Renal physiology: blood flow, glomerular filtration and plasma clearance

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Learning objectives

After reading this article, you should be able to:

- state what factors influence GFR
- explain the glomerular filtration barrier
- describe how GFR can be measured or calculated
- define criteria for the ideal filter marker

Abstract

The kidney depends on its blood flow (20–25% cardiac output) and glomerular ultrafiltration (20% renal plasma flow) to perform it's homoeostatic and excretory functions. More than 90% of blood flow serves the cortex. Selectivity of molecular filtration in the glomerulus is related to molecular size, shape and electrostatic charge of molecules, and structure of the glomerular filtration barrier with its negatively charged glycoproteins. Ultrafiltration is determined by the balance between hydrostatic and colloid osmotic pressures (Starling forces) in the glomerular capillary and Bowman's space. It is influenced by changes in renal plasma flow, altered surface area and changes in vascular resistance afforded by afferent and efferent arterioles (mediated by sympathetic nerve activity, vasoconstrictors and vasodilators). Autoregulation of renal plasma flow minimizes changes in volume of ultrafiltration (hence, filtered load) through myogenic and tubuloglomerular feedback mechanisms. Renal clearance measurements have practical application in terms of assessing renal plasma flow and glomerular filtration rate (creatinine, inulin) along with some other measurements but all have their limitations.

Keywords Autoregulation; blood flow; clearance; GFR; glomerulus; ultrafiltration

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Homoeostasis and excretion of metabolic waste products depends on normal kidney function which relies on: (1) adequate renal blood supply; (2) efficient production of plasma ultrafiltrate; and (3) modification of ultrafiltrate composition, through tubular reabsorption and secretion.

More than one litre of blood (blood cells plus plasma) flows through the kidneys every minute (one-quarter of cardiac output). More than 90% supplies the cortex and the rest supplies the medulla. Renal plasma flow is 600–650 ml/min, 20% (100 -140 ml/min) of which is filtered (glomerular filtration rate (GFR)) across the glomerular capillary wall into Bowman's space.

The epithelial Bowman's capsule, containing glomerular capillaries, is the first part of the nephron where the filtration process begins. The ultrafiltrate formed here then travels along the renal tubule for reabsorption and concentration of urine. The volume and composition of the filtrate is permitted due to the arrangement of the glomerular capillaries, the structure of the capillary wall and the visceral epithelial layer (podocytes) of the Bowman's capsule.

The glomerular filtration barrier (GFB)

The GFB consists of three elements that form a physical 'sieve' for filtration:

- The fenestrated *capillary endothelium* with pores (diameter 70 nm) that acts as a gross filter preventing the passage of red blood cells.
- The *basement membrane* composed of a porous matrix of collagen and proteoglycan fibrillae that allows the filtration of water and small solutes but prevents the passage of plasma proteins.
- *Epithelial layer with podocytes* that surrounds the glomerular capillaries. Spanning the gaps between the pedicles are thin membranous sheets containing pores (4 nm by 14 nm) which are the final barrier to molecular passage.

More recent high-resolution examination of the GFB also shows a complex glycocalyx overlying the endothelium and lining the urinary side of the podocyte cell membrane.

Passage of molecules across this barrier is determined first by molecular size and then by charge. Generally, neutral molecules with a molecular diameter less than 4 nm are freely filtered, whereas those with a radius exceeding 8 nm are not, irrespective of the charge they carry. For those molecules between 4 nm and 8 nm in diameter, the extent of filtration is determined by both their size and charge.

The glomerular basement membrane and the epithelial podocytes are covered with negatively charged glycoproteins. This affects the movement of molecules, which are greater than 4 nm and negatively charged. Similar sized but positively charged molecules pass more readily through the barrier, whereas filtration of negatively charged plasma proteins (e.g. albumin) is restricted due to the repulsion exerted by the proteoglycans.

All of this is confirmed when looking at the constituents of the glomerular ultrafiltrate. It contains low- molecular weight substances such as glucose, creatinine, electrolytes, etc., whereas

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larger macromolecules such as albumin and haemoglobin are found only in traces.

Forces involved in ultrafiltration

The formation of an ultrafiltrate of plasma is due to the Starling forces operating across the glomerular capillary wall. These are determined by the balance between the constriction of the afferent and the efferent arterioles. The amount of glomerular filtration can be altered by changes in these forces. It is the difference in resistance between these two points that determines the hydrostatic pressure and hence leads to filtration. Filtration is increased by constriction of the efferent arteriole and relative relaxation of the afferent arteriole. Conversely, if arteriolar resistance is very high or very low at both sites, there will be little net filtration pressures.

