Renal Physiology

David J. Leehey, M.D.
Professor of Medicine

Measurement of Renal Function

• There are 4 types of structures in the kidney
  – Glomeruli
  – Tubules
  – Interstitium
  – Blood vessels

• Renal function usually means glomerular function (glomerular filtration) or tubular function (urinary excretion)

Glomerular filtration

• The glomeruli filter the plasma, allowing passage of solutes according to size and charge.
• Normally, only small amounts of albumin and other larger proteins (globulins) are filtered, and then most of filtered proteins are reabsorbed and catabolized by renal tubules.
• Therefore, large amounts of albumin in the urine suggest glomerular disease.
Glomerular dynamics

- GFR = $K_f \left[ (P_H - P_{\text{fluid}}) - \pi \right]$
- $K_f$ = ultrafiltration coefficient
- In the absence of urinary obstruction, $P_{\text{fluid}}$ is fairly constant. Therefore an increase in $P_H$ or decrease in $\pi$ will increase GFR; on the other hand, a decrease in $P_H$ or increase in $\pi$ will decrease GFR.
Renal plasma flow

• Renal plasma flow can be estimated using para-aminohippuric acid (PAH) clearance since nearly 100% of PAH entering the renal circulation is excreted
• \( \text{RPF} = \frac{C_{\text{PAH}}}{\text{RBF}} \)
• \( \text{RBF} = \frac{\text{RPF}}{1-\text{Hct}} \)

Filtration fraction

• Filtration fraction (FF) = \( \frac{\text{GFR}}{\text{RPF}} \)
• Normally GFR is ~ 125 mL/min and RPF is ~ 625 mL/min; therefore FF ~ 20%
• A decrease in RPF will stimulate the intrarenal renin-angiotensin (RAS) system, resulting in constriction of the efferent arteriole (EE), increasing back pressure on the glomerular capillary and maintaining \( P_{\text{GC}} \), thus preserving GFR. FF is thus increased.
• An increase in RPF will increase \( P_{\text{GC}} \) and thus increase GFR. FF remains unchanged
The renal circulation

Glomerular Hemodynamics

Systemic hypertension would increase glomerular capillary pressure in absence of autoregulation
Renal autoregulation prevents transmission of systemic blood pressure to glomerular capillaries

Intrarenal RAS

Effect of lowering BP (or blood volume) on renal circulation and intrarenal RAS
Inhibition of RAS dilates efferent arterioles and lowers glomerular capillary pressure

Inhibition of RAS normalizes glomerular capillary pressure in the presence of hypertension

Dihydropyridine calcium antagonists abolish renal autoregulation and prevent normalization of glomerular capillary pressure
Measurement of glomerular filtration rate (GFR)

- Inulin clearance:
  - Inulin is a 5000 kD polysaccharide from the Jerusalem artichoke
  - It is freely filtered by the glomeruli and neither reabsorbed nor secreted and thus inulin clearance can be used to measure GFR.
  - Although inulin clearance is the "gold standard", in clinical practice, GFR is generally measured by creatinine clearance.

- Measured creatinine clearance:
  - When a substance is cleared from the blood by glomerular filtration, the excretion rate of the substance (assuming no secretion or reabsorption by the tubules) will equal the volume of plasma that is totally cleared of the substance. Therefore:
    - Plasma concentration $\times$ Clearance = Urine concentration $\times$ Urinary flow rate, or:
    - Clearance = (Urine concentration $\times$ Urinary flow rate) / Plasma concentration $[UV/P]$.

Creatinine clearance

- Creatinine excretion depends on creatinine generation by muscle as a byproduct of creatine metabolism.
- In the steady state creatinine production = creatinine excretion.
- Creatinine is freely filtered and not reabsorbed by the kidney (there is minimal secretion which can generally be ignored).
- Clearance = (Urine concentration $\times$ Urinary flow rate) / Plasma concentration $[UV/P]$.
- For example: If a patient excretes 1.0 L of urine in 24 hours (1440 min), and the plasma and urine creatinine concentrations are 1.0 mg/dL and 144 mg/dL, respectively, the creatinine clearance = (144 mg/dL $\times$ 1000 mL/1440 min) / 1.0 mg/dL = 100 mL/min.
Estimation of creatinine clearance

- Inverse creatinine. Since creatinine clearance (CCr) is inversely proportional to plasma creatinine (Cr), i.e. $CCr \sim 1/Cr$, a rough approximation of renal function can be obtained in this manner. For example, if CCr is 100 mL/min when Cr is 1.0 mg/dL, then CCr would be 50 mL/min when Cr is 2 mg/dL, 25 mL/min when Cr is 4 mg/dL, and 12.5 mL/min when Cr is 8 mg/dL.

