



Advanced Physiology

Lec.4 Renal physiology

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Autoregulation

The renal circulation is subject to **autoregulation** by the following mechanisms:
A myogenic response, with arteriolar smooth muscle contraction in response to increased vessel wall tension;

The renal circulation

The intranephron tubuloglomerular feedback system, which describes the coupling of distal nephron flow with single nephron glomerular filtration rate.

Humoral influences on the renal vasculature

These are mediated by the following substances:

Vasoconstrictors:

1. Angiotensin II
2. Noradrenaline
3. Thromboxane A₂, B₂
4. Leukotrienes D₄, C₄
5. Platelet-activating factor
6. Endothelin-1
7. Vasopressin
8. Vasodilators:
9. Prostaglandins E₁, E₂, I₂
10. Acetylcholine
11. Bradykinin
12. Nitric oxide
13. Atrial natriuretic peptide (ANP)

Processes involved in urine production

1- Glomerular filtration, which involves the passive formation of an ultrafiltrate (water and crystalloids) of the plasma, which is essentially blood cell and protein macromolecule free, at the glomerulus. Around 180 litres of glomerular filtrate is formed daily, of which 99% is reabsorbed by the tubules. The glomerulus functions as a size-selective, shape-selective and electrical charge-selective barrier for macromolecules. It is normally impermeable to molecules of the size of albumin (69 000 daltons) and larger. Cations are more readily filtered than anions for the same molecular radius.

2- Tubular secretion, from the peritubular capillary blood to the tubular lumen, which may be active or passive.

3- Tubular reabsorption from the tubular lumen to the blood, which is either active or passive. About two thirds of the glomerular filtrate is reabsorbed in the proximal tubule. The trans-tubular reabsorption or secretion of ions is facilitated by protein carriers or ion-specific channels.

4- Tubular metabolism.

Glomerular filtration

The process of **glomerular filtration** is determined by:

1- A **balance of Starling forces**, i.e. the hydrostatic and colloid osmotic forces acting across the glomerular capillary membrane. Glomerular capillary hydrostatic pressure, which is the main driving force, depends on the systemic arterial blood pressure, afferent arteriolar resistance and efferent arteriolar resistance.

2- **The capillary filtration coefficient.**

Ultrafiltration from the glomerular capillaries into Bowman's membrane occurs

through three **filtration barriers**:

Fenestrated endothelium of the glomerular capillaries. These are polygonal squamous epithelial cells with large open pores.

Basement membrane of Bowman's capsule. This comprises a lamina densa between two less dense cement layers.

Podocytes, or specialised epithelial cells of Bowman's capsule with numerous foot processes or pedicels that cover the basement membrane. The foot processes are separated by filtration slit diaphragms that contain pores.

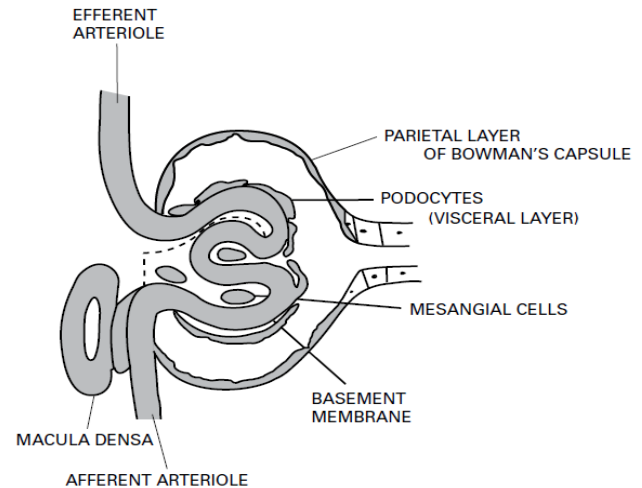


Figure 4.2 Glomerulus and glomerular capillary.

Glomerular filtration rate

The glomerular filtration rate is determined by the number of functioning glomeruli, which is proportional to kidney size and relates to the glomerular capillary surface area, and by the filtration rate at each single glomerulus.

The determinants for the single nephron glomerular filtration rate are:

Mean trans-capillary hydrostatic pressure difference (glomerular capillary hydrostatic pressure minus the pressure in Bowman's space);

Systemic plasma colloid osmotic pressure;

Glomerular plasma flow rate;

Glomerular capillary ultrafiltration coefficient.

The glomerular filtration rate can be represented as the filtration coefficient $\times$ the filtration pressure. The filtration coefficient is a function of the total capillary surface area and of the permeability per unit of surface area.

The range for the glomerular filtration rate is

60–80 ml/min per m^2 or

100–140 ml/min per $1.73m^2$

The rate falls with increasing age by about 1 ml/min per year beyond the age of 40 years.

The glomerular filtration rate can be measured by clearance techniques. The clearance of a marker substance that is not metabolised by the kidneys is a hypothetical measure of the volume of arterial plasma completely cleared of the marker in unit time, usually in one minute. It is a virtual and not a real volume of plasma.

The Cockcroft–Gault formula allows calculation of creatinine clearance from plasma creatinine.

$$\text{Creatinine clearance} = \frac{(140 - \text{age in years}) \times \text{lean body weight in kilograms}}{\text{plasma creatinine} \times 72}$$

In women, the result thus obtained is multiplied by 0.85.

The **filtration fraction** is the ratio of the glomerular filtration rate to the renal plasma flow, and represents the proportion of the renal arterial plasma flow removed by glomerular filtration. The normal value is around 0.2.

U = concentration of marker in urine (mg/ml)

V = flow rate of urine (ml/min)

P = plasma concentration of marker (mg/ml)

The clearance of either inulin or of endogenous creatinine is independent of

$$\text{Clearance} = \frac{(\text{Urine concentration} \times \text{urine volume per minute})}{\text{Plasma concentration}}$$

A marker for measurement of glomerular filtration rate should have the following properties:

Metabolically inert;

Free filtration at the glomerulus, with molecular weight compatible with unimpeded glomerular filtration;

No effect on the glomerular filtration rate;

Not reabsorbed, secreted or metabolised by the renal tubule;

No protein binding;

No extra-renal clearance;

Steady state level in plasma;

Easily measured in serum and urine;

Non-toxic.

Glomerular filtration rate in ml/min can be represented by the formula UV/P where

The clearance of either inulin or of endogenous creatinine is independent of the plasma concentration and of the rate of urine flow. Glomerular filtration rate can also be measured using chelating agents, such as ^{51}Cr -ethylene diamine tetra-acetic acid (EDTA) and ^{99}Tcm -diethylene triamine penta-acetate (DTPA). Endogenous creatinine clearance can be measured following collection of a timed overnight urine collection and an early morning blood sample. A 24 hour clearance measurement eliminates errors due to period variable bladder emptying and wash-out effects. One to two per cent of the total muscle creatine pool is converted daily to creatinine. Creatinine clearance is increased in renal failure, leading to an overestimation of glomerular filtration rate.

The measurement of inulin clearance is achieved by administration of a bolus dose followed by a constant infusion, until the plasma concentration is almost steady, typically after 90–120 minutes. Moderate diuresis is induced by the regular administration of fluid before and during the test. Timed urine specimens are collected, with blood samples being taken at the mid-points of the collection periods for assay. The glomerular filtration rate is taken as the mean for each period.

