membrane. These ultrastructural features are believed to impart a size-selectivity to the transcapillary movement of solutes, allowing small solutes (e.g., glucose) to move rather freely yet restricting the movement of macromolecules (e.g., albumin). However, the precise transendothelial pathways by which small and large solutes and water move across the blood capillaries is still a matter of debate.^{3,7–9}

The lymphatic capillaries, or initial lymphatics, can be distinguished from the blood capillaries by the following anatomical features. The endothelium of the initial lymphatics is not fenestrated and it lacks complex interendothelial junctions.¹⁰ The lumen is closed by the overlap of thin portions of adjacent endothelial cells. As opposed to the continuous basement membrane of blood capillaries, the lymphatic endothelium is surrounded by a fragmented basement membrane. However, they possess anchoring filaments attached at the abluminal aspect of overlapping endothelial cells that extend into the adjoining elastic and collagen fibers of the interstitial matrix and keep the lymphatic lumen patent (Fig. 1C).¹¹ These anchoring filaments consist of a continuum of elastic fibers (e.g., oxytalan, elaunin, and elastic fibers) of increasing elasticity extending from the initial lymphatic to fibrillar components (e.g., collagen) of the matrix.¹² Based on the ultrastructural features of the

initial lymphatics, it is generally accepted that the initial lymphatics have an extremely high hydraulic conductance and do not offer any significant restriction to the movement of solutes and water.

The interstitial matrix

The blood and lymph microvessels are situated and interact with the interstitium to regulate solute and water transport by the intestines. The interstitial matrix consists of a fluid phase which is distributed within structural components, i.e., fibrillar and non-fibrillar macromolecules.^{13–16} The major fibrillar components include collagens that provide tensile strength to the matrix and elastin fibers that provide elasticity. The non-fibrillar components include the mucopolysaccharides, referred to as glycosaminoglycans, the major one being hyaluronan. With the exception of hyaluronan, other glycosaminoglycans (e.g., heparin and heparin sulphate) are covalently bound to a protein core and referred to as proteoglycans. The glycosaminoglycans ensnare water, thereby regulating the hydration state of the interstitium. The extensive mechanical entanglement (e.g., cross-linking) of the glycosaminoglycans and collagens creates a gel-like matrix. The matrix is not a stable structure but a dynamic one; its components (e.g., collagen and hyaluronan) regularly turn over, being released from the matrix and resynthesized continuously. The interstitial matrix resists compression and expansion and offers structural support for various cellular components (mesenchymal cells), as well as the initial lymphatics. Although the matrix can resist expansion to a certain degree, it tends to fall apart when stretched as a result of disentanglement of the hyaluronan-collagen matrix.

Interstitial volume regulation

Basic principles

In the resting (non-transporting) gastrointestinal tract, the balance of hydrostatic and oncotic forces governing transcapillary fluid exchange favors net filtration of fluid from the blood to interstitial compartment (Fig. 2). To maintain a constant interstitial volume, the rate of transcapillary fluid filtration into the interstitium is balanced by an equal rate of interstitial fluid removal by the lymphatics. The exchange of fluid between the blood and interstitium is dependent on the hydrostatic and colloid osmotic pressure gradients exerted across the microvasculature and by the permeability and hydraulic conductance characteristics of the capillary barrier. Accordingly, the net transcapillary fluid movement can be described by the Starling relationship

$$J_{v,c} = K_{f,c} [(P_c - P_t) - \sigma_d (\pi_c - \pi_t)]$$

Where $J_{v,c}$ is the rate of net transcapillary fluid movement; capillary filtration when positive and capillary absorption when negative. $K_{f,c}$ is the capillary filtration coefficient and a measure of transcapillary hydraulic conductance and, as such, is dependent on both capillary surface area available for exchange and the capillary permeability to solutes and fluid. P_c is the capillary hydrostatic pressure and P_t is interstitial fluid pressure. The osmotic reflection coefficient (σ_d) refers to the fraction of the total oncotic pressure generated across a capillary membrane. Impermeant proteins generate 100% of their maximum oncotic pressure ($\sigma_d = 1$), whereas freely permeant proteins do not exert an oncotic pressure ($\sigma_d = 0$). The transcapillary oncotic pressure gradient ($\pi_c - \pi_t$) is primarily determined by the difference between plasma and interstitial protein concentrations. Estimates of the parameters of the Starling relationship (except P_t) have been measured using validated physiologic approaches, while P_t is generally calculated from the other measured parameters.^{3,13} Since

systematic analyses of the Starling forces have been undertaken in the small intestine, the focus herein will be on this tissue, with information relevant to the colon included where applicable.

Experimental values obtained from the resting (non-transporting) feline small intestine are shown in Figure 2. The magnitude and direction of transcapillary fluid movement is dependent on the net filtration pressure (NFP) or net absorptive pressure (NAP). These pressures are determined by the balance of transcapillary hydrostatic and oncotic pressures. In the example shown in Figure 2, the transcapillary hydrostatic pressure gradient is 10.4 mm Hg (12.6–2.4 mm Hg) and the transcapillary oncotic gradient is 10.8 (20.0–9.2 mm Hg). If the permeability of the capillaries to plasma proteins (i.e., σ_d) is not taken into account, the balance of these pressures (0.4 mm Hg NAP) would favor net capillary absorption of fluid from the interstitium. However, the σ_d for total plasma proteins in the intestine is 0.92 and thus the effective oncotic pressure gradient is reduced to approximately 9.9 mmHg. This results in a NFP of approximately 0.3 mmHg and favors the filtration of fluid from the capillaries into the interstitium. With the modulating effect of $K_{f,c}$, a net fluid filtration rate of 0.04 ml/min/100 gm results that is matched by an equal rate of lymph flow to yield a constant interstitial fluid volume.

