Capillary dynamics and the interstitial fluid—lymphatic system

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Abstract

The capillaries are the 'business end' of the circulatory system, where materials exchange between the plasma and tissues. Water-soluble molecules can diffuse through pores in the capillaries, and a Gibbs—Donnan equilibrium exists between the plasma and interstitium. There are several types of capillaries, which vary in their anatomical integrity and permeability. There is also a bulk flow of fluids between the plasma and interstitium, described by the Starling forces. Originally, these forces were thought to cause fluids to leave the capillaries at the arteriolar end and return at the venular end; the role of the lymphatics was to provide an 'overflow' mechanism due to protein leakage out of the capillaries. More recent work indicates that this concept needs modification. Lymph flow and interstitial colloidal osmotic pressure are now known to be greater than first thought, and the interstitium has a slightly negative hydrostatic pressure. It is now believed that filtration takes place along most of the capillary, and the lymphatic system plays a more important role in maintaining plasma—interstitium equilibrium and preventing oedema. The system acts as a 'closed' one in that the changes in fluid formation (e.g. following haemorrhage or cardiac failure) are self-limiting. However, in some circulations (e.g. those to the kidneys, glands and the gut), net fluid production or absorption is required. This requirement is fulfilled by an independence from the Starling forces, the systems behaving as 'open' ones.

Keywords Gibbs—Donnan equilibrium; interstitial fluid; oedema; Starling forces

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Learning objectives

After reading this article, you should be able to describe how:

- the physical properties of the capillary affect the movement of molecules across this barrier, with particular emphasis on the movement of water
- a balance between plasma and interstitial fluid is maintained (both the original concept of 'Starling forces' and newer views)
- the basic capillary/lymphatic system is changed in haemorrhage, when standing and after trauma, and when continuous production/reabsorption of fluid is required.

Exchange of materials across capillaries by diffusion

The main aim of the circulation, to enable materials to exchange between different parts of the body, is accomplished across the capillaries. The capillaries — a single layer of thin endothelial cells surrounded by a basal lamina — seem to be appropriate for this task. They form the minimal barrier that retains the integrity of the vascular system as a system of conduits, and yet allow the exchange of materials between the plasma and interstitium by diffusion. However, even though diffusion is by far the most important way in which exchange of small molecules takes place, for water-soluble molecules diffusion takes place across only a very limited area of the capillaries (i.e. the pores). By contrast, lipid-soluble molecules (e.g. ethanol and some general anaesthetic agents) can traverse the whole of the capillary.

A comparison of the rate of transfer of substances by diffusion and bulk flow has enabled the pore density and 'equivalent pore radius' to be calculated. This analysis indicates that the properties of muscle capillaries can be accounted for if less than 1% of its total surface area contains circular pores of a given size. Whilst it would be naive to look for these pores under the microscope, this evidence supports the view that it is the junctions *between* the endothelial cells that are the site of the 'pores', across which the diffusion of water-soluble molecules occurs. Large water-soluble molecules (e.g. proteins) traverse such pores with difficulty because of steric hindrance. These molecules tend to traverse capillaries in vacuoles instead by the process of cytopempsis (endocytosis followed by exocytosis). Although proteins cross capillaries slowly (often expressed as proteins 'leaking' out of capillaries), this process has important implications when the balance between plasma and interstitial fluid is considered (see below).

Because the interstitial fluid is protein-poor compared with the plasma, and because protein molecules have a net negative charge, diffusible ions will tend towards an equilibrium given by the Gibbs—Donnan equations. Consider a membrane that is impermeable to negatively charged protein molecules but permeable to all other ions. The compartments on the two sides of the membrane are denoted as compartments 1 and 2 in the following equations, which apply to the concentrations of the ions in the compartments at equilibrium.

- For each compartment: sum of all cations = sum of all anions, whether or not the particles can penetrate the membrane.

- For the *diffusible* monovalent ions: $[\text{cations}]_1 \times [\text{anions}]_1 = [\text{cations}]_2 \times [\text{anions}]_2$.

The concentration of each diffusible cation on the side of the membrane where there are more indiffusible protein anions (the plasma) is greater than the concentration on the side where there is less protein (the interstitium). The opposite holds for the diffusible anions, the concentration being less in the plasma than in the interstitium. However, the concentration difference is small. The concentrations of diffusible cations in plasma are about 1.04 times those in the interstitium, and the concentrations of diffusible anions are about 0.96 times those found in the interstitium.