Inverse relationship between creatinine clearance and plasma creatinine

![Graph showing inverse relationship between creatinine clearance and plasma creatinine](image)

Estimation of creatinine clearance (2)

- Cockroft-Gault equation
  
  $\text{Creatinine clearance (mL/min)} = \left[ (140 - \text{age}) \times \text{body wt (kg)} / 72 \times \text{plasma Cr} \right] \times 0.85 \ (\text{if female})$

- Still used to estimate GFR in special populations (e.g., spinal cord injured patients). In addition, the FDA still uses this equation when evaluating drug dosing.
Estimation of glomerular filtration rate (eGFR)

- Creatinine-based formulae: [Note: all of these formulae require a steady-state (stable) level of plasma creatinine and cannot be used in patients whose renal function is rapidly changing]

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**eGFR formulae**

- MDRD formulae:
  - The most commonly used 4-variable formula utilize serum creatinine, age, gender, and race.
    MDRD formula: $\text{eGFR (mL/min/1.73m^2)} = 186 \times \text{SCr}^{-1.154} \times \text{Age}^{-0.203} \times \begin{cases} 0.742 \text{ if female} \end{cases} \times \begin{cases} 1.21 \text{ if black} \end{cases}$

- CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation:
  
  **CKD-EPI formula**: $\text{eGFR (mL/min/1.73m^2)} = 141 \times \min(\text{SCr/k,1})^{1.209} \times \max(\text{SCr/k,1})^{0.993} \times \begin{cases} 1.018 \text{ if female} \end{cases} \times \begin{cases} 1.159 \text{ if black} \end{cases}$

  **NOTE:** You do not need to memorize these formulas! (this is why we have computers)

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**Chronic Kidney Disease (CKD)**

- In CKD, GFR will generally decline linearly with time at a rate dependent on the type and severity of kidney disease, the typical linear decline in GFR will be evident when GFR is plotted vs. time (see following Figure)
Tubular Function

• With CKD, loss of nephrons leads to loss of tubular as well as glomerular function
• However, it is possible to have isolated defects in tubular function in the face of normal or near-normal GFR

Fractional excretion

• Fractional excretion of a substance is the amount of that substance that is excreted into the urine relative to the amount of that substance that is filtered by the kidney. It thus depends on both glomerular and tubular function.
• Fractional excretion = Amount excreted / Amount filtered

• Note: Since fractional excretion is generally expressed as a percent and not a fraction, it can be defined simply as the percent of the filtered substance that is excreted into the urine.
Fractional excretion of sodium (FENa)

\[
FENa = \frac{(UNa \times V)}{(PNa \times GFR)}
\]

Substituting creatinine clearance (UCr x V/PCr) for GFR results in:

\[
FENa = \frac{(UNa \times V)}{(PNa \times (UCr \times V/PCr))}
\]

\[
FENa = \frac{(UNa/PNa) \times (PCr/UCr) \times 100}{(\%)}
\]

What is the FENa in healthy people?

- Most healthy people on standard American diets have a FENa of \(\approx 1\%\). Let us see why.
- A typical American diet contains about 6 grams of sodium daily. Since 1 mmol of sodium = 23 mg, this is 261 mmol.

- In the steady state, what is ingested must be excreted (mostly in the urine, with small amounts in stool and sweat).
- **How much sodium is excreted?** Let us assume that 250 mmol/day of sodium appears in the urine.
- **How much sodium is filtered?** Plasma sodium x GFR, i.e., 140 mmol/L x 180 L/day = 25200 mmol/day.
- **Fractional excretion of sodium (FENa) = (250 mmol/25200 mmol) x 100 = 1\%**
Patient 1

- A 50-year-old man with moderately severe CKD (estimated GFR by creatinine-based formula of 25 mL/min/1.73m²) is seen in clinic. His physical examination is normal and he has no peripheral edema.