Interstitial over-hydration

Uncompensated increases in transcapillary fluid filtration would lead to edema formation, the eventual disruption of the mucosal epithelial lining, and potential movement of interstitial fluid into the gut lumen (filtration secretion). Fortunately, moderate increases in capillary fluid filtration (e.g., increases in capillary pressure) result in appropriate adjustments in the Starling forces to prevent over-hydration of the interstitium.¹⁷ For example, an increase in capillary pressure induced by acute venous hypertension results in an instantaneous increase in the net filtration pressure (NFP). This leads to enhanced transcapillary filtration of protein-poor fluid into the interstitium. As interstitial fluid volume increases, P_i rises and interstitial proteins are diluted, resulting in a decrease in π_i . These compensatory adjustments in interstitial forces oppose further capillary fluid filtration by reducing net filtration pressure (NFP). The increase in P_i also increases the driving pressure for lymphatic filling and the rise in lymph flow drains some of the excess fluid from the interstitium. Although not experimentally verified, it is generally held that during interstitial hydration, the anchoring filaments exert tension on the initial lymphatics, widening the lumen and opening the interendothelial junctions, thereby facilitating the movement of large amounts of water and macromolecules from the interstitial spaces into the lymphatics.¹¹ The net result of the compensatory adjustments in interstitial forces is a new steady-state with a slightly increased interstitial volume and an elevated lymph flow.¹ A similar analysis in the colon indicates that qualitatively similar compensatory adjustments in interstitial forces and lymph flow occur in response to an increase in capillary hydrostatic pressure.¹⁸

The factors that prevent excessive increases in interstitial volume in response to an increase in capillary fluid filtration rate are referred to as edema safety factors.^{1,13,19} These safety factors are quantifiable in terms of mm Hg. The relative contributions of the various edema safety factors in the feline small intestine and canine colon for an increment in capillary pressure of 12–13 mm Hg are shown in Figure 3. In both tissues, the increases in oncotic pressure gradient and interstitial fluid pressure are the major safety factors against edema, while lymph flow plays a minor role, particularly in the colon. The comparatively minor contribution of the lymphatic safety factor in the colon is most likely due to the paucity of the lymphatics in this tissue (Fig. 1B).

The total safety factor against edema in the small and large intestine is around 15 mm Hg.^{1,13} Increments in capillary pressure in excess of 15 mm Hg lead to unopposed

transcapillary fluid filtration, severe edema, disruption of the epithelial lining, and eventually exudation of fluid across the mucosa into the lumen (filtration secretion).^{20,21} As is the case for lymph flow, the driving force for filtration secretion is interstitial fluid pressure. For example, when intestinal villus interstitial fluid pressure is increased to approximately 9 mm Hg (range, 6–12 mm Hg), filtration secretion ensues.²¹ Ultrastructurally, there is evidence that the mucosal epithelial barrier is compromised when P_t rises to these levels, with separation of portions of the epithelium from the basal lamina (“bleb formation”) to frank loss of epithelial cells.²¹ Thus, not only is the hydraulic conductivity of the mucosal membrane increased, the permeability to macromolecules is also increased such that interstitial proteins enter the lumen, therefore the composition of the secreted fluid resembles that of lymph.¹³

Interstitial dehydration

Compensatory adjustments in the Starling forces also serve to prevent interstitial dehydration when capillary filtration rate is reduced.²² For example, acute arterial hypotension results in a decrease in capillary pressure that can initially reverse the net filtration pressure (NFP) to a net absorptive pressure (NAP). The resultant movement of fluid out of the interstitium and into the capillaries causes a reduction in interstitial volume that, in turn, decreases interstitial fluid pressure and increases interstitial oncotic pressure. These compensatory readjustments in interstitial forces not only hamper further movement of fluid out of the interstitial space but actually result in a small net capillary filtration pressure. The decrease in interstitial fluid pressure reduces lymphatic filling and decreases lymph flow. Collectively, these responses result in a new steady-state transcapillary fluid balance at a slightly reduced interstitial volume, capillary filtration rate, and lymph flow.

As with the safety factors against edema, the safety factors that prevent interstitial dehydration are also quantifiable in terms of mm Hg.^{1,13} The relative contributions of the various edema safety factors in the feline small intestine for a decrement in capillary pressure of 6.5 mm Hg are shown in Figure 3. A reduction in interstitial fluid pressure is the major factor opposing dehydration, while the increased interstitial oncotic pressure and lymph flow play more minor roles.

Intestinal water absorption

As mentioned above, interstitial fluid volume is maintained within a relatively narrow limit by matching any changes in transcapillary fluid movement to corresponding changes in lymph flow draining the tissue. Interstitial fluid volume can also be affected by the rate of fluid absorption across the mucosal epithelium. During absorption, fluid enters and expands the interstitium. In this situation, appropriate alterations in the Starling forces allow for the removal of absorbate by the capillaries and lymphatics, thereby preventing excess interstitial fluid accumulation, i.e., edema.

Role of the interstitial matrix

The physiochemical characteristics of the interstitial matrix confer three functional properties to the interstitium that are relevant to intestinal solute and water transport: hydraulic conductivity, compliance, and macromolecular exclusion.^{13–16} The hyaluronan-collagen matrix immobilizes interstitial fluid such that the hydraulic conductivity of the interstitium is relatively low. However, during fluid absorption, there is an increase in interstitial fluid volume (and matrix hydration). The resultant expansion and disentanglement of matrix components, as well as the loss of some of the components from the interstitium (e.g., hyaluronan^{23,24}) greatly increases hydraulic conductivity of the

interstitial matrix (Fig. 4). For example, doubling the interstitial volume can increase the hydraulic conductance a 800–1000 fold.

The compliance characteristics of the interstitium also influence the hydrostatic forces operating across the blood and lymph capillaries and consequently the rate of fluid movement across their endothelial membranes. The interstitial compliance curve (fluid pressure/fluid volume) has two components (Fig. 4)^{13,17}. At normal (or low) interstitial volume the compliance is low, i.e., small increments in volume result in large increases in interstitial pressure. There is an abrupt change in interstitial compliance when interstitial volume increases by 3–5 ml/100 gm; further increments in volume result in much smaller increases in interstitial pressure. It is presumed that the inflection point in the compliance curve is a result of the disruption of the hyaluronan-collagen matrix.