Not all capillaries have the same structure as the 'continuous' capillaries found in the muscles. In most cerebral capillaries, endothelial cells are joined by tight junctions. This arrangement reduces their permeability to water-soluble molecules and gives rise to the concept of the blood–brain barrier. However, since the brain needs a ready supply of molecules, those such as amino acids and glucose are transported across the capillaries by specific carriers. The process is one of facilitated diffusion and shows Michaelis–Menton kinetics, which postulate a reversible combination of the molecule with a carrier, rather than those of Fick's law of diffusion, for which no carrier is required (simple diffusion). The differences between these kinetics are shown in Figure 1.

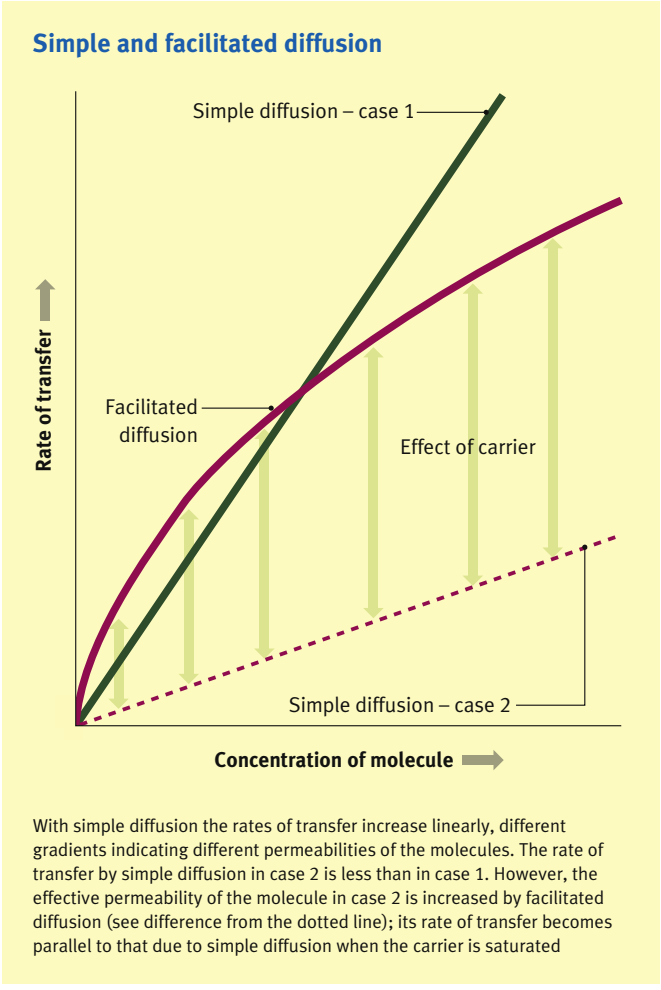


Figure 1

The capillaries of endocrine and exocrine glands, the gut and the kidney are described as 'fenestrated'. The fenestrations (or windows) exist throughout the whole of the capillary surface. They may not be actual holes in the membrane but rather covered by a very thin and, possibly, incomplete 'plug'. Whatever their detailed structure, permeability to water and water-soluble molecules is much higher than that of skeletal muscle capillaries. Such permeability properties are appropriate in tissues where there is a net transfer of fluid into or out of the plasma (net absorption in the case of the gut, or secretion/excretion in the case of glands and the kidney). For capillaries in the liver, spleen and bone marrow, there are actual gaps between loosely connected endothelial cells, and the term 'discontinuous' is used to describe them. Here, there is free passage of cells, chylomicra and proteins between the tissue and the plasma, in addition to the transfer of smaller molecules.

Associated with capillaries are cells called pericytes when referring to capillaries in the circulation in general. Mesangial cells (found between capillaries in the kidney) and astroglia (stellate cells with extensions, called podocytes, forming an envelope around the capillaries) may be closely related to pericytes. The detailed function of these cells is unknown, but they are generally believed to maintain the structural and biochemical 'integrity' of the capillary cells. This structural integrity probably includes the intercellular junctions as well as the carriers involved in facilitated diffusion. In the kidney, the mesangial cells show contractile properties and are probably involved in controlling glomerular filtration.

