Renal Perfusion and Filtration

Alan Stephenson
BBSG 503 – Systems Biology
Daily Intake and Output of Water

• Intake:
  – Fluids ingested 2100 mls
  – Metabolism 200 mls
    • Total 2300 mls

• Output
  – Skin (insensible) 350 mls
  – Lungs (insensible) 350 mls
  – Sweat 100 mls
  – Feces 100 mls
  – Urine 1400 mls
    • Total 2300 mls

The most important mechanism by which the body maintains a balance between water intake and output as well as the electrolyte composition is by controlling the rates at which the kidneys excrete them.
Multiple Functions of the Kidneys

- Excretion of metabolic wastes and foreign chemicals
- Regulation of water and electrolyte balance and body fluid osmolarity
- Regulation of acid base balance
- Regulation of arterial pressure
- Secretion, metabolism and excretion of hormones
Excretion of metabolic wastes and foreign chemicals

- Urea – metabolism of amino acids
- Creatinine – muscle creatine
- Uric acid – nucleic acids
- Bilirubin – hemoglobin breakdown
- Hormone metabolites
- Toxins including pesticides, drugs and food additives
Regulation of body fluid osmolarity and electrolyte concentration

• For maintenance of homeostasis, excretion of water and electrolytes must match intake

In general, we consciously control what we eat and drink and our kidneys compensate. An abrupt increase in sodium intake will be followed by a delayed increase in sodium excretion which is triggered by the accumulation in ECFV. This change alters hormonal levels which induce an increase in sodium excretion to return levels to normal.
Regulation of acid base balance

• Kidneys contribute to acid base balance along with the lungs
  – Kidneys are the only mechanism by which products of protein metabolism can be eliminated
    • Sulfuric acid
    • Phosphoric acid
    • Organic acids
Regulation of arterial pressure

- In the long term they contribute by excreting salt and water.
- In the short term, the kidneys contribute by secreting vasoactive factors such as renin which leads to angiotensin II, a vasoactive agent.
Secretion, metabolism and excretion of hormones

- Kidneys secrete erythropoietin which stimulates the production of RBCs
  - Stimulus is hypoxia
  - Kidneys produce virtually all of it
- Kidneys secrete renin, an enzyme important in blood pressure regulation
Anatomy of the Kidneys

Each kidney weighs ~ 150 g and is about the size of your fist.
Renal Blood Q = ~ 22% of C.O. or 1100 ml/min

RA branches to form the arcuate arteries and afferent arterioles which feed into the glomerular capillaries where large amounts of fluid and solutes (no protein) are filtered to begin urine formation.

The end of the glomerular capillaries feed into the efferent arteriole which leads to a secondary capillary network, the peritubular capillaries that surround the renal tubules.

The peritubular capillaries drain into the veins of the venous system which run parallel to the arteriolar vessels.
Renal circulation has two capillary networks in series
- The glomerular and
- The peritubular capillaries
These are separated by the efferent arteriole which helps to regulate the hydrostatic pressure in both sets of capillaries.

High P in glomerular capillaries (~60 mmHg) causes rapid fluid filtration

Lower P in peritubular capillaries (~13 mmHg) permits fluid reabsorption

By changing the resistance of the afferent and efferent arterioles, the kidney is able to adjust the rate of fluid filtration and tubular reabsorption in response to homeostatic need.
Functional Unit of the Kidney
The nephron

Each kidney has ~ 1 million nephrons each capable of forming urine. There is no capacity of make new nephrons and as you age, the number of functioning ones decreases by 10% every 10 years after age 40.

Each nephron contains
1. a glomerulus - filters
2. long tubule – urine production
Glomerulus – a network of branching and anastomosing glomerular capillaries with high hydrostatic pressure

Glomerular capillaries are covered with epithelial cells and they are encased in Boman’s capsule.

Fluid filtered by the glomerular capillaries is collected here and enters the proximal tubule in the cortex of the kidney.
Proximal tubule → loop of Henle (medulla) → macula densa (controls nephron function) → distal tubule (cortex) → collecting tubule → cortical collecting tubule → collecting duct.
Regional Differences

Cortical nephrons penetrate only a short distance into medulla

Juxtamedullary nephrons
• long loops of Henle
• efferent arterioles extend down the outer medulla, divide into specialized peritubular capillaries that form vasa recta
• play an important role in concentrating urine
Urine composition is a function of

- Glomerular filtration
- Reabsorption of substances from the renal tubules into the blood
- Secretion of substances from the blood into the renal tubules
- Excretion

\[ \text{Excretion} = \text{Filtration} - \text{Reabsorption} + \text{Secretion} \]
Advantages of filtering large amounts of solutes and reabsorbing most of it

• Allows kidneys to rapidly remove waste products
• Allows all the body fluids to be filtered and processed by the kidneys many times a day
  – Plasma volume ~ 3 L
  – GFR ~ 180 L/day
GFR ~ 125 ml/min

• Composition of Glomerular Filtrate
  – Protein free
  – Devoid of cellular elements inc. RBCs
  – Electrolyte composition is similar to that in plasma
    • Exception is plasma calcium and fatty acids that are bound to plasma proteins

• GFR ~ 20% renal plasma flow
  – Determined by
    • Balance of colloid and hydrostatic forces
    • $K_f$ (Permeability and Surface area, PS)
  – Higher filtration due to high $K_f$ and high hydrostatic pressure

• Filtration fraction = GFR / renal plasma flow
Glomerular Capillary Membrane

3 layers
- epithelium
- basement membrane
- endothelium

Despite the large fenestrations, the negative charges on the endothelium prevent the filtrations of plasma proteins.