The interstitial matrix behaves like a mesh of a given porosity and is able to exclude large molecules from the fluid phase. For example, in the normally hydrated interstitium, albumin is excluded from approximately 40% of the total water space (Fig. 4).²⁵ The hyaluronan component appears to contribute more than the collagen component to this phenomenon, in part due to its anionic nature and negative charge.¹⁵ When interstitial volume increases, the degree of albumin exclusion is reduced presumably due to expansion of the matrix and increased porosity of the mesh. With large increases in interstitial fluid volume, the decrement of albumin exclusion is accelerated as the interstitial matrix expands. Overall, the net effect is an increased ability of water and solutes (including proteins) to move more freely throughout the mucosal interstitium during absorption.

Role of interstitial hydrostatic and oncotic pressures

The most important physiologic consequences of the interstitial volume expansion associated with intestinal fluid absorption are the alterations of interstitial hydrostatic and oncotic pressures.¹³ Based on experimental data and mathematical modeling approaches,²⁶ it is predicted that interstitial hydrostatic pressure should increase and interstitial oncotic pressure should decrease (Fig. 5). These changes enhance the removal of absorbed fluid from the lamina propria by: 1) opposing further capillary filtration and converting filtering capillaries to absorbing capillaries and 2) providing an increased hydrostatic pressure for lymphatic filling.

Estimates of interstitial hydrostatic pressure during fluid absorption have been obtained by either direct measurements of lacteal pressure²⁷ or, indirectly, by calculation of interstitial pressure from measurements of the other parameters in the Starling equation.²⁸ Estimates of interstitial oncotic pressure during absorption have been obtained by measuring lymph protein concentration (or oncotic pressure).²⁸ The alterations in interstitial hydrostatic and oncotic pressures as a function of fluid absorption rate are presented in Figure 5. At low absorption rates (< 0.30 ml/min/100 gm), interstitial hydrostatic pressure increases dramatically in accordance with the compliance characteristics of the intestinal interstitium (see Fig. 4). On the other hand, interstitial oncotic pressure only decreases modestly. At higher absorption rates (around 0.30–0.40 ml/min/100 gm), interstitial volume has increased sufficiently to alter the compliance of the matrix and interstitial fluid pressure rises less dramatically with further increments in absorption rate (interstitial volume). At this moderate absorption rate, interstitial oncotic pressure begins to drop dramatically. At high absorption rates (> 60 ml/min/100 gm), there are minimal changes in either interstitial hydrostatic or oncotic pressures, with further increments in absorption rate.

Role of interstitial lymphatics and capillaries

The rise in interstitial hydrostatic pressure produced by fluid absorption should lead to an increased rate of intestinal lymph formation. That this occurs in the small intestine has been demonstrated experimentally.¹³ The magnitude of the increase in lymph flow can vary considerably depending on tonicity of the fluid placed in to the lumen, portal venous pressure, intraluminal pressure, motility, etc. If these factors are minimized, the rate of fluid absorption becomes the major determinant of intestinal lymph flow.²⁵ The dependence of lymph flow on fluid absorption rate likely results from the fact that interstitial volume and hydrostatic pressure are related to absorption rate.

The relative fraction of absorbed fluid that is removed from the mucosal interstitium by the lymphatics and capillaries is dependent on absorption rate (Fig. 6). At low absorption rates ($< 0.20 - 0.30$ ml/min/100 gm), the lymphatics are the primary route by which the absorbate is removed, accounting for as much as 80% of the total volume removed from the interstitium.²⁹ At higher absorption rates, the reverse holds, i.e., capillaries are the major route by which the absorbate is removed. The differential role of capillaries and lymphatics in removing the absorbate when absorption rate is altered is consistent with the compliance characteristics of the mucosal interstitium (Fig. 4). At low absorption rates, interstitial compliance is low and hydrostatic pressure increases dramatically while tissue oncotic pressure is virtually unaltered. The increased hydrostatic pressure should preferentially drive fluid into the lymphatics because the hydraulic conductance of these vessels is much greater than that of the capillaries. As the fluid absorption rate increases, tissue oncotic pressure falls and the driving force for capillary fluid absorption increases disproportionately to the driving force for lymphatic filling (Fig. 5). This occurs because both interstitial hydrostatic and oncotic pressures act across the capillary wall, but only tissue pressure impacts lymphatic filling. Thus, at high absorption rates, the absorbate is preferentially removed from the interstitium by the capillaries.

Although alterations in interstitial hydrostatic and oncotic pressures induced by interstitial volume expansion are the primary determinants of capillary removal of absorbed fluid, other vascular alterations can modify the final outcome, i.e., alterations in capillary pressure, capillary surface area, and vascular permeability. Capillary pressure may increase during net fluid absorption because of the well documented hyperemia which occurs in response to certain nutrients (e.g., glucose, lipids) in the lumen.^{13,30} The increase in capillary pressure would tend to oppose interstitial fluid pressure, thereby reducing the net driving force for fluid absorption by the capillaries. Some nutrients (e.g., lipids) can also increase in vascular permeability (decrease in σ_d).³¹ A decrease in the osmotic reflection coefficient would diminish the effective transcapillary oncotic pressure gradient, thereby reducing the net driving force for fluid absorption by the capillaries. Capillary hydraulic conductance ($K_{f,c}$) is also increased during the absorption of certain nutrients²⁸. This can be achieved by either increases in capillary permeability or surface area (capillary recruitment), or both. An increase in $K_{f,c}$ would amplify the effects of changes in interstitial hydrostatic and oncotic pressures and more readily drive fluid into the capillaries during absorption.

Colonic water absorption: a special case

There is a relative dearth of information on how the forces governing transcapillary fluid exchange are altered by water absorption in the colon. Estimates of capillary or interstitial pressure during absorption are not available. Colonic lymph flow is not affected by electrolyte-coupled water absorption over a wide range of absorption rates ($0.2 - 0.9$ ml/min/100 gm), indicating that the capillaries are the major route by which the absorbate is removed from the interstitium⁶. This is not entirely surprising considering that the

capillaries are in very close proximity to the transporting epithelium (1 μm), while the lymphatics are rather sparse and located as far as 400 μm from the surface epithelium. As mentioned above, interstitial hydrostatic and oncotic pressure gradients drive absorbed fluid into the capillaries, while only hydrostatic pressure would promote lymphatic filling. While it would be expected that water absorption should reduce interstitial oncotic pressure in the colonic mucosa, an analysis of colonic lymph protein flux during absorption suggests that the transcapillary oncotic pressure gradient remains unchanged. The proposed existence of a small “juxtacapillary interstitial fluid compartment” in the space (1 μm) between the capillaries and transporting epithelium may explain the discrepancy.²⁰ Since the lymphatic vessels are farther removed from the transporting epithelium in the colon (300–400 μm) than their counterparts in the small intestine (50 μm), juxtacapillary hydrostatic and oncotic pressures may be profoundly altered within this local compartment without detectable changes at the level of the initial lymphatics located in the basal region of the mucosa.