Exchange of material across capillaries by bulk flow: the role of the lymphatic system

Although the main exchange function of capillaries is achieved by diffusion, fluid and dissolved substances are continuously being exchanged between the vascular space and the interstitium by bulk flow, and continuously returned by the same mechanism to the vascular space via the lymph. The net balance of this movement determines the amount of fluid in the tissue. If there is too little fluid in the tissue, it becomes dehydrated, while excessive fluid collection causes oedema. Knowledge of the forces governing bulk flow, and the ability to define the alteration that has occurred, increases our understanding of a patient's condition and enables the response to treatment to be predicted.

Fluid movement across the capillary wall

Movement of fluid across the walls of the capillaries and post-capillary venules is governed by four forces, known collectively as Starling forces. They can be divided into two groups: hydraulic (or hydrostatic) pressures and osmotic (or oncotic) pressures. The fluid in the capillary is subject to hydrostatic pressure (Pc), which forces fluid across the wall and out of the capillary. This pressure is opposed by hydrostatic pressure in the interstitial fluid outside the capillary (Pi), which attempts to force fluid into the capillary.

The capillary wall acts as a selectively permeable membrane, which produces much greater restriction on the movements of large protein molecules. As a result, the protein in the plasma exerts an oncotic pressure (πc) to draw water into the capillary. This, in turn, is offset by the oncotic pressure of the interstitial fluid itself (πi), which also contains protein. The net force

driving water out of the capillary is the difference between the hydrostatic pressure gradient across the wall (attempting to move fluid out) and the oncotic pressure gradient (attempting to draw fluid in). The rate at which water moves by bulk flow across a given area of capillary wall is dependent not only on the net force (described above) but also on the permeability of the capillary wall to water, which is expressed as the capillary filtration coefficient (Kc). The unit for this constant (volume/unit time/unit area/unit pressure gradient) is cm^3/second/dyne.

The net rate of fluid movement out of the capillary is represented by equation 1.

$$\text{Flow per unit area} = Kc[(Pc - Pi) - (\pi c - \pi i)] \quad (1)$$

where Kc is the capillary filtration coefficient, Pc is the capillary hydrostatic pressure, Pi is the interstitial hydrostatic pressure, πc is the capillary oncotic pressure, and πi is the interstitial oncotic pressure.

By convention, equation 1 has a positive value if fluid is moving out of the capillary, and a negative value if fluid is moving into it. The significance of the permeability of the capillary wall is emphasized by considering the different types of capillaries. Continuous capillaries have low capillary filtration coefficients, while those of the fenestrated and cerebral capillaries are higher and lower, respectively.

Equation 1 allows calculation of the transcapillary movement of fluid at any single point on the capillary wall. Because blood is flowing along the capillary, down its hydrostatic pressure gradient, the hydrostatic pressure will fall from the arteriolar to the venular end of the capillary (Figure 2). In the past it was thought that fluid moved out of the capillary at the arteriolar end and was drawn back in at the venular end, with any excess fluid being returned to the cardiovascular system via the lymph.

Recent developments

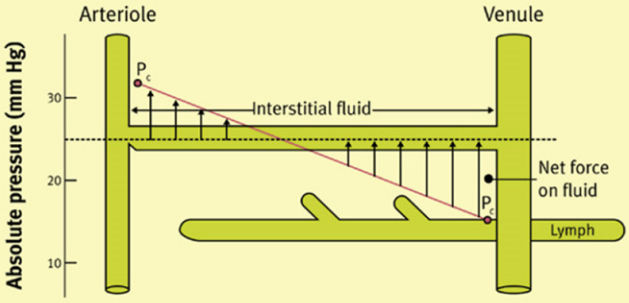
Magnitude of lymph flow – most general textbooks of physiology argue that the Starling forces lead to the production of about 4 litres of lymph per day in a healthy adult. This figure is derived from measurements of lymph flow in the thoracic duct. However, the rate of lymph production and the flow in the pre-nodal afferent vessels (those before the lymph nodes) are likely to be substantially higher (Figure 3), because up to half the water is reabsorbed into capillaries from the lymph in the lymph nodes (again, under the influence of Starling forces). This results in a reduction in lymph volume being delivered to the post-nodal efferent vessels and an increase in lymph protein concentration. As a consequence of this finding and recent advances in techniques for measuring interstitial pressures, the idea of net filtration at the arteriolar end and absorption of fluid at the venular end of capillaries has been reconsidered. Current ideas suggest that, in a large number of capillaries, there is little reabsorption under normal conditions. The balance is therefore shifted in favour of filtration more than was thought previously, accounting for the higher rate of lymph production. These new ideas represent a development of the Starling hypothesis rather than a refutation of it.