**TABLE 26-1**

Filterability of Substances by Glomerular Capillaries
Decreases with Increasing Molecular Weight

<table>
<thead>
<tr>
<th>Substance</th>
<th>Molecular Weight</th>
<th>Filterability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>18</td>
<td>1.0</td>
</tr>
<tr>
<td>Sodium</td>
<td>23</td>
<td>1.0</td>
</tr>
<tr>
<td>Glucose</td>
<td>180</td>
<td>1.0</td>
</tr>
<tr>
<td>Inulin</td>
<td>5,500</td>
<td>1.0</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>17,000</td>
<td>0.75</td>
</tr>
<tr>
<td>Albumin</td>
<td>69,000</td>
<td>0.005</td>
</tr>
</tbody>
</table>

[1 = freely filterable]
Determinants of GFR
GFR = $K_f \times \text{Net Filtration Pressure}$

Net filtration pressure
(10 mm Hg) = Glomerular hydrostatic pressure
(60 mm Hg) - Bowman's capsule pressure
(18 mm Hg) - Glomerular oncotic pressure
(32 mm Hg)
Resistance to Flow

In fluid mechanics, the hydraulic resistance, \( R \), may be defined as the ratio of the pressure drop, \( P_i - P_o \), to flow, \( Q \). Then, by rearrangement of Poiseuille’s Law, the hydraulic resistance equation is obtained:

\[
Q = \pi (P_i - P_o) \frac{(r^4)}{8 \eta l}
\]

Since: \( R = \frac{(P_i - P_o)}{Q} \)

Then: \( R = \frac{8 \eta l}{\pi r^4} \)

Or: \( (P_i - P_o) = Q \times R \)

And, finally: \( BP = CO \times TPR \)
Increased $P_{GC}$ increases GFR

- $P_{GC}$ (Pressure of the glomerular capillaries) $\sim$ 60 mmHg
- Changes in $P_{GC}$ are the primary means by which GFR is altered under physiological conditions
- Determined by
  - Arterial pressure
  - Afferent arteriolar resistance
  - Efferent arteriolar resistance
Increasing afferent arteriolar resistance decreases both blood flow and GFR.

Increasing efferent arteriolar resistance decreases blood flow but increases GFR.
Since the increase in efferent resistance also decreases renal blood flow, the filtration fraction and GCOP increase.

• Therefore if the increase in efferent arteriolar resistance is severe or prolonged, GFR will fall because the rise in osmotic pressure exceeds the increase in hydrostatic pressure such that the net force of filtration decreases.
Renal Blood Flow

• In the average 70 Kg male, combined Q through both kidneys \( \approx 1100 \text{ ml/min} \) (22% of C.O.) or \( \approx 360 \text{ ml/min/100g} \)
  – Q >> metabolic need
  – Supplies plasma for glomerular filtration

• \( Q = \Delta P/R \)
  – Q = (Renal artery pressure – Renal vein pressure)
    Total renal vascular resistance
Resistance to Flow

In fluid mechanics, the hydraulic resistance, R, may be defined as the ratio of the pressure drop, $P_i - P_o$, to flow, Q. Then, by rearrangement of Poiseuille’s Law, the hydraulic resistance equation is obtained:

$$Q = \pi (P_i - P_o) (r^4)/8\eta l$$

Since:

$$R = (P_i - P_o)/Q$$

Then:

$$R = 8\eta l/\pi r^4$$

Or:

$$(P_i - P_o) = Q \times R \text{ or } Q = \Delta P/R$$

And, finally:

$$BP = CO \times TPR$$
Roles served by Renal Blood Flow

• Sustain filtration and excretion of end products of metabolism
• Rapidly alter body fluid volumes and composition
• Serve a hemodynamic reservoir in severe shock (Q can be reduced to very low levels)
• Deliver sufficient oxygen and nutrients to the kidneys
## Approximate Pressures and Resistances in the Circulation of a Normal Kidney

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Pressure in Vessel (mmHg)</th>
<th>% Total Renal Vascular Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beginning</td>
<td>End</td>
</tr>
<tr>
<td>Renal artery</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Interlobar, arcuate and interlobular arteries</td>
<td>~100</td>
<td>85</td>
</tr>
<tr>
<td>Afferent arteriole</td>
<td>85</td>
<td>60</td>
</tr>
<tr>
<td>Glomerular capillaries</td>
<td>60</td>
<td>59</td>
</tr>
<tr>
<td>Efferent arteriole</td>
<td>59</td>
<td>18</td>
</tr>
<tr>
<td>Peritubular capillaries</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Interlobar, arcuate and interlobular veins</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Renal vein</td>
<td>4</td>
<td>~4</td>
</tr>
</tbody>
</table>
Resistance controlled by SNS, hormones and local internal mechanisms. Increase in resistance $\rightarrow$ decrease in flow and decrease in resistance $\rightarrow$ increase in flow if $\Delta P$ remains constant.