Nutrient coupled fluid absorption

Fluid absorption in the small intestine is linked to the transport of hydrolytic products of food digestion. Both blood flow and lymph flow are increased when nutrients are placed in the lumen of the small intestine, with lipids exerting more dramatic responses than carbohydrates and proteins.^{30,32,33} The available information in the literature allows for an analysis of the changes in interstitial forces as well as transcapillary and lymphatic fluid fluxes that occur during the absorption of glucose/electrolytes or oleic acid in the small bowel.

Glucose/electrolyte-coupled water absorption

Figure 7 presents a steady-state analysis of the alterations in transcapillary forces and flows which occur at a given absorption rate (0.74 ml/min/100 gm) induced by perfusion of the small intestine with a 20 mM glucose solution.¹³ As fluid enters the mucosa, the interstitium expands, resulting in an increase of interstitial hydrostatic pressure (P_i) of 2 mm Hg and a decrease in interstitial oncotic pressure (π_i) of 1.8 mm Hg (compare to Fig.2). The microcirculatory responses to glucose absorption (vasodilation and an increase in perfused capillary density) increase capillary pressure (P_c) by 1.1 mm Hg and double capillary hydraulic conductance ($K_{f,c}$). Glucose/electrolyte-coupled absorption does not alter the osmotic reflection coefficient (σ_d). These responses to glucose absorption serve to convert the net filtration pressure to a net absorptive pressure (NAP) of 2.3 mm Hg. This absorptive force, coupled to the doubling of the capillary surface area, drives 82% of the absorbate (0.61 ml/min/100 gm) into the capillaries. The increase in interstitial fluid volume and pressure results in a 3-fold increase in lymph flow that removes the remaining 18% of the absorbate (0.13 ml/min/100 gm) from the interstitium.

Oleic acid-coupled water absorption

A systematic analysis of the capillary and interstitial forces has also been performed during fluid absorption induced by perfusion of the small intestine with 5 mM micellar oleic acid.³³ For similar rates of fluid absorption (0.62 ml/min/100 gm with oleic acid vs 0.74 ml/min/100 gm with glucose), the adjustments in capillary and interstitial forces induced by 5 mM oleic acid are qualitatively similar to those noted with 20 mM glucose (Table 1). However, there are significant quantitative differences worth noting.

Oleic acid increased interstitial fluid pressure to 7.1 mm Hg; a pressure level greater than that (4.4 mmHg) noted with glucose. This larger increment in interstitial fluid pressure indicates that the interstitial volume increased to a greater extent with oleic acid than with glucose despite the fact that the rate of fluid absorption was greater with glucose. The

significantly greater hyperemic response to oleic acid resulted in a greater increase in capillary pressure (3 mm Hg) than noted with the glucose-induced hyperemia (1 mm Hg). The net result was that the decrease in the transcapillary hydrostatic pressure gradient was greater with oleic acid than with glucose (3.2 vs 1.2 mm Hg).

The transcapillary oncotic pressure gradient detected during oleic acid absorption was similar to that noted with glucose. However, since σ_d was decreased to 0.7 by oleic acid, the *effective* transcapillary oncotic pressure gradient was actually decreased by oleic acid. This reduction in *effective* oncotic pressure diminished the ability of capillaries to absorb water and is likely to be a major cause of the greater increase in interstitial volume observed with oleic acid.

Collectively, oleic acid resulted in a net absorptive pressure of only 1.3 mm Hg, compared to 2.3 mm Hg with glucose absorption. The capillary hydraulic conductance ($K_{f,c}$) increased to greater extent with oleic acid than with glucose (0.33 vs 0.26 ml/min/mm Hg/100 gm), somewhat offsetting the lower net absorptive pressure. Nonetheless, 70% of the absorbate was removed by the capillaries with oleic acid as compared to 82% with glucose.

Lymph flow increased approximately by 3-fold with glucose and 5-fold with oleic acid. The greater increment in lymph flow rate noted with oleic acid is attributed to the higher interstitial fluid pressure incurred with oleic acid than with glucose (7.1 mm Hg vs 4.4 mm Hg). In addition, oleic acid increases the frequency of villus contractions while glucose does not.³⁴ This increase in villus contraction frequency would also facilitate lymph flow (Fig. 8). Thus, during oleic acid-induced fluid absorption, 30% of the absorbate was removed from the interstitium by the lymphatics, while only 18% of the absorbate was removed by the lymphatics during glucose-induced absorption.

Chylomicron transport

The process by which fatty acids are absorbed is dependent on their chain length and water solubility. Most medium and short chain fatty acids are water soluble and readily absorbed by the enterocytes and enter either the capillaries or lymphatics. The absorption of the relatively water insoluble long chain fatty acids is more complex. Long chain fatty acids are incorporated into bile salt micelles to increase their water solubility and enhance their absorption by enterocytes. After entering the cells, the fatty acids are re-esterified into triglycerides, provided with a glycoprotein coat, and enter the interstitium as chylomicrons.

