Introduction to Renal Diagnostics

The kidneys are **paired retroperitoneal organs** that weigh about 150 grams each and are the size of a man's clenched fist. Each kidney is lined by fibrous capsule for protection and it is organized into the **calyces, cortex, and medulla**.

They **receive 25% of cardiac output** through the renal arteries that branch into interlobar arteries and further into arcuate and interlobular arteries that give rise to the afferent arterioles.

The functional unit of the kidney is the nephron with **each kidney having approximately 1.3 million nephrons for various functions** which include:

1. Excretion of metabolic waste products via ultrafiltration
Blood pressure control
2. Water and electrolyte balance
3. Acid-base balance
4. Secretion of hormones such as erythropoietin
5. Metabolism of hormones
6. Excretion of excess hormones

The Renal Corpuscle

The renal corpuscle or Malpighian corpuscle is the main filtration unit of the kidney nephron. It is an ovoid structure that measures 150 µm–250 µm and is made up of two main constituents which include:

**The glomerulus**

It is formed by **invagination of the loops of capillaries into the blind loop of the nephron** that encapsulates it. The glomerular structure is made up of:

- **Smooth muscle cells** that are known as mesangial cells.
- **Endothelial cells** that have spaces known as fenestrae for ultrafiltration. These cells are arranged into an outer lamina rara externa, middle lamina densa and an inner lamina rara interna made up of negatively charged heparan sulfate to attract and allow passage of positively charged ions as it repels away negatively charged particles.

**Double Walled Bowman’s Capsule**

It has an **inner visceral layer of cells** that are in close association with the capillaries. They are lined by foot processes (pedicels) that contain podocytes.

The **outer layer of parietal cells** is made up of squamous epithelium. In between the two layers is the enclosed bowman’s space that forms a conduit for the ultrafiltrated substance.
Glomerular filtrate refers to the fluid that passes into the Bowman's capsule. It is made up of plasma components that are approximately 70 kDa.

Glomerular filtration rate is the quantity of glomerular filtrate that is formed in all nephrons of both kidneys.

The estimation of GFR relies on a substance that is easily filtered through the glomeruli without being absorbed or secreted in the tubules. The calculation is done by estimating the level of the substance in urine and comparing it with the plasma concentration of the substance.

Creatinine clearance

Thus, creatinine clearance can be estimated by:

\[
125 \text{ ml/min} = \frac{\text{Urine concentration (mg/ml)} \times \text{urine flow (ml/min)}}{\text{Arterial plasma levels (mg/ml)}}
\]

The normal estimated creatinine clearance is 125 ml/min.

A new formula of estimated creatinine clearance (eCCr) was published in 2010 that made the equation simpler and easier to use.

- **eCCr in males** = subject's weight in kg / serum creatinine
- **eCCr in females** = subject's weight in kg x 0.84 / serum creatinine

Creatinine

Creatinine is a breakdown product of creatine phosphate in muscle. Creatinine is produced at a constant rate in the body, and is excreted unchanged by the kidneys. Therefore, measuring creatinine in the serum has been long considered to be an easy way to assess kidney's function. Creatinine clearance, which is easier to measure than GFR, can be utilized to estimate GFR.

Inulin clearance was used in the past to estimate GFR in patients suspected to have kidney impairment. Nowadays, creatinine clearance has been widely accepted as a reasonably accurate measure of kidney function and the assessment of inulin clearance is
no longer recommended in patients with kidney dysfunction.

**Glomerular dynamics**

Filtration across the glomerular capillaries is controlled by forces of the sterling equilibrium as follows:

- Hydrostatic arteriole pressure which is approximately +60 mmHg
- Plasma colloid osmotic pressure estimated at -32 mmHg
- Capsular hydrostatic pressure which is -18 mmHg
- Permeability of the capillaries

Thus,

\[
GFR = K_f = ((H_g - H_t) - (O_g - O_t))
\]

Where:

\[K_f\] = glomerular ultrafiltration coefficient that represents permeability and effective filtration.

\[H_g\] = glomerular hydrostatic pressure.

\[H_t\] = tubular hydrostatic pressure.

\[O_g\] = glomerular osmotic pressure.

\[O_t\] = tubular osmotic pressure.

**Estimated GFR**

Clearly, the above-mentioned equation is quite complicated for daily practice. An easier, more practical, formula was recently published and validated that can be used to estimate GFR based on serum creatinine.

\[
eGFR = 186 \times ([\text{serum creatinine in micromol/L}] \times 0.0011312)^{-1.154} \times (\text{age in years})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black})
\]

**Alterations in any of the above parameters**

*Alteration in any of the above parameters can cause a change and imbalance of the equilibrium* to favor either an increase or reduction in the glomerular filtration rate.

**Contraction of cells/vasoconstriction** causes reduced permeability and thus reduces the glomerular filtration rate. This may arise from:

- Release of vasoconstrictors such as angiotensin II, vasopressin, norepinephrine, histamine, endothelins, platelet activating factor.
- Reduced surface area of filtration that also reduces the total area for permeability.

**Reduction of blood pressure in arteries** alters filtration, thus favoring a fall in the glomerular filtration rate. This may be due to:

- Lower hydrostatic pressures.
- Reduction of renal blood flow, such as in hypotension.

