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

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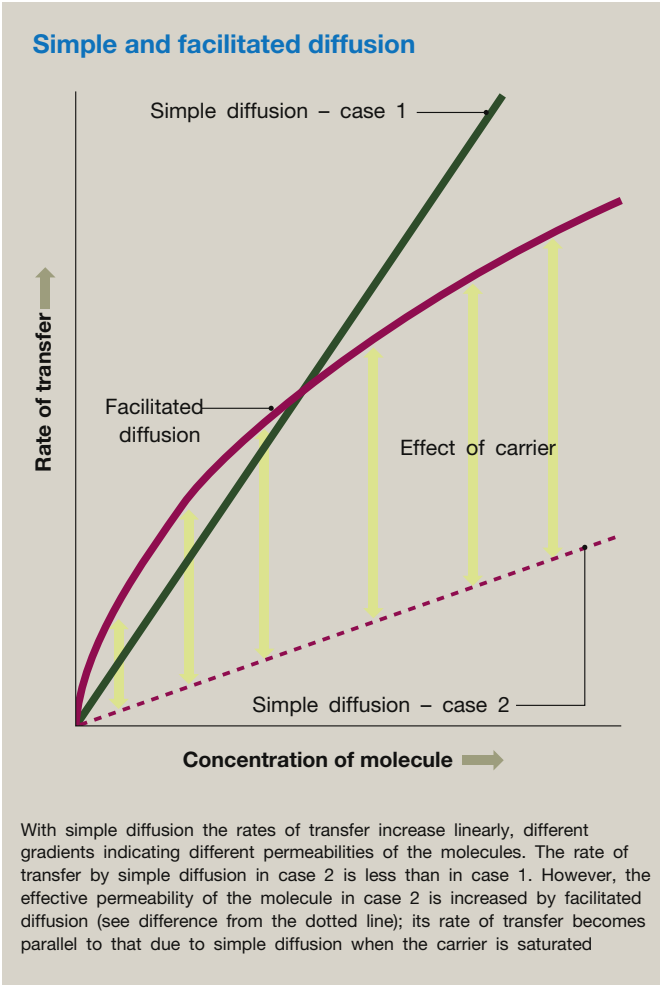
anions, the concentration being less in the plasma than in the interstitium. However, the concentration difference is small. The concentrations of diffusible cations in plasma are about 1.04 times those in the interstitium, and the concentrations of diffusible anions are about 0.96 times those found 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.

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.



With simple diffusion the rates of transfer increase linearly, different gradients indicating different permeabilities of the molecules. The rate of transfer by simple diffusion in case 2 is less than in case 1. However, the effective permeability of the molecule in case 2 is increased by facilitated diffusion (see difference from the dotted line); its rate of transfer becomes parallel to that due to simple diffusion when the carrier is saturated

Figure 1

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 (P_c), 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 (P_i), 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 (π_c) to draw water into the capillary. This, in turn, is offset by the oncotic pressure of the interstitial fluid itself (π_i), 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