Glomerular Filtration Rate and Renal Perfusion
Objective

• Review the basic renal processes
• Review glomerular filtration rate and the factors that regulate it
• Emphasize the importance of fractional excretion, clearance and filtration fraction concepts
Summary of renal function

Help maintain a constant extracellular environment for adequate functioning of cells

– Excretion of some waste products of metabolism eg. Urea, uric acid.

– Excretion of water and electrolytes

– Regulate the excretion individually water and solutes

– Maintain pH, Regulate acid-base balance

– Secrete certain hormones

– Excrete drugs
Figure 1a: Organization of renal vascular system and nephron
Figure 1b: Parts of the Nephron
• Glomerular filtration is the flow of fluid from the glomerular capillaries into the Bowman’s capsule. The volume filtrate formed per unit time is called glomerular filtration rate

• The rate of glomerular filtration averages 135-180L/day in a normal adult.
Figure 3: Filtration barrier
Figure 2: concentration of solutes in tubular fluid in the proximal tubule
Figure 4a: Size and Charge effect on filterability
Figure 4b: Size and Charge effect on filterability
Determinants of GFR

- Fluid movement across the glomerulus is determined by Starling forces, being proportional to the permeability of the membrane and to the balance between the hydraulic and oncotic pressure gradients  [Fig 4: illustration from The Renal System, Churchill Livingstone, 2001]

\[
GFR = K_f \times (\Delta \text{hydraulic pressure} - \Delta \text{oncotic pressure}) \\
= K_f \times (P_{GC} - P_{BS} - (\pi_{GC} - \pi_{BS})) \\
= K_f \times (P_{GC} - P_{BS} - \pi_p)
\]
$K_f$ is the product of the permeability of the capillary wall and the surface area available for filtration.

$P_{GC}$ and $P_{BS}$ are hydrostatic pressures in the glomerular capillary and Bowman’s space, respectively.

$\pi_p$ and $\pi_{BS}$ are oncotic pressures in the plasma entering the glomerulus and the Bowman’s space, respectively.
**Fig 5:**

Forces Involved in Glomerular Filtration

\[ P_t = P_{BS} \]
Filtration equilibrium is the gradient favoring filtration at the afferent arteriole but it falls before the efferent arteriole because of the elevation of plasma oncotic pressure. The hydrostatic pressures in the glomerulus in Bowman’s space remains relatively constant but capillary oncotic pressure progressively rises due to the filtration of protein free fluid.
Filtration Fraction

- Filtration Fraction (FF) is GFR/RPF
- In low effective circulatory volume, FF is increased because RPF is more decreased proportionately than GFR.
- The higher FF increases the plasma oncotic pressure of the peritubular capillaries and promotes tubular reabsorption. Similarly, the hydrostatic pressure decreases in the tubules, but the hydrostatic pressure of the peritubular capillaries decrease even more and allows the tubulointerstitial gradient to be higher and favour further volume reabsorption.
Regulation of GFR

What decreases GFR?

• Decrease in permeability eg. Renal disease, diabetic nephropathy, hypertension
• Increase in Bowman’s space hydrostatic pressure eg urinary obstruction
• Increase in oncotic pressure of capillaries eg. High plasma protein levels
• Decrease in glomerular capillary hydrostatic pressure
  – Decrease in arterial pressure
  – Decrease in Ang II levels
  – Increase in sympathetic activity ie. vasoconstriction
• What determines glomerular capillary hydrostatic pressure?
  – Aortic pressure
  – Resistance at the afferent arteriole
  – Resistance at the efferent arteriole

• By regulating arteriolar resistance, permits the rapid regulation of GFR through changes in glomerular capillary hydrostatic pressure. [Fig 7: illustration from The Renal System, Churchill Livingstone, 2001]
Figure 7

Changes in Resistance of Afferent and Efferent Arterioles

Afferent arteriole

Efferent arteriole

Glomerulus

Glomerular filtrate

GFR ↑

Afferent arteriole dilatation

Efferent arteriole constriction

Afferent arteriole constriction

Efferent arteriole dilatation

△ Normal
△ Efferent Vasoconstriction
△ Afferent Vasoconstriction
○ Overview

GFR ↓
What is Autoregulation?

- GFR and RPF remain almost constant over a wide range of arterial pressures [Fig 6: illustration from The Renal System, Churchill Livingstone, 2001]
- Since the GFR and RPF are maintained in parallel, autoregulation must be mediated through changes in the arteriolar resistance.
- Example, if systemic arterial pressure rises, than an increase in afferent arteriolar resistance prevents the pressure from being sensed by the glomerulus, permitting glomerular capillary hydrostatic pressure and GFR to not increase and remain constant.
- Two mechanisms responsible for autoregulation:
  - Myogenic mechanism
  - Tubuloglomerular feedback
- Vascular smooth muscle contracts in response to increased stretch—stretch receptors in the wall of afferent arterioles
Figure 8: Autoregulation
Tubuloglomerular feedback

• Changes in GFR induced by changes in tubular flow rate [Fig 7a and 7b: illustrations from The Renal System, Churchill Livingstone, 2001]
• Mediated by specific cells in macula densa
• Sense changes in the delivery of chloride
• Alterations in the local release of adenosine
• Induce constriction of afferent arteriole
What is Clearance?