Chylomicrons are large particles (400–3000 Å radius) that cannot cross the capillary endothelium. Instead, chylomicrons must traverse the interstitium to reach the initial lymphatics. Movement of chylomicrons through the interstitium is facilitated by the increased interstitial volume during fluid absorption. The increased hydration of the interstitium disrupts the matrix structure (e.g., release of hyaluronan²³) and decreases macromolecular exclusion in the interstitial gel (see Fig. 4), thereby allowing particles the size of chylomicrons to traverse the interstitium with relative ease. Expansion of the interstitial matrix also exerts tension on the overlapping leaves of the endothelial cells by the anchoring filaments, thereby separating the endothelial cells (see Fig. 1C). The chylomicrons enter the initial lymphatics primarily through these large interendothelial cell gaps. This scenario is supported by reports that the rate of chylomicron transit to the lymphatics is directly related to the extent of interstitial hydration.³⁵

Intestinal fluid secretion

Solute-coupled secretion

Although the small intestine is generally considered an absorptive organ, it can be induced to secrete fluid under certain conditions, some of which are most likely pathologic, e.g., cholera toxin. Although a systematic assessment of the Starling forces governing transcapillary fluid exchange during active secretion has not been undertaken in the small intestine, information about the qualitative alterations in individual components of the Starling relationship is available. The luminal secretion induced by cholera toxin, VIP, or theophylline is devoid of protein, supporting the premise that active fluid secretion occurs across an intact mucosal membrane.¹³ In addition, these secretagogues decrease small intestinal lymph flow, indicative of a decrease in interstitial volume and pressure. Furthermore, villus lacteal pressure decreases during secretion-induced by cholera toxin, supporting the contention that interstitial volume decreases.³⁶ Finally, there is evidence that cholera-toxin increases blood flow (and presumably capillary pressure) and $K_{f,c}$,³⁷ which would favor capillary filtration. Collectively, these isolated observations, in conjunction with mathematical modeling approaches, allow for a reasonable prediction of the changes in Starling forces during active secretion in the small intestine (Fig. 9).

The adjustments in interstitial forces during active secretion are analogous to those noted during dehydration of the interstitium induced by arterial hypotension. At the onset of active secretion, protein-free fluid is drawn from the interstitium across an intact mucosal membrane and into the lumen. Assuming a normal (low) interstitial compliance a small decrement in interstitial volume would decrease P_t to 0.2 mm Hg and increase π_t to 10 mm Hg. These changes in interstitial forces, coupled to a 1.0 mm Hg increment in capillary pressure (due to vasodilation), should increase net capillary filtration pressure from 0.03 to 4.20 mm Hg. The capillary filtration induced by these alterations in interstitial forces would be further enhanced by an increase in $K_{f,c}$ of approximately 30%. Since lymph flow ceases due to the fall in P_t , all of the capillary filtrate is available for the secretory process.

In the colon, induction of active secretion (theophylline) has no effect on lymph flow.⁶ This is not entirely surprising considering the paucity and localization of the lymphatics to the basal portion of the colonic mucosa (Fig.1B). The fluid required for solute-coupled secretion in the colon is derived solely from the capillaries, likely due to local alterations in the forces governing transcapillary fluid exchange within the juxtacapillary compartment immediately adjacent to the secreting epithelium.

Passive “filtration” secretion

Filtration secretion is characterized by the passive movement of interstitial fluid across a disrupted mucosal epithelium (separation and loss of epithelial cells). Because the epithelial lining is compromised, the concentration profile of the proteins appearing in the secreted fluid resembles that of interstitial fluid or lymph. Any combination of alterations in the Starling forces that result in sufficient increases in interstitial volume to raise interstitial hydrostatic pressure above 9 mm Hg (range 6–12 mm Hg) can result in filtration secretion. Examples include excessive elevations in venous pressure (> 25 – 30 mm Hg)²⁰ or plasma dilution (plasma oncotic pressure below 5 mm Hg).³ In addition, excessive levels of agents that: 1) increase capillary pressure and capillary permeability (e.g., histamine³⁸ and glucagon³⁹) and/or 2) directly disrupt the mucosal epithelial integrity (e.g., oleic acid⁴⁰) can induce filtration secretion. From a physiologic and clinical point of view, the case of fatty acid-induced filtration secretion is interesting. For example, oleic acid in the lumen at low concentrations (approximately 5 mM) increases capillary hydrostatic pressure and permeability, yet fluid absorption still occurs (Table 1). Increasing the luminal concentration

of oleic acid progressively reduces fluid absorption and eventually result in a reversal to filtration secretion.⁴¹⁻⁴² A portion of this effect is due to the dose-dependent oleic acid induced cytotoxicity to epithelial cells.⁴⁰⁻⁴³ Interestingly, ricinoleic acid (the active principal of castor oil) exhibits the same effects as oleic acid on intestinal fluid secretion, albeit it is more potent.⁴¹

Transient analyses of the relationship between filtration secretion and lymph flow have been undertaken using acute venous hypertension, plasma dilution, or infusion of PGE₁.⁴⁴⁻⁴⁵ In general, there is an initial rapid and dramatic increase in lymph flow, followed by a decrease and eventual cessation of flow at the onset of filtration secretion. The immediate increase in lymph flow is due to the increase in interstitial hydrostatic pressure associated with the increase in interstitial volume. The decrease in lymph flow is believed to be due to the decompression of the interstitial compartment (and reduction in hydrostatic pressure) as a result of venting of fluid through the disrupted epithelium by filtration secretion.

Unresolved issues

The principal function of intestinal lymphatics is to maintain interstitial volume within relatively normal limits during water absorption and during systemic alterations in capillary filtration (e.g., acute portal hypertension). Although experimental and mathematical modeling approaches have yielded some significant advances in understanding lymphatic function some significant issues of clinical relevance remain unresolved.

With respect to nutrient and water absorption, information is lacking on how specific nutrients impact the role of the lymphatics in removal of absorbed fluid. It is unclear whether the relative contribution of lymph vessels to removal of interstitial fluid during absorption of peptides or amino acids differs from that elicited by glucose absorption. Also, is the relative contribution of the lymphatics to the removal of the absorbate during lipid absorption dependent on fatty acid chain length? These are not trivial issues, since lipids are being targeted as delivery vehicles for drugs with poor bioavailability⁴⁶ and the lymphatics are considered as a potentially desirable delivery system for chemotherapy targeting the lymph nodes.⁴⁷

While enhanced capillary filtration induced by acute venous hypertension can lead to filtration secretion in experimental animals, diarrhea is not a prominent feature in patients with chronic portal hypertension, despite portal pressures as high as 50 mm Hg.⁴⁸ Two compensatory adjustments may explain this apparent discrepancy: 1) increased solute-coupled fluid absorption that offsets the passive secretory flux and/or 2) adaptive changes (e.g., lymphangiogenesis, increased mucosal epithelial resistance) are elicited that diminish or prevent filtration secretion.