Interstitial forces are generally regarded as negligible; however, this is an oversimplification. Not only do they make a significant contribution to the transcapillary movement of fluid,

Filtration–reabsorption pattern along the length of an 'average' capillary

a Traditional view

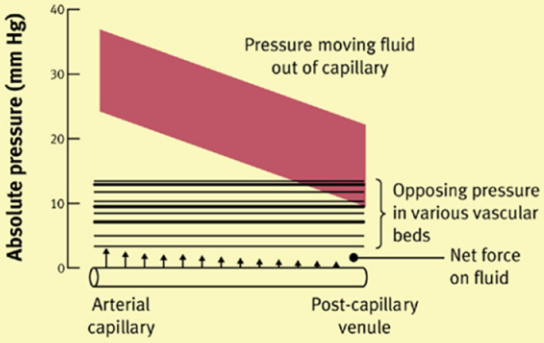
Traditional view with filtration at the arteriolar end and absorption at the venular end. The net effect is a small degree of filtration with return via lymph



Source: Folkow B, Neil E. *Circulation.* London: Oxford University Press, 1977.

b Modern view

Modern view emphasizing the importance of interstitial forces. Predominantly filtration along entire length of the capillary. The net effect is greater filtration than with traditional view, again with return via lymph



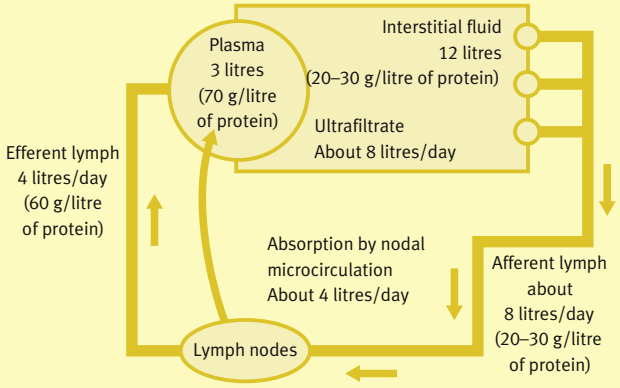
Source: Levick J R. Changing Perspectives on Microvascular Fluid Exchange. In: Jordan D, Marshall J, eds. *Cardiovascular Regulation.* London: Portland Press, 1999.

Figure 2

but they are also variable and thus provide a dynamic modulation of flow. Our appreciation of the importance of the extravascular forces has been increased by the advent of new techniques to measure these pressures accurately.

• **Interstitial oncotic pressure** – plasma proteins are found in peripheral lymph, and enter the lymph by leaking out of the capillaries (pores in most capillary walls are just large enough to enable this to occur) and by being transported across capillaries in vesicles. The size of this 'leak' can be quantified by assessing the ratio of the oncotic pressure exerted by a given concentration of protein to the oncotic pressure that would be exerted if the membrane were completely impermeable to the protein. This ratio is called the reflection coefficient (σ). A membrane completely impermeable to protein (but freely permeable to water) has a reflection coefficient of 1, while a coefficient of 0 indicates that the membrane is equally permeable to protein

Overview of the extravascular circulation of fluid in a 65 kg adult



Source: Levick J R. Changing Perspectives on Microvascular Fluid Exchange. In: Jordan D, Marshall J, eds. *Cardiovascular Regulation*. London: Portland Press, 1999: 127–52.

