1. Introduction to Glomerular Filtration

Introduction to Glomerular Filtration

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2. Objectives

Objectives

- Define the glomerular filtrate
- Review the determinants of the glomerular filtration rate (GFR)
- Review how renal plasma flow (RPF) and GFR are affected by auto-regulation
- Understand the mediators of GFR regulation
- Discuss clearance and estimations of GFR

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3. Glomerular Filtrate

**Glomerular Filtrate**

- The glomerulus is a bag of highly specialized capillaries
- Fluid movement from capillary to filtrate is governed by Starling’s forces and intrinsic membrane properties
  - Hydraulic pressure (P)
  - Oncotic pressure (P)
  - Membrane properties ($K_p$
- Unique properties of the glomerular capillary are:
  - Increased hydraulic pressure
  - Increased permeability
  - Location between 2 arteriolar beds (afferent and efferent)

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4. Starling’s Forces

**Starling’s Forces**

- Net ultrafiltration pressure ($P_{UF}$) is the difference between the hydrostatic pressure (P) and the oncotic pressure (P)
- Hydrostatic Pressure
  - $P_{GC}$ - Hydrostatic pressure in the Glomerular Capillary
  - $P_{BS}$ - Hydrostatic pressure in Bowman’s Space
- Oncotic pressure
  - $P_{GC}$ - Oncotic pressure in the Glomerular Capillary
  - $P_{BS}$ - Oncotic pressure in Bowman’s Space

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5. Filtration Pressure

The filtration pressure is:

\[ P_{UF} = \Delta P - \Delta \Pi \]

\[ \Delta P = (P_G - P_B) \]

\[ \Delta \Pi = (\Pi_G - \Pi_B) \]

\[ P_{UF} = (P_G - P_B) - (\Pi_G - \Pi_B) \]

\[ P_{UF} = (P_G + \Pi_B) - (P_B + \Pi_G) \]

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6. Filtration Pressure

- As the glomerular filtrate in virtually protein free, \( \Pi_B = 0 \) and the equation is reduced to:
  \[ P_{UF} \approx P_G - (P_B + \Pi_G) \]

- In an experimental model:
  \[ P_G \approx 49 \text{ mm Hg} \]
  \[ P_B \approx 14 \text{ mm Hg} \]
  \[ \Pi_G \approx 19 \text{ mm Hg} \]
  \[ P_{UF} = 49 - (14 + 19) = 16 \text{ mm Hg} \]

- However, forces are not constant throughout the length of the glomerular capillary:
  - \( \Pi_G \) rises as protein-free filtrate is removed from the capillary
  - The ultrafiltration pressure falls from a high at the afferent end to a low at the efferent end

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7. Euvolemia

![Euvolemia Table]

8. Glomerular Membrane

Filtration is also related to the membrane characteristics ($K_f$)

- $K_f$ is influenced by:
  - The glomerular capillary surface area ($S$)
  - The membrane permeability ($L_p$)

$K_f = S \cdot L_p$
9. Membrane Properties

Membrane Properties

- The glomerular membrane consists of the endothelium, the glomerular basement membrane, and the epithelium
- It is highly permeable to water and small molecules
- Cells and large molecules are reflected
- Negatively charged heparin sulfate incorporated into membrane repel anionic molecules greater than cationic

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10. Filtration Barrier

Filtration Barrier

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11. Endothelium

12. Endothelium
13. Glomerular Epithelium (podocytes)

14. Foot Process and Slit Diaphragm
15. Glomerular Filtration Rate

**Glomerular Filtration Rate**

GFR is the product of the membrane properties and the filtration pressures

\[
\text{SNGFR} = K_f \cdot P_{UF}
\]

\[
\text{SNGFR} = K_f \cdot (\Delta P - \Delta \Pi)
\]

\[
\text{SNGFR} = K_f \cdot (P_{GC} - (P_{BS} + \Pi_{GC}))
\]

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16. Factors that Affect GFR

**Factors that Affect GFR**

\[
\text{SNGFR} = K_f \cdot (P_{GC} - (P_{BS} + \Pi_{GC}))
\]

<table>
<thead>
<tr>
<th>Direct Determinants of GFR</th>
<th>Conditions that Increase GFR</th>
<th>Conditions that Decrease GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>(K_f)</td>
<td>Mesangial cell relaxation increases glomerular capillary surface area</td>
<td>Mesangial cell contraction reduces glomerular capillary surface area</td>
</tr>
<tr>
<td>(P_{GC})</td>
<td>Afferent arteriole dilation Efferent arteriole constriction Systemic hypertension</td>
<td>Afferent arteriole constriction Efferent arteriole dilation</td>
</tr>
<tr>
<td>(P_{BS})</td>
<td>Increased tubular pressure from obstruction of the tubule or extra-renal urinary system</td>
<td></td>
</tr>
<tr>
<td>(\Pi_{GC})</td>
<td>Hypoalbuminemia High renal plasma flow (oncotic pressure rises slower with ultrafiltration)</td>
<td></td>
</tr>
</tbody>
</table>

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Filtration Fraction

- The filtration fraction (FF) is the part of renal plasma flow (RPF) that is filtered/diverted into the tubule:
  \[ \text{FF} = \frac{\text{GFR}}{\text{RPF}} \]
- FF changes with ultrafiltration pressure
- With an increased FF, the oncotic pressure of the efferent arteriole increases, facilitating reabsorption of tubular fluid

Auto-regulation

- The kidney guards filtration carefully
- This is accomplished by the glomerulus being situated between 2 arteriolar beds. Vascular tone in these 2 beds:
  - protects the delicate glomerular architecture at times of high blood pressure
  - preserves GFR at times of low systemic blood pressure