Another clinically relevant issue is the time-course of the functional recovery of lymphatics after acute intestinal mucosal injury and inflammation (e.g., ischemia/reperfusion, radiation enteritis). During the repair of an acutely injured mucosa, both angiogenesis and lymphangiogenesis occur to restore mucosal function. Lymphangiogenesis is also a feature of experimental inflammatory bowel disease (chronic inflammation), characterized by enlarged and tortuous lymph vessels.⁴⁹ Do the newly formed lymph vessels perform as efficiently as normally developed lymph vessels?

Several recent developments should provide the driving force for addressing some of the unresolved issues related to lymphatics and intestinal water transport. First, there is a growing clinical interest in the role of intestinal lymphatics in various pathologies. For example, lymphatics are currently being considered as important conduits for the delivery of toxic substances from an injured gut mucosa into the systemic circulation to cause multiple

organ failure.^{32,50,51} One of these toxic substances may be hydrolytic products of lipid digestion (e.g., oleic acid).⁵² There is also increasing interest in the role of lymphatics in tumour metastasis⁵³ and protein-losing enteropathies.⁵⁴ Increasing availability of specific markers for lymphatics and genetically modified animal models for the study of lymphatic function also hold much promise for moving this field of investigation forward. ^{55,56}

Acknowledgments

DNG is supported by grants from the National Institutes of Diabetes and Digestive and Kidney Diseases (P01 DK43785) and the National Heart Lung and Blood Institute (HL26441)

References

1. GRANGER DN, BARROWMAN JA. Microcirculation of the alimentary tract I. Physiology of transcapillary fluid and solute exchange. *Gastroenterology*. 1983; 84:846–868. [PubMed: 6337911]
2. CASLEY-SMITH, J.; GANNON, BJ. Intestinal microcirculation: spatial organization and fine structure. In: Shepherd, A.; Granger, D., editors. *Physiology of the Intestinal Circulation*. Raven Press; New York: 1984. p. 9-31.
3. GRANGER, DN.; KVIETYS, PR.; PERRY, MA.; BARROWMAN, JA. The microcirculation and intestinal transport. In: Johnson, LR., editor. *Physiology of the Gastrointestinal Tract*. 2. New York: Raven Press; 1987. p. 1671-1697.
4. ARAKI K, FURUYA Y, KOBAYASHI M, MATSUURA K, OGATA T, ISOZAKI H. Comparison of mucosal microvasculature between the proximal and distal human colon 1. *J Electron Microsc.* 1996; 45:202–206.
5. KVIETYS, PR.; GRANGER, DN. Physiology, pharmacology and pathology of the colonic circulation. In: Shepherd, AP.; Granger, DN., editors. *Physiology of the Intestinal Circulation*. New York: Raven Press; 1984. p. 131-142.
6. KVIETYS PR, WILBORN WH, GRANGER DN. Effects of net transmucosal volume flux on lymph flow in the canine colon. Structural-functional relationship. *Gastroenterology*. 1981; 81:1080–1090. [PubMed: 7286586]
7. RIPPE B, HARALDSSON B. Transport of macromolecules across microvascular walls: the two-pore theory. *Physiol Rev*. 1994; 74:163–219. [PubMed: 8295933]
8. RENKIN EM. Multiple pathways of capillary permeability. *Circ Res*. 1977; 41:735–743. [PubMed: 923024]
9. CURRY FR. Microvascular solute and water transport. *Microcirculation*. 2005; 12:17–31. [PubMed: 15804971]
10. BENOIT, JN.; ZAWIEJA, DC. Gastrointestinal lymphatics. In: Johnson, LR., editor. *Physiology of the Gastrointestinal Tract*. 3. New York: Raven Press; 1994. p. 1669
11. LEAK LV, BURKE JF. Ultrastructural studies on the lymphatic anchoring filaments. *J Cell Biol*. 1968; 36:129–149.
12. GERLI R, IBBA L, FRUSCHELLI C. A fibrillar elastic apparatus around human lymph capillaries. *Anat Embryol (Berl)*. 1990; 181:281–286. [PubMed: 2337247]
13. GRANGER, DN.; KVIETYS, PR.; KORTHUIS, RJ.; PREMEN, AJ. *Handbook of Physiology, The Gastrointestinal System I*. Vol. Chapter 39. Bethesda MD: American Physiological Society; 1989. Microcirculation of the intestinal mucosa; p. 1405-1474.
14. PELOSI P, ROCCO PR, NEGRINI D, PASSI A. The extracellular matrix of the lung and its role in edema formation. *An Acad Bras Cienc*. 2007; 79:285–297. [PubMed: 17625682]
15. COMPER WD, LAURENT TC. Physiological function of connective tissue polysaccharides. *Physiol Rev*. 1978; 58:255–315. [PubMed: 414242]
16. GRANGER, H. Physicochemical properties of the extracellular matrix. In: Hargens, A., editor. *Tissue fluid pressure and composition*. Williams and Wilkins; Baltimore: 1980. p. 43-61.
17. MORTILLARO NA, TAYLOR AE. Interaction of capillary and tissue forces in the cat small intestine. *Circ Res*. 1976; 39:348–358. [PubMed: 954164]