**An increase in the oncotic pressure** that reduces glomerular filtration rate may arise from:

- Edema within the renal capsule that obstructs the flow of blood.
Ureteral obstruction that exerts retrograde pressure on the kidney.

**Ultrafiltration**

These changes in glomerular dynamics allow for the kidney to maintain its functions, even in extreme states. The main function of the kidney is ultrafiltration to filter out toxins such as nitrogenous waste products from the blood and re-take back fluids, glucose, and electrolytes.

Blood is filtered out from the capillaries through the various layers of the glomerular filtration barrier beginning with passing through capillary endothelium fenestrae measuring 70–100 nm in size, then through the basement membrane filled with collagen, and finally through the foot processes of podocytes by size and charge to flow into the bowman’s space and later collecting tubules.

The passage of molecules via these narrow pathways is due to:

1. The hydrostatic pressure created by contraction of smooth muscle cells surrounding the capillaries.
2. The glomeruli drain into the efferent arterioles which are high-pressure vessels.
3. A high amount of blood available for ultrafiltration.

Ultrafiltration is a function of pressure and:

**Size**

Molecules up to 70 kDa can pass through the endothelial fenestrae and those molecules measuring 20–30 nm can pass through the foot processes of the podocytes.

**Charge**

The basement membrane contains negatively charged heparan sulfate that serves to repel other negatively charged molecules while attracting positively charged molecules for their passage.

**Glomerular Blood Flow and its Regulation**

Central to the regulation of glomerular filtration rate is blood pressure and blood that must be availed for ultrafiltration; thus, it is essential that the kidneys receive 25% of cardiac output with minimal interruption.

Renal plasma flow (RPF) is the amount of substance excreted per unit time divided by the arteriovenous difference. In the laboratory, this measure is done via assessing the flow of a substance such as P-amminohippuric acid (PAH) since it is not synthesized, metabolized, or stored in the kidney. 90% of PAH is excreted in a single inoculation thus the calculation of RPF can be done by:

\[
\text{Effective renal plasma flow (625 ml/min) = Urine P-amminohippuric acid (mg/ml) x urine flow (ml/min) / Plasma P-amminohippuric acid (mg/ml)}
\]

The term effective renal plasma flow is used to signify that the plasma estimate is from a peripheral venous sample as opposed to the ideal renal venous sample. The extraction ratio of PAH is 0.9 and this can be used to correct the effective renal plasma flow into renal plasma flow.

\[
\text{Renal plasma flow = effective renal plasma flow (ERPF) / Excretion ratio}
\]
Which is

\[ (700 \text{ml/min}) = 630 \text{ml/min}/0.9 \]

The glomerular capillary pressure averages 40% of the systemic arteries and drops progressively from the:

1. Afferent arteriole,
2. Glomerular capillaries,
3. Afferent arterioles, and finally
4. To the venous system.

**The Renin Angiotensin Aldosterone System**

It is a system tasked with the regulation of kidney blood flow and arteriole pressure. It is made up of:

- Renal nerves,
- Juxtaglomerular apparatus/cells,
- Convoluted tubules, and
- The loop of Henle.

The control is achieved via an autoregulation mechanism that relies on:

- Myogenic mechanism guided by the law of Laplace and smooth muscle cell contraction.
- Tubuloglomerular feedback via the juxtaglomerular cells and the macula densa.

**Autoregulation** is an internal adaptive mechanism found in organs such as the heart, kidney, and brain to maintain body homeostasis. The kidney tubules respond to sodium concentration and arteriole pressure in that:

**Angiotensin I**

When sodium concentration in the urinary filtrate is low or when blood pressure falls, the macula cells in the ascending loop release Prostaglandin E2 that activates renal nerves by direct action of norepinephrine on β-adrenergic receptors of the juxtaglomerular cells to release proteolytic enzyme renin which converts angiotensinogen into angiotensin I.

Angiotensinogen is a peptide synthesized in the hepatocytes and later released into circulation where it remains for 5 hours before complete metabolism. It is converted into angiotensin I by cleavage of 10 amino acids.

**Angiotensin II**

Angiotensin converting enzyme (ACE) from the pulmonary vasculature cleaves a further 2 amino acids from the decapeptide angiotensin I to convert it into angiotensin II.
Angiotensin II has the end effects of:

1. **Induced vasoconstriction** via angiotensin II receptors and this, in turn, increases **blood pressure and vascular resistance**.
2. **Sodium and water retention**.
3. **Vasopressin release** that causes fluid retention.
4. **Norepinephrine** release that increases adrenergic activity such as cardiac function by inducing hypertrophy.
5. **Decreased renal protein kinase C**.
6. **Aldosterone** release that causes salt (NaCl) and water retention.

These effects **signal the need to reduce the amount of filtrate** and thus the need to raise the glomerular filtration rate.

The **contrary happens when urinary filtrate sodium levels are increased or fluid level is high** causing a reduced prostaglandin release and minimal activation of the renin angiotensin aldosterone system; thus, reduced glomerular filtration rate and reduced blood flow into the glomerulus.

However, the **renin angiotensin aldosterone system comes with deleterious effects** such as cardiac remodeling via myocardial hypertrophy.

**References**


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