An increase or decrease in renal artery pressure has little effect on renal blood flow or GFR between 80 and 170 mmHg.
Distribution of blood flow within the kidney

Cortex receives 98-99% of total renal blood flow

Flow to the medulla is supplied via the vas recta which is very important for concentrating urine.
Physiologic Control of GFR and Renal Blood Flow

• Renal vasculature is well innervated by SNS and strong activation of SNS $\rightarrow$ marked decrease in GFR and renal blood flow
  – Important in reducing GFR during severe, acute disturbances
  – Little sympathetic tone in normal individual

• Angiotensin II – more impact on efferent arteriole
  – Levels usually rise when systemic arterial pressure falls so the result will be the maintenance of GFR
  – Also get decreased flow through peritubular capillaries which increases reabsorption of sodium and water
Autoregulation of RBF and GFR

Main function of autoregulation in the kidney is to maintain relatively constant GFR and the precise control of renal secretion of water and solutes.

RBF and GFR are generally autoregulated in parallel with maintenance of GFR the more important component.

 Normally, GFR is 180 L/day and reabsorption is 178.5 L/day (1.5 L excreted)
W/o autoregulation, a 25 mmHg increase in BP would increase GFR by 25%. If reabsorption remained constant, urine flow would increase to 46.5 L/day (30x)
Autoregulation

- Occurs via myogenic and tubuloglomerular feedback (TGF) mechanisms
- Occurs in afferent arteriole
- Myogenic autoregulation depends on stretch activated ion channels in VSM which when stretched allow Ca to enter leading to contraction.

TGF occurs between the macula densa cells (which contain secretory Golgi cells) and the juxtaglomerular cells of the afferent arteriole. An increase in fluid delivery and NaCl transport at MD increase (increased GFR or decreased PT reabsorption, ↑ in cell Na and Cl and decreases flow through afferent arteriole
Tubuloglomerular feedback contributes to renal autoregulation
Link between [sodium] in the macula densa and RBF

Renal blood flow and GFR per se are not the primary variables controlled by TGF.

The main purpose is to ensure constant delivery of sodium chloride to the distal tubule.
Renin/Angiotensin

Ang II is a potent vasoconstrictor primarily of efferent arteriole. Also acts on the adrenal cortex inducing the release of aldosterone which stimulates sodium reabsorption and in the proximal tubule NaHCO$_3$ reabsorption. At higher concentrations, Ang II contracts mesangial cells (which decreases filtration) and causes generalized vasoconstriction including both afferent and efferent arterioles which helps to maintain central blood pressure at the expense of renal blood flow and filtration.
Use of Clearance Methods to Quantify Kidney Function

The rates at which different substances are *cleared* from the plasma provide a useful way of quantitating the effectiveness with which the kidneys excrete various substances. By definition, the **renal clearance** of a substance is the **volume of plasma that is completely cleared of the substance by the kidneys per unit time**.

Clearance can be used to quantify the rate at which:
- **blood flows through the kidneys** as well as the basic functions of the kidneys:
  - glomerular filtration,
  - tubular reabsorption, and
  - tubular secretion.

\[ C_s = \frac{U_s \times V}{P_s} \text{ units = ml/min} \]

Where:
- \( C_s \) = The clearance rate of the substance
- \( U_s \) = Urine concentration of the substance
- \( V \) = Urine flow rate
- \( P_s \) = Plasma concentration of the substance

Example: If the plasma passing through the kidneys contains 1 milligram of a substance in each milliliter and if 1 milligram of this substance is also excreted into the urine each minute, then 1 ml/min of the plasma is "cleared" of the substance. Thus, **clearance refers to the volume of plasma that would be necessary to supply the amount of substance excreted in the urine per unit time.**
**Inulin Clearance** Can Be Used to Estimate GFR

If a substance is freely filtered (filtered as freely as water) and is not reabsorbed or secreted by the renal tubules, then the rate at which that substance is excreted in the urine \((U_s \times V)\) is equal to the filtration rate of the substance by the kidneys \((GFR \times P_s)\).

A substance that fits these criteria is inulin, a polysaccharide molecule with a molecular weight of about 5200. Inulin, which is not produced in the body, is found in the roots of certain plants and must be administered intravenously to a patient or experimental animal to measure GFR.

Inulin is not the only substance that can be used for determining GFR. Other substances that have been used clinically to estimate GFR include creatinine.
If GFR suddenly decreases by 50%, the kidneys will transiently filter and excrete only half as much creatinine, causing accumulation of creatinine in the body fluids and raising plasma concentration ($P_{Cr}$). Plasma concentration of creatinine will continue to rise until the filtered load of creatinine ($P_{Cr} \times GFR$) and creatinine excretion ($U_{Cr} \times V$) return to normal and a balance between creatinine production and creatinine excretion is reestablished. This will occur when plasma creatinine increases to approximately twice normal.