18. RICHARDSON PD, GRANGER DN, MAILMAN D, KVIETYS PR. Permeability characteristics of colonic capillaries. *Am J Physiol.* 1980; 239:G300–G305. [PubMed: 7425132]
19. TAYLOR AE. Capillary fluid filtration. Starling forces and lymph flow. *Circ Res.* 1981; 49:557–575. [PubMed: 7020975]
20. YABLONSKI ME, LIFSON N. Mechanism of production of intestinal secretion by elevated venous pressure. *J Clin Invest.* 1976; 57:904–915. [PubMed: 947959]
21. LEE JS. Epithelial cell extrusion during fluid transport in canine small intestine. *Am J Physiol.* 1977; 232:E408–E414. [PubMed: 851184]
22. GRANGER DN, MORTILLARO NA, PERRY MA, KVIETYS PR. Autoregulation of intestinal capillary filtration rate. *Am J Physiol.* 1982; 243:G475–G483. [PubMed: 7149030]
23. REED RK, TOWNSLEY MI, PITTS VH, LAURENT TC, TAYLOR AE. Increased lymphatic flux of hyaluronan from cat intestine during fat absorption. *Am J Physiol.* 1992; 263:G6–11. [PubMed: 1636716]
24. REED RK, TOWNSLEY MI, LAURENT TC, TAYLOR AE. Hyaluronan flux from cat intestine: changes with lymph flow. *Am J Physiol.* 1992; 262:H457–H462. [PubMed: 1539704]
25. GRANGER DN, MORTILLARO NA, KVIETYS PR, RUTILI G, PARKER JC, TAYLOR AE. Role of the interstitial matrix during intestinal volume absorption. *Am J Physiol.* 1980; 238:G183–G189. [PubMed: 7369367]
26. BENOIT, JN.; NAVIA, CA.; TAYLOR, AE.; GRANGER, DN. Mathematical model of intestinal transcapillary fluid and protein exchange. In: Shepherd, AP.; Granger, DN., editors. *Physiology of the Intestinal Circulation.* New York: Raven Press; 1984. p. 275–287.
27. LEE JS. Lymph capillary pressure of rat intestinal villi during fluid absorption. *Am J Physiol.* 1979; 237:E301–E307. [PubMed: 474755]
28. GRANGER DN, PERRY MA, KVIETYS PR, TAYLOR AE. Capillary and interstitial forces during fluid absorption in the cat small intestine. *Gastroenterology.* 1984; 86:267–273. [PubMed: 6690353]
29. GRANGER DN, TAYLOR AE. Effects of solute-coupled transport on lymph flow and oncotic pressures in cat ileum. *Am J Physiol.* 1978; 235:E429–E436. [PubMed: 696864]
30. CHOU CC, KVIETYS P, POST J, SIT SP. Constituents of chyme responsible for postprandial intestinal hyperemia. *Am J Physiol.* 1978; 235:H677–H682. [PubMed: 736156]
31. GRANGER DN, PERRY MA, KVIETYS PR, TAYLOR AE. Permeability of intestinal capillaries: effects of fat absorption and gastrointestinal hormones. *Am J Physiol.* 1982; 242:G194–G201. [PubMed: 7065182]
32. FANOUS MY, PHILLIPS AJ, WINDSOR JA. Mesenteric lymph: the bridge to future management of critical illness. *JOP.* 2007; 8:374–399. [PubMed: 17625290]
33. GRANGER DN, KORTHUIS RJ, KVIETYS PR, TSO P. Intestinal microvascular exchange during lipid absorption. *Am J Physiol.* 1988; 255:G690–G695. [PubMed: 3189557]
34. WOMACK WA, BARROWMAN JA, GRAHAM WH, BENOIT JN, KVIETYS PR, GRANGER DN. Quantitative assessment of villous motility. *Am J Physiol.* 1987; 252:G250–G256. [PubMed: 3826351]
35. TSO P, PITTS V, GRANGER DN. Role of lymph flow in intestinal chylomicron transport. *Am J Physiol.* 1985; 249:G21–G28. [PubMed: 4014464]
36. LEE JS, SILVERBERG JW. Effect of cholera toxin on fluid absorption and villus lymph pressure in dog jejunal mucosa. *Gastroenterology.* 1972; 62:993–1000. [PubMed: 5029082]
37. CEDGARD S, HALLBACK DA, JODAL M, LUNDGREN O, REDFORS S. The effects of cholera toxin on intramural blood flow distribution and capillary hydraulic conductivity in the cat small intestine. *Acta Physiol Scand.* 1978; 102:148–158. [PubMed: 626095]
38. LEE JS, SILVERBERG JW. Effect of histamine on intestinal fluid secretion in the dog. *Am J Physiol.* 1976; 231:793–798. [PubMed: 970459]
39. GRANGER DN, KVIETYS PR, WILBORN WH, MORTILLARO NA, TAYLOR AE. Mechanism of glucagon-induced intestinal secretion. *Am J Physiol.* 1980; 239:G30–G38. [PubMed: 7396000]