Figure 3

and water, and there would be no oncotic effect. Most continuous and fenestrated capillaries have reflection coefficients in the range 0.8—0.95, with values of 1 being found in only a few areas of the body (e.g. the capillaries with tight junctions in the brain). Because the reflection coefficient is less than 1, the oncotic pressure exerted by the proteins is proportionately less than it would be otherwise, and the Starling equation needs to be modified to take this into account (equation 2).

$$\text{Flow per unit area} = \text{Kc}[(\text{Pc} - \text{Pi}) - \sigma(\pi\text{c} - \pi\text{i})] \qquad (2)$$

where σ is the reflection coefficient.

In a number of tissues (e.g. muscle, skin), because of this protein leakage into the interstitium, the interstitial oncotic pressure is 30—60% of the plasma oncotic pressure, which is higher than previously reported. The magnitude of the forces favouring the movement of water back into the capillary is therefore less than that previously thought.

- **Interstitial fluid pressure** is defined as the interstitial pressure that is not attributable to the oncotic pressure exerted by the interstitial proteins. It is difficult to measure accurately because the interstitial space consists of a mesh of small molecular chains (glycosaminoglycans) and water, which together constitute a gel. Attempts to measure this pressure directly have involved implanting hollow capsules into tissue and recording the pressure in the fluid that collects inside the capsules; however, the extent to which the results are influenced by inflammatory responses due to implantation of the capsule has been difficult to determine. Nevertheless, recent measurements of the interstitial fluid pressure indicate that it is zero or negative (sub-atmospheric) in many normal tissues, and therefore can contribute to the 'sucking' of water from the capillary into the interstitium. In addition, the glycosaminoglycans have hygroscopic properties and so exert their own osmotic effect. Gravity has little effect on this pressure because of the gel-like composition of the interstitium. Thus, tissue fluid pressure contributes little to driving fluid back into the capillaries in a number of normal tissues (even when the tissue is below heart level with respect to gravity), and in some circumstances may aid movement of fluid out of the capillary.

A shift in balance: current ideas suggest that the forces favouring movements of water into the capillary (equation 2) are smaller than originally thought. Consequently, it is now considered that, at steady state, there is net filtration along almost the entire length of the capillary in many tissues (Figure 2b), rather than filtration at the arteriolar end and absorption at the venular end (Figure 2a). However, it is possible to achieve net absorption transiently in most tissues, and sustained absorption in others (see below).

Interdependence of filtration rate and Starling forces: changes from the steady state

Interstitial oncotic pressure helps to determine the net capillary filtration rate and is, in turn, influenced by it. Therefore, a change in filtration rate would alter the amount of water added to the interstitium, the interstitial protein concentration and thus the interstitial oncotic pressure. Conversely, any alteration in the interstitial oncotic pressure would change the filtration rate (equation 2). This interdependence means that the system behaves like a closed system (see below) and that any changes in the Starling forces tend to be self-limiting. This promotes stability within the tissue and buffers any change in filtration rate that may arise as a consequence of altered intravascular forces. Two situations are described below.

A fall in capillary hydrostatic pressure (Pc) leading to transient fluid absorption (e.g. following haemorrhage) — during mild or moderate haemorrhage, the arterial baroreceptor reflex maintains mean arterial blood pressure. However, this reflex results in an increase in sympathetic vasoconstrictor drive to the arterioles. The consequent increase in arteriolar vascular resistance leads to a fall in the downstream capillary hydrostatic pressure; this can be sufficient to reduce the force moving water out of the capillary (Pc — Pi) to below that favouring an inward movement (πc — πi), which leads to net absorption (equation 2). However, the absorptive state is usually transient, because the removal of water from the interstitium in turn causes the interstitial oncotic pressure to rise, thus opposing capillary absorption and re-establishing filtration (albeit at a reduced rate). This effect is also aided by tissue dehydration causing a reduction in the interstitial hydraulic pressure. Although the absorptive state is transient, some studies have shown that about 500 ml of interstitial water enter the plasma during about 30 minutes.

Finally, it is important to note that some tissues with active arteriolar vasomotion, such as skin and skeletal muscle, are in the non-steady state, alternating between absorption (during arteriolar constriction) and filtration (during arteriolar dilatation) for a significant amount of time. This mechanism may help to remove considerable quantities of fluid from the interstitium.

