Renal blood flow, glomerular filtration and plasma clearance

John C Atherton

Normal functioning of the kidneys to subserve homeostasis and excretion of metabolic waste products depends on: an adequate blood supply; production of an ultrafiltrate of plasma; and the ability to modify the composition of the filtrate through reabsorption from and secretion into the tubule.

About 25% of cardiac output (>1 litre/min) is directed to the kidneys, but the distribution is not uniform. Almost 100% supplies the cortex, through the glomerular capillaries and peritubular capillaries that surround the proximal and distal convoluted tubules (Figure 1). Only about 10% enters the medulla, of which less than 3% reaches the inner medulla. Renal plasma flow is 600–650 ml/min, of which 100–140 ml/min is filtered (glomerular filtration rate (GFR)) across the glomerular capillary wall into Bowman's space. The magnitude and selectivity of the filtration process is possible because of the arrangement of the capillaries within Bowman's space, the structure of the capillary wall, and the visceral epithelial layer (podocytes) of Bowman's capsule with which it is in intimate contact (Figure 2a).

The three main barriers (Figure 2b) to filtration are: the fenestrated capillary endothelium with pores (diameter 70 nm) that acts as a gross filter preventing the passage of blood cells; the basement membrane consisting of a porous matrix of extracellular proteins; and an epithelial layer with podocytes and foot-like processes (pedicels) that surround the glomerular capillaries. Thin membranous sheets containing pores (4 nm by 14 nm) span the gaps (filtration slits, width 25–60 nm) between the pedicels.

The passage of large molecules is limited, but haemoglobin (molecular diameter 6.5 nm) and some small plasma proteins (e.g. albumin; molecular diameter about 7 nm) can pass through the filtration barrier, albeit in small amounts. However, electrostatic charge is as important as the size and shape of the molecule. In general, neutral molecules with a molecular diameter less than 4 nm are freely filtered, but molecules (irrespective of charge) with diameters exceeding 8 nm are not filtered. Between 4 and 8 nm diameter the extent of filtration depends on size and charge. This can be explained by the presence of negatively charged glycoproteins on the filtration barriers (Figure 2b).

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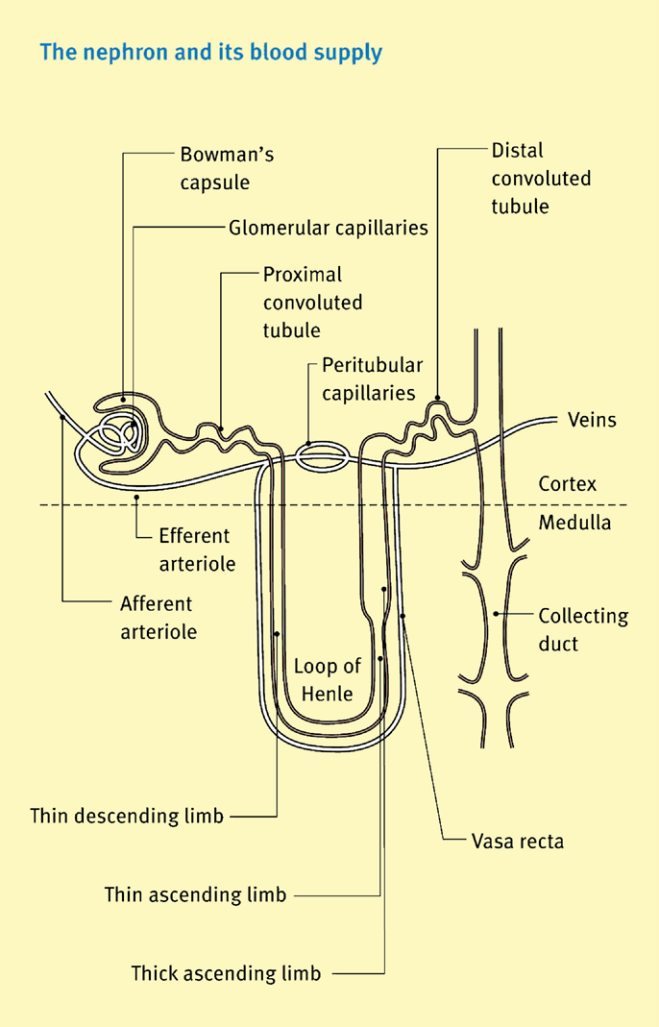

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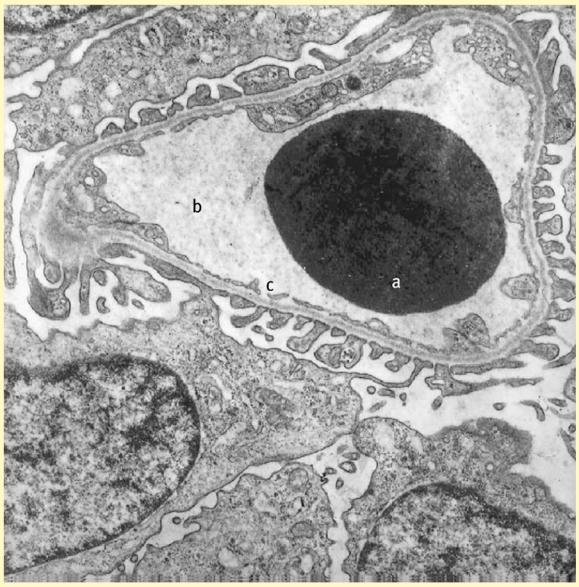
Thus, for molecules of similar size but opposite charge, cationic molecules pass more readily through the barrier; but negatively charged plasma proteins with molecular diameters less than 8 nm do not pass easily.