Question

- What is the expected FENa?
  A. Still 1%
  B. Less than 1%
  C. Greater than 1%

- How much sodium is excreted?
  Still 250 mmol/day (unless the patient has restricted dietary sodium intake)

- How much sodium is filtered?
  In this instance, if the GFR is 25% of normal, i.e. 45 L/day rather than 180 L/day, the amount of sodium filtered will be 45 L/day × 140 mmol/L = 6300 mmol/day.

- Fractional excretion of sodium = (250 mmol/63000 mmol) × 100 = 4%
Important Points

• FENa should increase as GFR decreases.
• A “normal” FENa in someone with severe CKD means that either the patient is not ingesting sodium or there is a stimulus (such as decreased renal blood flow) for the kidney to reabsorb sodium.

Acute Renal Failure

• CKD -- generally a linear decline in GFR with time.
• Acute renal failure -- linear increase in plasma creatinine concentration (“delta creatinine”). Do NOT use eGFR to assess renal function.
• Slowing of “delta creatinine” indicates renal function is improving.
• Continued improvement in kidney function will lead to fall in plasma creatinine concentration (a negative “delta creatinine”).

The arrow indicates an acute renal insult (such as ischemia or acute toxic exposure). Triangles depict serum creatinine concentration which continues to rise until creatinine excretion again equals creatinine generation and then falls as excretion exceeds generation.
A decrease in renal plasma flow (RPF) stimulates the intrarenal renin-angiotensin system (RAS), leading to constriction of the efferent arteriole. This serves to maintain hydrostatic pressure in glomerular capillaries ($P_{Gc}$) and GFR, increasing filtration fraction (GFR/RPF). A resulting decrease in $P_{Gc}$ and increase in $n_a$ leads to increased reabsorption of solute and water by the tubules.

Causes of Acute Renal Failure

- Acute renal failure (ARF) is now referred to by the acronym “AKI” which can mean “acute kidney injury” or “acute kidney impairment”
- Differential diagnosis of AKI
  - Pre-renal (decreased renal blood flow)
  - Renal (kidney injury)
    - Tubular (most common)
    - Glomerular (acute glomerulonephritis)
    - Interstitial (acute interstitial nephritis)
    - Vascular (acute vasculopathy/vasculitis) (least common)
  - Post-renal (urinary obstruction)

Urinary indices

- FENa
- FExe (fractional excretion of urea)
- Urine specific gravity and osmolality
- Urinalysis
Differential Diagnosis of AKI

<table>
<thead>
<tr>
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<th>Pre-renal</th>
<th>Renal</th>
<th>Post-renal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine sodium</td>
<td>&lt; 20 mmol/L</td>
<td>&gt;20 mmol/L</td>
<td>variable</td>
</tr>
<tr>
<td>Fractional excretion of sodium (FENa)</td>
<td>&lt;1%</td>
<td>&gt;1%</td>
<td>variable</td>
</tr>
<tr>
<td>Fractional excretion of urea (FEurea)</td>
<td>&lt;35%</td>
<td>&gt;35%</td>
<td>variable</td>
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<tr>
<td>Urine specific gravity</td>
<td>&gt;1.015</td>
<td>~1.010</td>
<td>variable</td>
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<tr>
<td>Urine osmolality</td>
<td>&gt;350 mmol/kg</td>
<td>&lt;350 mmol/kg</td>
<td>variable</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Hyaline casts</td>
<td>Granular casts; may have hematuria, proteinuria, and/or pyuria depending on etiology</td>
<td>Hyaline casts; may have hematuria, pyuria</td>
</tr>
</tbody>
</table>

Patient 1

- A 22-year-old medical student is taking renal physiology, and as part of the course, he submits a plasma sample and a 24-hour urine for determination of creatinine clearance. His plasma creatinine is 1.0 mg/dL and his 24-hour urine contains 1440 mg of creatinine in a volume of 1.0 L.