The GFR is determined by two major forces: the net filtration pressure (hydrostatic and colloid osmotic forces acting across the glomerular capillary membrane) and also the capillary filtration coefficient (K_f) (the product of the permeability and filtering surface area of the capillaries).

$$GFR = \text{Net filtration pressure} \times K_f$$

Fluid movement out of the glomerular capillary is promoted by hydrostatic pressure in the glomerular capillary (P_G) and colloid osmotic pressure in Bowman's space (π_B). As blood flows through the Bowman's capsule it travels from the wide lumen of the afferent arteriole through the glomerular capillary to the narrower lumen of the efferent arteriole. This creates an acute pressure change, raising the hydrostatic pressure of the glomerular capillaries and driving the filtrate out of the glomerular capillaries and into Bowman's capsule. Generally, the oncotic pressure in Bowman's capsule is discounted when calculating the net filtration rate as large protein molecules do not traverse the glomerular capillary wall.

The actions of these forces are opposed by colloid osmotic pressure of the glomerular capillary (π_G) and intra-renal pressure (mainly hydrostatic pressure in Bowman's capsule (P_B)).

Thus, the net ultrafiltration pressure (normally around 10–15 mmHg at afferent arteriolar end) and fluid movement out of the capillary (GFR – Glomerular Filtration Rate) can be represented as:

$$GFR = K_f \text{ x } (P_G - P_B - \pi_G + \pi_B)$$

Factors influencing GFR

Changes in Starling forces (above) are influenced by a number of different mechanisms, including hormones, the sympathetic nervous system, autoregulation and other feedback controls.

Renal plasma flow (RPF) – the blood flow to the glomerulus is an important determinant of GFR as it is this that provides the resistance necessary to generate the hydrostatic pressure required for ultrafiltration. This flow is determined by the pressure gradient across the renal vasculature, divided by the total renal vascular resistance:

$$\text{Renal plasma flow} = \frac{(\text{Renal artery pressure} - \text{Renal vein pressure})}{\text{Total renal vascular resistance}}$$

Autoregulation – the kidneys self-regulate their blood flow by adjusting vascular resistance according to changes in perfusion pressure (blood pressure) to maintain constancy of GFR and RPF independent of renal perfusion pressure. The equation, renal blood flow = perfusion pressure/renal vascular resistance, clearly illustrates this. Within blood pressure range of 80–180 mmHg, changes in blood pressure are not accompanied by significant changes in renal plasma flow or GFR. This functions to set a basal level of vasomotor tone, which is further refined by the other factors discussed below. Autoregulation also serves as a buffer to the glomerular capillaries and parenchyma, preventing transmission of systemic hypertension and preventing infrarenal barotrauma.

This autoregulatory mechanism comprises two components that lead to a change in preglomerular vascular resistance: the renal myogenic response and tubuloglomerular feedback (TGF). Evidence suggests that the myogenic response protects the glomerular capillaries against rapid elevations in blood pressure, whereas the more delayed TGF is involved in maintaining RBF and GFR in response to sustained blood pressure reductions.

The myogenic feedback mechanism ensures that RPF and GFR are maintained at a relatively constant rate. As blood pressure increases the ensuing stretching of the smooth muscle cells in the walls of the arteriole elicits plasma membrane depolarization, activating voltage-gated L-type Ca^{2+} channels. The rise in cytosolic calcium leads to rapid muscle contraction and vasoconstriction. Conversely, when blood pressure drops, the smooth muscle cells relax to a lower resistance. As a consequence of this rapid signalling pathway, there is little change in renal blood flow despite changes in renal perfusion pressure.

The TGF mechanism involves the juxtaglomerular apparatus and a paracrine signalling mechanism that senses increases in the concentration of sodium chloride (NaCl) in tubular fluid reaching the macula densa cells. These specialized cells, located at the junction of the loop of Henle and the distal tubule, respond to changes in the sodium concentration of tubular fluid. Initiating a cascade of events, which lead to changes in afferent arteriolar resistance. If GFR increases, flow past the macula densa increases, the afferent arteriole constricts and consequently renal plasma flow and GFR decrease. If GFR declines, the converse occurs. This mechanism maintains constancy of the filtered load delivered to the reabsorptive sites in the renal tubules while at the same time preventing transmission of elevations in arterial pressure from being transmitted to the glomerular capillaries and damaging the glomerulus.

Changes in sympathetic nerve activity – Afferent (predominantly) and efferent arteriolar resistance is affected by α-adrenoceptor-mediated vasoconstriction. The altered arteriolar resistance leads to changes in hydrostatic pressure in the glomerular capillaries which consequently changes the rate of filtration. In moderate stimulation a decrease in the RPF is seen without an equivalent change in GFR, suggesting that the principal effect is vasoconstriction of the efferent arteriole. More

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