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19. Renal Resistance

20. Auto-regulation

- Despite wide swings in mean arterial pressure, the glomerular perfusion pressure ($P_{GC}$) remains within a narrow range.
  - Efferent arteriolar tone is critical to maintaining $P_{GC}$ at low blood pressures.
  - Afferent arteriolar tone is critical to protecting $P_{GC}$ at high blood pressures.
21. Mediators of GFR Regulation

Mediators of GFR Regulation

- Mediators of GFR will affect one of these elements:
  \[ SNGFR = K_f \cdot (P_{GC} - (P_{BS} + P_{GC})) \]
- Local factors
  - Vascular tone
  - Tubuloglomerular feedback
- Hormonal factors
  - Angiotensin II
  - Prostaglandin
  - Sympathetic activity

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22. Vascular Tone

Vascular Tone

\[ \uparrow P_1 \quad \downarrow P_2 \]

Afferent arteriole \[ \downarrow P_{GC} \]

Efferent arteriole

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23. **Tubuloglomerular Feedback**

The glomerular filtrate is sensed by the macula densa of the distal convoluted tubule:

- Low tubular flow results in proximal Na\(^+\) and Cl\(^-\) reabsorption, stimulating renin release.
- High tubular flow with high distal Cl\(^-\) delivery increases afferent arteriolar tone and reduces GFR.

24. **Angiotensin II**

- Generated in response to renin catalyzing cleavage of angiotensinogen to angiotensin I, and converting enzyme cleavage to angiotensin II.
- Renin is released from the juxtaglomerular apparatus in response to low distal tubule Cl\(^-\) or sympathetic nerve activity.
- Angiotensin II results in:
  - Efferent arteriolar vasoconstriction
  - Increased filtration fraction
  - Increased blood pressure from systemic vasoconstriction
25. Angiotensin Blockade and GFR

![Angiotensin Blockade and GFR](chart.png)

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26. Sympathetic Activity and Prostaglandins

- **Sympathetic Activity**
  - Low blood pressure leads to baroreflex activation of the carotid body and sympathetic discharge
  - Stimulates efferent > afferent arteriolar vasoconstriction, preserving GFR
  - Leads to renin release from the JGA

- **Prostaglandins**
  - Released in response to AII and sympathetic activity
  - Acts to vasodilate the afferent arteriole and maintain renal blood flow despite vasoconstrictors
  - Effect is blocked by NSAIDs

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27. Mediators of GFR

28. Clearance

Clearance

- Clearance of a substance is the volume of plasma from which that substance is completely removed by the kidney per unit of time.

  Renal Artery  Renal Vein
  ![Diagram showing clearance process]

- Clearance equals
29. Measuring Glomerular Filtration Rate

Measuring Glomerular Filtration Rate

- A substance that is freely filtered from the plasma and not secreted or absorbed by the tubule will have a clearance that equals GFR.
  
  \[
  \text{Filtered load} = \text{Urinary excretion of } x \\
  \text{Filtered load} = P_x \cdot \text{GFR} \\
  P_x = \text{plasma concentration of substance } x \\
  \text{Urinary excretion of } x = U_x \cdot V \\
  U_x = \text{urine concentration of substance } x \\
  V = \text{urine flow rate (per unit time)} \\
  P_x \cdot \text{GFR} = U_x \cdot V \\
  \therefore \ GFR = C_x = \frac{U_x \cdot V}{P_x} \\
  C_x = \text{clearance of substance } x
  
- Inulin is such a marker, where \( C_{\text{inulin}} = \text{GFR} \).

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30. Measuring Renal Plasma Flow

Measuring Renal Plasma Flow

- If a substance is not only freely filtered, but also secreted such that all substance reaching the kidney is cleared, then:

\[
C_x = \text{RPF}
\]

- Clearance equals

- Para-aminohippuric acid (PAH) is such a molecule whose clearance equals RPF.

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31. Factor Influencing Clearance

Factor Influencing Clearance

- GFR begins declining in men and women at around age 35
- GFR is lower for women than for men
- GFR is related to lean body mass, gender, age, and diet

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32. Estimating GFR

Estimating GFR

- **Inulin**
  - Freely filtered, without tubular secretion or reabsorption
  - Expensive, requires infusion, and not readily available

- **Creatinine Clearance**
  - Freely filters, but also secreted
  - Secretion is variable
  - Requires a timed urine collection with single plasma Cr value

- **Serum Creatinine**
  - Errors in variable secretion are magnified
  - Inexpensive, simple

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Formulas for Monitoring Kidney Function and Estimating GFR...

- **1/Cr**

- **Cockcroft-Gault**
  \[
  \text{Cr Clearance} = (140 - \text{age}) \times (\text{wt in Kg}) \times (0.85 \text{ if female}) / 72 \times (P_{cr})
  \]

- **MDRD equation**
  \[
  \text{GFR} = 170 \times [P_{cr}]^{-1.154} \times [\text{Age}]^{-0.203} \times [0.742 \text{ if patient is female}] \times [1.212 \text{ if patient is black}]
  \]

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Summary

- The glomerular filtration rate is determined by Starling’s forces and the intrinsic properties of the glomerular membrane according to the equation:
  \[
  \text{GFR} = S \times Lp \times (P_{GC} - (P_{BS} + \Pi_{GC}))
  \]

- Auto-regulation and preservation of the GFR is achieved by adjusting the filtration fraction according to the formula:
  \[
  \text{FF} = \text{GFR} / \text{RPF}
  \]

- Clearance of a substance is the volume of plasma from which that substance is completely removed per unit of time. If a substance is neither secreted or reabsorbed:
  \[
  C_x = \text{GFR} = U_x \times V / P_x
  \]

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