Increases in capillary hydrostatic pressure (Pc) causing increased filtration — mean capillary hydrostatic pressure can be elevated as a result of reduced arteriolar constriction, or increased venous pressure (e.g. as a consequence of heart failure). This increase in hydrostatic pressure results in an increase in net filtration (equation 2). However, the increased filtration is soon buffered because the resulting addition of water

to the interstitium decreases interstitial oncotic pressure and thus reduces one of the forces favouring movement of water out of the capillary. A new steady state is therefore re-established, albeit at a slightly elevated level of filtration. Interstitial pressure need not rise appreciably if the tissue is distensible.

Sustained absorption and filtration

From the preceding discussion, it seems that sustained absorption of interstitial fluid into the capillaries is impossible. However, this is not the case, as some specialized areas (e.g. renal peritubular capillaries, intestinal mucosa, lymph nodes) exhibit sustained absorption. The key feature in these areas is that the interstitium is supplied with fluid *independent* of capillary filtration, thus breaking the close inter-relationship between tissue oncotic pressure and capillary filtration. Thus, some of the fluid added to the interstitium by the renal convoluted tubules, the enterocytes of the gut or afferent lymph vessels is absorbed into the capillaries. This does not result in a dilution of the plasma proteins because of continuous replacement by 'fresh' blood. Also, any excess fluid or protein (or lipid in the case of gut capillaries) does not accumulate in the interstitium since it is washed away by the lymphatic system. In these ways, the capillary is able to sustain absorption of fluid from the interstitium. Put differently, the continuous absorption of fluid is possible in these cases because the tissue is acting as part of an 'open' system (as opposed to the two situations considered above, where the tissue is acting more as a 'closed' system). In the same way, open systems also allow the continuous production of interstitial fluid that, after changes produced by metabolically active tissues, becomes an exocrine or endocrine secretion. It is noteworthy that, in cases where continuous fluid formation or absorption occurs, fenestrated capillaries are involved; the high capillary filtration coefficients (see above) enable greater movement of fluid by bulk flow.

Blood flow to the cortical nephrons of the kidney is a special case. When the glomerular and peritubular flows are considered together, they tend to act like a closed system (the rate of urine production normally amounting to only a small fraction of the plasma flows involved). However, when considered separately, the glomeruli show continuous fluid formation and the peritubular networks show continuous fluid reabsorption. This is achieved not only by the pressures but also by the oncotic pressures that are present in the system. In the glomeruli, the high blood pressures (due to wide-bore afferent arterioles and narrow-bore efferent arterioles) result in fluid formation (the glomerular filtration rate), and the oncotic pressure of the plasma leaving the glomeruli and going to the peritubular networks is raised by about one-fifth compared with normal plasma. Uptake of reabsorbed tubular fluid into the peritubular capillaries is promoted by the raised oncotic pressure as well as the lower blood pressure in these capillaries (which are placed downstream from the narrow-bore efferent arterioles). The process is continuous because both the peritubular blood and the tubular fluid are being continuously replaced. It is interesting to note that some degree of interdependence between filtration and reabsorption (mediated by oncotic pressure) exists in this system, and is one of the factors contributing to glomerulo-tubular balance. For example, any rise in glomerular filtration will also increase the oncotic pressure of the peritubular capillaries and so increase reabsorption of tubular fluid back into the blood stream.

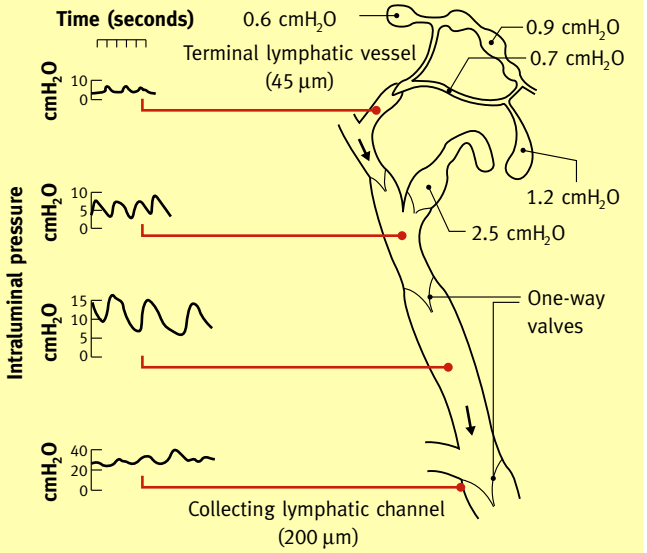
Lymph formation and return to the vascular space

There is a net addition of fluid into the interstitium from the capillaries in most tissues. This fluid, together with plasma proteins that have leaked out of the capillaries, must be removed by the lymphatic system to prevent build-up of interstitial fluid and the development of tissue oedema. In this regard, the lymphatic system can be considered as an overflow system or safety valve.