• The clearance of a substance is the volume of plasma from which that substance is cleared by the kidneys per unit time. Each substance in the plasma has its own distinct clearance value but it is always in the form of volume of plasma per time.

• To measure GFR
  – Substance able to achieve constant plasma concentration
  – Freely filtered at the glomerulus
  – Not reabsorbed or secreted

• Filtered substance (eg inulin) = excreted substance
  \[ \text{GFR} \times P_{\text{in}} = U_{\text{in}} \times V \]

• Use creatinine clearance as estimate of GFR
  – Creatinine clearance = \( U_{\text{cr}} \times V/P_{\text{cr}} \)
Fractional excretion

F.E. is defined as the excretion of sodium divided by the filtered load of Na$^+$$\text{.}$

Fractional excretion = mass excreted /mass filtered

\[ \text{FE}_{\text{Na}} = \frac{U_{\text{Na}} \times V}{P_{\text{Na}} \times \text{GFR}} \times 100 \]

Can use creatinine clearance as an estimate for GFR
Renal Plasma Flow

- PAH delivery to kidney = PAH excretion
  \[ \text{ERPF} \times P_{\text{PAH}} = U_{\text{PAH}} \times V \]

Note: PAH only 85-90% is removed by kidney on single pass, thus it will underestimate renal plasma flow (filtered and secreted)
Renal Handling of PAH

Figure 8

Renal plasma flow =

\[ C_{PAH} = \frac{U_{PAH} \times V}{P_{PAH}} \]
What regulates RBF?

• Hormonal effects: renin-angiotensin II, aldosterone, sympathetic nervous system and prostaglandins

• Local (constant) effects of autoregulation and tubuloglomerular feedback
Renin-Angiotensin system

- Angiotensinogen produced in the liver (also present in the proximal tubule) and is cleaved by renin released from renal juxtaglomerular cells to generate angiotensin 1.
- Angiotensin 1 is converted by angiotensin-converting enzyme into angiotensin II.
- ACE is found in vascular endothelial cells
Renin: released when there is an increase in sympathetic activity (eg. Hypotension, volume depletion)

– Initiation of steps towards increasing Ang II levels
Ang II:

1. *Renal sodium and water retention*
   Angiotensin II promotes salt and water retention and thus expands the plasma volume.
   - stimulates sodium reabsorption of the proximal tubule
   - increases secretion of aldosterone from the adrenal cortex, which enhances sodium transfer in the cortical collecting tubule.
2. **Systemic vasoconstriction**

Angiotensin II produces arteriolar vasoconstriction and elevated systemic vascular resistance and in turn increases systemic blood pressure. The vascular action of angiotensin II involves enhanced sensitivity to release of norepinephrine. This results into release of substances that mediate vasoconstriction whereas vasodilator prostaglandins tend to minimize the increase in vascular resistance.
3. Regulation of GFR

Angiotensin II also regulates GFR and renal blood flow. This will be described later. Angiotensin II can affect renal blood flow and GFR by constricting the efferent and afferent glomerular arterioles. Though angiotensin II affects both afferent and efferent arterioles, the efferent arteriole has a smaller diameter and increase in efferent arteriolar resistance will be as much as 3 times greater than the afferent arteriole.
Angiotensin II increase in levels in e.g. Low blood pressure state

- Increase aldosterone secretion
- Increase systemic vascular resistance
- Afferent arteriole vasoconstriction and lower GFR
Intrinsic control
- Myogenic reflex
  - Afferent arteriole smooth muscle tone

Tubuloglomerular feedback
- Filtrate flow sensed by distal tubule
  - Systemic arteriole vasoconstriction
  - Increase aldosterone release
  - Promote Na and water absorption in PT

Extrinsic Control
- Renin-Ang-Aldosterone
  - SNS
  - Systemic arteriole vasoconstriction
- Ang II
  - Afferent arteriole
What is the significance of the juxtaglomerular apparatus?

1. Macula densa, mesangial cells and Renin producing granular cells of the afferent and the efferent arterioles

2. Important player in the tubuloglomerular feedback mechanism
34 year female donates a kidney to her sister. Her serum creatinine before surgery is 88 umol/L and a month after surgery, her serum creatinine is 120 umol/L.

• Why did her serum creatinine go up?
• What has happened to her GFR, urine creatinine and renal plasma flow?
56 yo male is diagnosed with renal disease. His calculated GFR is 40 ml/min (normal 120ml/min).

• What may happen to his fractional excretion of sodium? Usually he takes in 150mEq/day of sodium.

• What will happen to his serum creatinine and urine creatinine?