40. KVIETYS PR, SPECIAN RD, GRISHAM MB, TSO P. Jejunal mucosal injury and restitution: role of hydrolytic products of food digestion. *Am J Physiol.* 1991; 261:G384–G391. [PubMed: 1887887]
41. AMMON HV, THOMAS PJ, PHILLIPS SF. Effects of oleic and ricinoleic acids on net jejunal water and electrolyte movement. Perfusion studies in man. *J Clin Invest.* 1974; 53:374–379. [PubMed: 11344549]
42. KVIETYS PR, WILBORN WH, GRANGER DN. Effect of atropine on bile-oleic acid-induced alterations in dog jejunal hemodynamics, oxygenation, and net transmucosal water movement. *Gastroenterology.* 1981; 80:31–38. [PubMed: 7450408]
43. LAPRE JA, TERMONT DS, GROEN AK, VAN DER MR. Lytic effects of mixed micelles of fatty acids and bile acids. *Am J Physiol.* 1992; 263:G333–G337. [PubMed: 1415545]
44. GRANGER DN, MORTILLARO NA, TAYLOR AE. Interactions of intestinal lymph flow and secretion. *Am J Physiol.* 1977; 232:E13–E18. [PubMed: 835698]
45. GRANGER DN, SHACKLEFORD JS, TAYLOR AE. PGE1-induced intestinal secretion: mechanism of enhanced transmucosal protein efflux. *Am J Physiol.* 1979; 236:E788–E796. [PubMed: 443432]
46. CHAKRABORTY S, SHUKLA D, MISHRA B, SINGH S. Lipid—an emerging platform for oral delivery of drugs with poor bioavailability. *Eur J Pharm Biopharm.* 2009; 73:1–15. [PubMed: 19505572]
47. XIE Y, BAGBY TR, COHEN MS, FORREST ML. Drug delivery to the lymphatic system: importance in future cancer diagnosis and therapies. *Expert Opin Drug Deliv.* 2009; 6:785–792. [PubMed: 19563270]
48. GRANGER DN, BARROWMAN JA. Microcirculation of the alimentary tract. II Pathophysiology of edema. *Gastroenterology.* 1983; 84:1035–1049. [PubMed: 6339310]
49. JURISIC G, DETMAR M. Lymphatic endothelium in health and disease. *Cell Tissue Res.* 2009; 335:97–108. [PubMed: 18648856]
50. LEE MA, YATANI A, SAMBOL JT, DEITCH EA. Role of gut-lymph factors in the induction of burn-induced and trauma-shock-induced acute heart failure. *Int J Clin Exp Med.* 2008; 1:171–180. [PubMed: 19079671]
51. SCHMID-SCHONBEIN GW. Biomechanical aspects of the auto-digestion theory. *Mol Cell Biomech.* 2008; 5:83–95. [PubMed: 18589497]
52. PENN AH, SCHMID-SCHONBEIN GW. The intestine as source of cytotoxic mediators in shock: free fatty acids and degradation of lipid-binding proteins. *Am J Physiol Heart Circ Physiol.* 2008; 294:H1779–H1792. [PubMed: 18263716]
53. SLEEMAN JP, THIELE W. Tumor metastasis and the lymphatic vasculature. *Int J Cancer.* 2009; 125:2747–2756. [PubMed: 19569051]
54. RADHAKRISHNAN K, ROCKSON SG. The clinical spectrum of lymphatic disease. *Ann N Y Acad Sci.* 2008; 1131:155–184. [PubMed: 18519969]
55. SHIN WS, ROCKSON SG. Animal models for the molecular and mechanistic study of lymphatic biology and disease. *Ann N Y Acad Sci.* 2008; 1131:50–74. [PubMed: 18519959]
56. BRUYERE F, NOEL A. Lymphangiogenesis: in vitro and in vivo models. *FASEB J.* 2010; 24:8–21. [PubMed: 19726757]

Figure 1.

A. The capillary and blood circulations of the intestinal villus. (Adapted from Guyton, A.C. & J.E. Hall. 2006. Textbook of Medical Physiology, Chapter 65. pg 813. Elsevier. Philadelphia). **B.** The mucosal-submucosal lymphatic organization of the small and large intestine. Adapted from Kvietys *et al.*6 **C.** Anchoring filaments of the initial lymphatics. Adapted from Leak and Burke.11

Figure 2.

Starling forces and capillary membrane parameters in the small intestine under control (non-transporting) conditions. $J_{v,c}$, rate of transcapillary fluid movement; $K_{f,c}$, capillary filtration coefficient; P_c , capillary hydrostatic pressure; P_t , interstitial hydrostatic pressure; σ_d , osmotic reflection coefficient; π_c , plasma oncotic pressure; π_t , interstitial oncotic pressure; NFP, net capillary filtration pressure. Adapted from Granger *et al.*¹³

Figure 3.

The safety factors against interstitial edema in the cat intestine and dog colon for an increment in capillary pressure of 12.0–13.2 mmHg as well as the safety factors against interstitial dehydration in the small intestine during a decrement in capillary pressure of 6.5 mmHg. Adapted from Granger and Barrowman.¹

Figure 4. Interstitial fluid pressure, hydraulic conductance, and macromolecular exclusion as a function of interstitial volume. Adapted from Granger *et al.* 13

Figure 5. Interstitial hydrostatic (P_t) and oncotic (π_t) pressures as a function of net fluid absorption rate. Adapted from Granger *et al.*¹³

Figure 6. Percent of interstitial volume absorbed by the blood and lymph capillaries as a function of net fluid absorption. Adapted from Granger and Taylor.²⁹

Figure 7.

Effects of net fluid absorption on Starling forces and membrane parameters in the small intestine. $J_{v,c}$, rate of transcapillary fluid movement; $K_{f,c}$, capillary filtration coefficient; P_c , capillary hydrostatic pressure; P_t , interstitial hydrostatic pressure; σ_d , osmotic reflection coefficient; π_c , plasma oncotic pressure; π_t , interstitial oncotic pressure; NAP, net capillary absorptive pressure. Adapted from Granger *et al.*¹³

Figure 8.
Relationship between intestinal lymph flow and villus contraction frequency.

Figure 9.

Effects of active (solute-coupled) fluid secretion on Starling forces and capillary membrane parameters in the small intestine. $J_{v,c}$, rate of transcapillary fluid movement; $K_{f,c}$, capillary filtration coefficient; P_c , capillary hydrostatic pressure; P_t , interstitial hydrostatic pressure; σ_d , osmotic reflection coefficient; π_c , plasma oncotic pressure; π_t , interstitial oncotic pressure; NFP, net capillary filtration pressure. Adapted from Granger *et al.*¹³

Table 1

Comparison of the alterations of in the parameters of the Starling equation during glucose and oleic acid absorption

Parameters	Control	Glucose	Oleic acid
<i>Transmucosal flow</i> ¹	0.0	0.74	0.62
<i>Transcapillary forces</i> ²			
$(P_c - P_t)$	10.5	9.3	7.3
$(\pi_c - \pi_t)$	11.0	12.6	12.3
σ_d ³	0.92	0.92	0.70
$\sigma_d(\pi_c - \pi_t)$	10.2	11.6	8.6
$(P_c - P_t) - \sigma_d(\pi_c - \pi_t)$	+ 0.3	- 2.3	- 1.3
K_{fc} ⁴	0.13	0.26	0.33
<i>Transcapillary flow</i>	+ 0.04	- 0.61	- 0.43
<i>Lymphatic driving force (P_t)</i>	2.4	4.4	7.1
<i>Lymphatic flow</i>	0.04	0.13	0.19

¹ All flows are in ml/min/100 gm.

² All forces are in mm Hg.

³ The osmotic reflection coefficient (σ_d) is unitless.

⁴ The capillary filtration coefficient (K_{fc}) is in ml/min/mm Hg/100 gm. Data from Granger *et al*28:31.