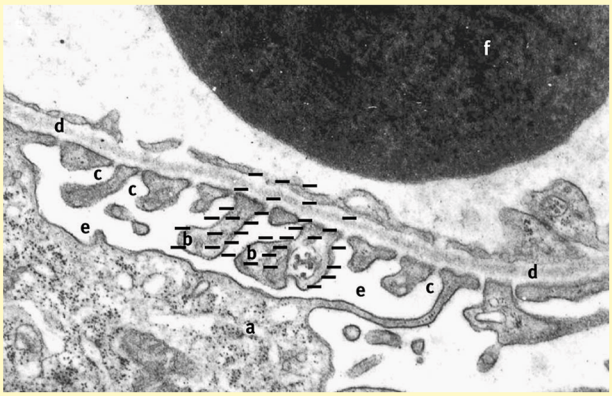
Mesangial cells found between capillaries within the glomerular tuft have at least three important functions in the filtration process. They exhibit contractile properties, thereby influencing the surface area over which ultrafiltration occurs. They have a structural role in the glomerular tuft and can secrete extracellular matrix. They are actively phagocytic, preventing accumulation within the extracellular matrix of macromolecules that have escaped through the basement membrane of the capillaries (i.e. they keep the filter clean). They also secrete prostaglandins and cytokines that may enhance the inflammatory response to invasion of the extracellular matrix by immune complexes (the basement membrane surrounds only part of the glomerular capillaries).

Forces involved in ultrafiltration

Forces involved in the formation of an ultrafiltrate of plasma are the Starling forces operating across the glomerular capillary wall (Figure 3). Forces that promote fluid movement out of the



2a Electron micrograph (x 24,000) through a glomerular capillary and surrounding podocytes.
a red blood cell; **b** capillary lumen; **c** endothelial cells.



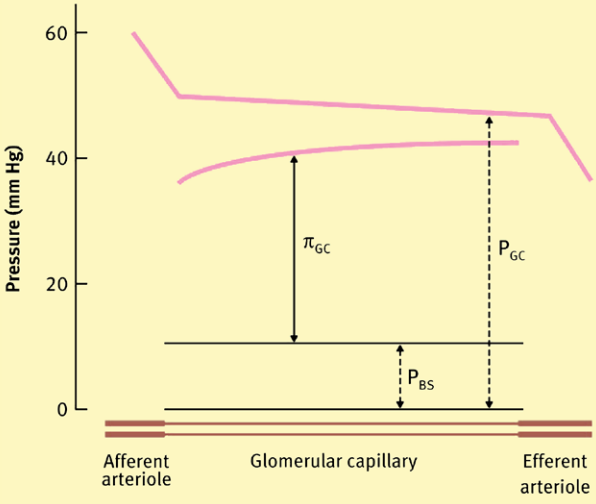
2b Area of fenestrated glomerular capillary wall (x 70,000).
a podocyte;
b pedicels;
c filtration slits;
d basement membrane;
e Bowman's space;
f red blood cell.
Negative charges on the pedicels, basement membrane and endothelial cells are indicated by bars.

glomerular capillary are hydrostatic pressure in the glomerular capillary (P_{GC}) and colloid osmotic pressure in Bowman's space (π_{BS}). The forces that oppose fluid movement from the glomerular capillary are colloid osmotic pressure (π_{GC}) and intrarenal pressure (mainly hydrostatic pressure in Bowman's space (P_{BS})). Thus, net ultrafiltration pressure can be represented as $(P_{GC} - P_{BS}) - (\pi_{GC} - \pi_{BS})$. However, since large protein molecules do not traverse the glomerular capillary wall, π_{BS} can be discounted. Hence, net ultrafiltration pressure and fluid movement out of the capillary (GFR) equal $P_{GC} - (P_{BS} + \pi_{GC})$ and K_f $(P_{GC} - (P_{BS} + \pi_{GC}))$, respectively, where K_f is the ultrafiltration coefficient that takes account of the surface area of the glomerular capillary as well as the permeability per unit of surface area.

At the afferent arteriolar end of the capillary, net ultrafiltration pressure is about 10–15 mm Hg. The ensuing fluid movement without significant protein movement results in a rise in π_{GC}; net ultrafiltration pressure is reduced. Fluid moves out of the capillary until the forces promoting and opposing fluid movement from the capillary are equal. At this point (ultrafiltration pressure equilibrium) fluid movement from the capillary ceases. It is thought that this equilibrium is reached in some species (e.g. rat) but not in others (e.g. humans).

The relationship between these forces operating across a glomerular capillary is different from a systemic capillary. Hydrostatic pressure declines along the length of the systemic capillary and there is no difference between the colloid osmotic pressure at the arterial and venous ends of the capillary. Fluid moves out of the capillary at the arteriolar end into the capillary at the venous end; fluid always moves out of the glomerular capillary. The reason for this difference is primarily because the glomerular capillary is in series with the afferent and efferent arterioles; the balance of vascular resistances is such that only a small decline in hydrostatic pressure occurs along the length of the glomerular capillary.

Starling forces and ultrafiltration along a glomerular capillary



P_{GC} and P_{BS}, hydrostatic pressure in glomerular capillary and Bowman's space, respectively; π_{GC}, colloid osmotic pressure on glomerular capillary plasma

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Factors influencing GFR

Changes in GFR can be mediated by changes in K_f and/or changes in the Starling forces.

Renal plasma flow (RPF) is also an important determinant of GFR. The arrangement of the glomerular capillaries, in series between two sets of arterioles, the resistances of which can be changed independently, means that it is possible to produce changes in GFR that are both in parallel to and divergent from