  - What is his creatinine clearance?

    - His creatinine clearance (CCr) can be determined by the formula:

      \[
      \text{Clearance} = \frac{(\text{Urine concentration} \times \text{Urinary flow rate})}{\text{Plasma concentration} \times [\text{UV/P}]}
      \]

    - \[
    \text{CCr} = \frac{(1440 \text{ mg/L} \times 1 \text{ L} / 1440 \text{ min})}{1 \text{ mg/dL} \times 1 \text{ mg/min} / 0.01 \text{ mg/mL} = 100 \text{ mL/min}}
    \]

- Ten years later, he is a nephrology attending, and decides to recheck his plasma creatinine. He is dismayed to find that it is now 2.0 mg/dL. He repeats the test several times over the next several days and gets the same result each time (indicating he has CKD). What is his 24-hour urine creatinine now?

  - (A) 1440 mg
  - (B) 720 mg
  - (C) Cannot be determined
What is his creatinine clearance now?
(A) 100 mL/min
(B) 50 mL/min
(C) Cannot be determined

Patient 2

A 65-year-old nephrologist undergoes coronary artery bypass surgery (CABG) after which he develops AKI. His plasma creatinine was 1.0 mg/dL pre-operatively. On the first post-operative day his plasma creatinine is 2.0 mg/dL. On the second post-operative day it is 2.8 mg/dL, and on the third post-operative day it is 3.2 mg/dL. He is non-oliguric and not fluid overloaded and has no electrolyte abnormalities.

Is his renal function worsening or improving on post-operative day 3?
(A) Worsening
(B) Improving
• Do you predict that he will need dialysis?
  (A) Yes
  (B) No

Tubular Physiology

• Proximal convoluted tubule (PCT) -- bulk solute and water reabsorption
• Loop of Henle -- reabsors electrolytes (primarily sodium, potassium, and chloride).
• Distal convoluted tubule (DCT) and collecting duct (CD) -- fine tune sodium excretion and regulate potassium and acid-base balance.
• In the absence of antidiuretic hormone (ADH), the thick ascending limb (TAL) of the loop of Henle, the DCT, and the CD are impermeable to water, which allows formation of dilute urine.
• ADH increases water permeability in the CD, allowing urine concentration.
Tubular physiology: PCT

Tubular physiology: TAL

Tubular physiology: DCT
Tubular physiology: CCT

Tubular Pathophysiology

- PCT dysfunction leads to a characteristic disorder called Fanconi syndrome.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Glucosuria</th>
<th>Phosphaturia</th>
<th>Hypokalemia</th>
<th>Hypophosphatemia</th>
<th>Hypocalciuria</th>
<th>Hypouricemia</th>
<th>Aminoaciduria</th>
<th>Tubular proteinuria</th>
</tr>
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</table>

- TAL dysfunction leads to Bartter’s syndrome, characterized by salt wasting, hypokalemia, and metabolic alkalosis. Hypomagnesemia is mild and hypercalciuria is present. Loop diuretics such as furosemide (Lasix) can cause identical metabolic disturbances.

- DCT dysfunction results in Gitelman’s syndrome, characterized primarily by hypokalemia, hypomagnesemia, and hypocalciuria. Thiazide-type diuretics cause similar disturbances, although for reasons not well understood, hypomagnesemia is much more severe in Gitelman’s syndrome than in patients taking thiazides.

RAAS
Other endocrine functions of the kidney

Site of action of hormones acting on kidney

Patient 3

- A 70-year-old woman is admitted to the intensive care unit (ICU) with abdominal pain and sepsis. Examination reveals hypotension (BP 90/50 mmHg), obtundation, and cool extremities. The serum creatinine is 3.0 mg/dL which one month previously was 1.0 mg/dL. The urinalysis reveals a specific gravity of 1.010 and is negative for blood and protein. On microscopic exam, there are many granular but no cellular casts. The FENa is 4% and the FEurea is 50%.
• What is the most likely diagnosis?
  (A) Acute glomerulonephritis
  (B) Acute tubular injury
  (C) Decreased renal blood flow (pre-renal failure)
  (D) Acute interstitial nephritis