The lymphatic system consists of the afferent lymphatic vessels, lymph nodes and the efferent lymphatic vessels, with the largest lymphatic vessel being the thoracic duct, which ultimately returns fluid to the blood. The filtrate initially enters the fine lymphatic capillaries, which are similar in appearance to blood capillaries in that they consist of an endothelial cell layer, but they also have large intercellular pores and are thus highly permeable to both water and larger molecules such as protein. The lymphatic capillaries merge with the larger afferent lymphatic trunk, and fluid movement is aided along the vessel by contractions of smooth muscle within the lymphatic vessel (Figure 4). Where the lymph vessels travel through skeletal muscle, activity in surrounding skeletal muscle also aids fluid movement, analogous to the muscle pump moving blood in the veins. These contractions transiently increase pressure within segments of the lymphatic vessels and, because of the presence of one-way valves in the lymph vessels, the fluid can only move away from the lymphatic capillaries (Figure 4) and is returned to the blood circulation mainly via the thoracic duct.

Summary of fluid movements

Fluid formation and reabsorption involve the Starling forces, but the balance that was once believed to exist between formation



Interstitial fluid and proteins enter the low pressure terminal lymphatic vessels and are propelled forward through the one-way valves towards the thoracic ducts by contraction of surrounding smooth and skeletal muscle

Source: Holliday M A. Extracellular fluid and its proteins: dehydration, shock and recovery. *Pediatr Nephrol* 1999; **13:** 989–95.

Figure 4

and reabsorption is now believed to apply less often. Accordingly, the perceived role of the lymphatic system has also changed. Instead of being a system that deals with the effects of protein leakage out of the capillaries, it is now believed to offset the inbalance that generally exists because of an excess of fluid formation over fluid reabsorption. The overall scheme can be widened to include those instances where net fluid formation (e.g. glandular secretions and urine excretion) or fluid absorption (substances absorbed from the gut) are involved (Figure 5).

Clinical sequelae

In addition to acute hypovolaemia (e.g. following haemorrhage) and heart failure, which have already been discussed, the Starling forces are important in a number of clinical situations and in responses associated with daily life. Because clinical reality is often complex, the following descriptions of clinical situations have been simplified.

Orthostasis: the effect of gravity can cause marked changes in some tissue fluids. Venous blood and lymph (being columns of fluid, and not like interstitial fluid, which is bound in a gel) are particularly affected by gravitational forces. Arterial blood is less affected due to the higher pressures involved (so reducing the effect of gravity). Thus, in the upright individual, blood and lymph pool in the veins and lymphatic vessels, respectively. When an individual is standing or sitting, in the absence of rhythmic muscular contractions, this is unopposed and capillary pressure is increased, leading to elevated net capillary filtration (equation 2). The increased capillary filtration is further enhanced by increased leakage of albumin from the capillary, partly because of increased protein movement with the increased movement of fluid through the 'pores' (described above), and partly because of increased permeability to albumin as a consequence of enhanced sympathetic activity. The increased permeability to albumin, in turn, increases filtration because of a reduction in the difference between capillary and interstitial oncotic pressure, and a reduced reflection coefficient. The increased filtration, coupled with an initial reduction in lymph drainage, leads to increased fluid content of the dependent tissues, which continues until tissue expansion and stretching of the skin cause a sufficient increase in interstitial hydrostatic pressure to return filtration to normal levels. Many readers will have been painfully aware of this when putting shoes back on again at the end of a long flight!

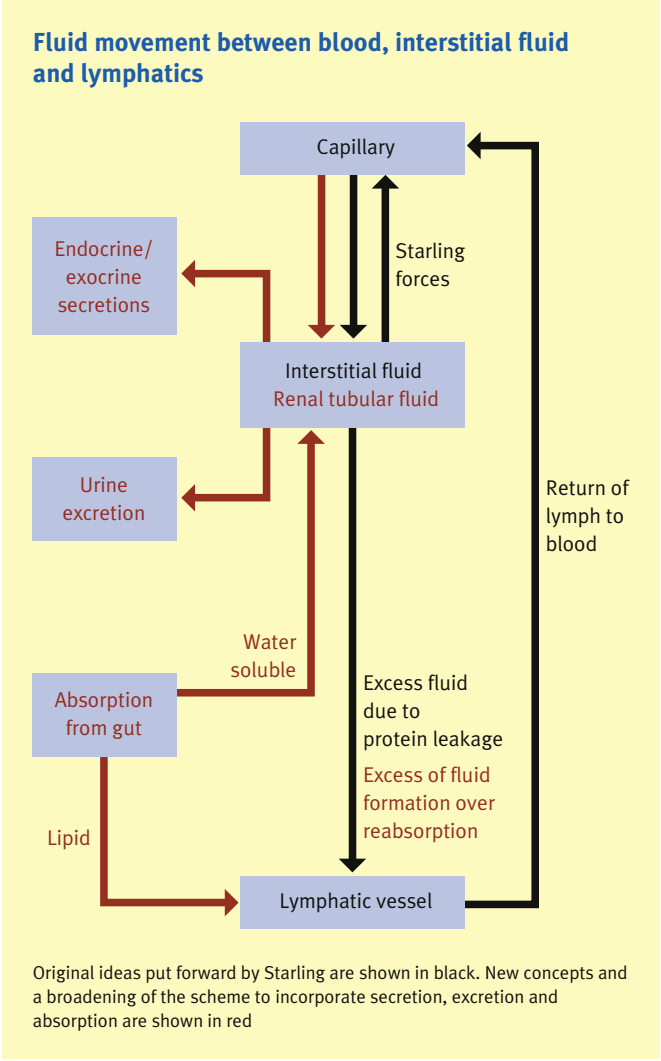


Figure 5

Increased capillary permeability following trauma: there can be periods of tissue hypoxia following trauma, as a result of hypovolaemia, haemodynamic changes initiated by the response to tissue injury, and subsequent nociception. These factors, coupled with subsequent reperfusion during resuscitation, can lead to reperfusion injuries and an inflammatory response. In some circumstances, the inflammatory response can become widespread. Additionally or alternatively, there may be an inflammatory response in the lungs, leading to adult respiratory distress syndrome. One consequence of the inflammatory response is increased vascular permeability to proteins. The increased leakage of protein from the vasculature causes a reduction in the forces opposing filtration of fluid out of the capillary, and thus tissue oedema. Following burn injuries, this is a particular problem at the sites of the burn and, to a lesser extent, elsewhere, because of the presence of circulating vasoactive agents and widespread inflammatory response. This combination leads to oedema, the fluid having a high albumin content.

Fluids used for resuscitation: traditionally, initial resuscitation involved intravenous administration of isotonic crystalloid (or sometimes colloid) solutions (e.g. 0.9% saline or Ringer's lactate). Recent studies advocate the use of hypertonic solutions (e.g. 7.5% saline with 6% dextran) in some circumstances. This newer treatment is thought to confer several advantages. First, it produces an additional increase in intravascular volume by increasing capillary osmotic pressure and thus drawing interstitial fluid into the circulation. Also, smaller volumes of hypertonic solutions are given compared with isotonic solutions, an advantage when the transport of large, heavy packs of fluid is an issue (e.g. in the military setting). Finally, some hypertonic solutions may attenuate the secondary inflammatory response and decrease the resultant development of tissue oedema (this is currently an area of intensive research).

Reduction in plasma protein concentration: there are a number of situations in which plasma protein concentrations are reduced markedly. In nephrotic syndrome, there is a sudden reduction in plasma albumin (and thus plasma oncotic pressure) with profound proteinuria and loss of albumin into the interstitial fluid. In other situations, the liver is unable to synthesize adequate quantities of plasma proteins due to many factors, including severe malnutrition with a carbohydrate-rich, protein-poor diet (kwashiokor). Predictably, the reduced plasma oncotic pressure leads to increased capillary filtration (equation 2) and tissue oedema, as is clearly evident in the 'pot-belly' of starving children. ◆