Part I
Clinical Chemistry of the Kidney and Renal-Associated Physiology

Kidney Anatomy and Function
(Lecture 1)
Functions of Kidney

A) Regulation of water
B) Regulation of electrolytes
C) Acid-base regulation
D) Elimination of waste products
   ➢ Metabolic (urea, ammonia, creatinine, etc.
   ➢ Toxins
E) Endocrine
   ➢ Prostaglandins
   ➢ Renin-Angiotensin
   ➢ Erythropoetin
F) Regulation of bone growth through regulation of calcium and phosphate excretion
   ➢ Directly through excretion of these ions
   ➢ Vitamin D synthesis

Components of Urinary System

A) 2 Kidneys
   ➢ Average size for each – 11 cm long x 5-7.5 cm wide x 2.5 cm deep
B) 2 Ureters
   ➢ Tubes consisting of fibrous outer, muscular middle, and mucous inner layers
   ➢ Average dimension for each – 25-30 cm long, 4-5 cm diameter
C) 1 Bladder
   ➢ Collapsible “bag” that can store up to 0.5 L of urine
   ➢ Activity controlled by parasympathetic nervous system
D) 1 Urethra
   ➢ Tube through which urine exits the body from the bladder
Figure 1 (Chapter 1): The Urinary System

Figure 2 (Chapter 1): Cross-Sectional View of Kidneys in Body
Figure 3 (Chapter 1): Inaccurate Diagram of Kidney Processes

Figure 4 (Chapter 1): Accurate Diagram of Kidney Processes
Kidney Anatomy
Two Types of Kidney Cell Tissues (Renal Parenchyma)

A) Cortex
- Outer portion of kidney
- Brownish pink color, granular appearance
- Contains glomeruli and certain tubules (proximal and distal)
- 75% of renal parenchyma is cortex

B) Medulla
- Inner portion of kidney
- Deeper color with striated patterns, which are coned shaped (each cone called renal pyramid)
- 8-18 renal pyramids per kidney
  (Cortex surrounds renal pyramids, above pyramids called cortical archs and in-between called renal columns)
- Contains Loop of Henle and collecting ducts
Pathway of Blood Flow Through the Kidney

Abdominal Aorta → Renal Artery → Segmental Artery (Five) → Interlobar Artery →

Arcurate Artery → Interlobular Artery → Afferent Arteriole →

Glomerulus → Efferent Arteriole

Peritubular Capillary Network
(Cortical glomeruli – majority of glomeruli)

Vasa Recta Capillary Network
(Juxtamedullary glomeruli)

Interlobular Vein
Arcuate Vein
Interlobar Vein
Renal Vein

Figure 5 (Chapter 1)
Pathway of Blood Flow Through the Kidney

Abdominal Aorta → Renal Artery → Segmental Artery (FIVE) → Interlobar Artery →

Arcuate Artery → Interlobar Artery → Afferent Arteriole →

Glomerulus → Efferent Arteriole

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Interlobular Vein → Arcuate Vein → Interlobar Vein → Renal Vein

Vasa Recta Capillary Network (Juxtamedullary glomeruli)

Interlobular Vein → Arcuate Vein → Interlobar Vein → Renal Vein
Figure 8 (Chapter 1): Diagram of Vasculature Going Into and Out of Glomerulus

Figure 9 (Chapter 1): Diagram of Filtration Process in Glomerulus
Figure 10 (Chapter 1): Simplified Diagram of Glomerular Membrane

Layers of the Glomerular Membrane

A) Capillary Endothelial Cells
   Sheets on inside of capillary wall has many fenestrae (holes 500 - 1000 Å in diameter)

B) Basement Membrane
   Inner portion of kidney
   Course filter of glomerular membrane consisting of a meshwork of proteoglycan fibrillae, collagen, and glycoproteins that have large spaces through which plasma can filter

C) Epithelial Cell Barrier
   1) Interdigitation of foot processes of podocytes
      Epithelial cells called podocytes protrude in branches eventually into small club shaped structures called foot processes. These interdigitate, with separation between the foot processes (called slit pores) being 250 to 400 Å in width

   2) Filtration Slit Membrane
      Layer 40-60 Å thick of unknown material that is attached to the foot processes giving rectangular pores 40 by 140 Å Acts as fine filter of glomerular membrane
Permeability of various substances through the glomerular membrane

<table>
<thead>
<tr>
<th>Molecular Weight</th>
<th>Permeability</th>
<th>Example Substance</th>
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<tbody>
<tr>
<td>5200</td>
<td>1.00</td>
<td>Inulin</td>
</tr>
<tr>
<td>30,000</td>
<td>0.5</td>
<td>Very small protein</td>
</tr>
<tr>
<td>69,000</td>
<td>0.005</td>
<td>Albumin</td>
</tr>
</tbody>
</table>

Permeability = \[
\frac{[\text{substance in filtrate}]}{[\text{substance in plasma}]} = 1 \quad \text{(full permeability)}
\]

= 0 \quad \text{(no permeability)}
### Order and Classification of Tubular System

**A) Proximal Tubule** (starts after Bowman’s Space)
- 1) Early Proximal Convoluted Tubule
- 2) Late Proximal Convoluted Tubule
- 3) Proximal Straight Segment (Pars Recta)

**B) Loop of Henle** (starts at medulla)
- 1) Descending Thin Segment
- 2) Ascending Thin Segment
- 3) Ascending Thick Segment

**C) Distal Tubule** (starts at point where tubular system passes by renal corpuscle)

**D) Connecting Segment**

**E) Collecting Tubules**
- 1) Cortical Collecting Tubule (starts at end of distal tubule)
- 2) Medullary Collecting Duct (starts at medulla ends at papilla)
Renal Ductule System from Medulla to Ureter
(Tubular system through which urine passes)

Coalescing Collecting Ducts
(as progress down medulla)

Eventually forms 10-25 large Collecting Ducts (Capillary Ducts of Bellini) at the apex (Papilla) of each Renal Pyramid

Minor Calyx
(2-3 Minor Calyces drain into each Major Calyx)

Major Calyx
(There are 3 Major Calyces per kidney)

Renal Pelvis

Ureter
Figure 6 (Chapter 1)

Figure 13 (Chapter 1): Different Nephron Types
Pathway of Blood Flow Through the Kidney

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Arcuate Artery → Interlobular Artery → Afferent Arteriole →
Glomerulus → Efferent Arteriole

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(Cortical glomeruli—majority of glomeruli)
Interlobular Vein → Arcuate Vein → Interlobar Vein → Renal Vein

Vasa Recta Capillary Network
(Juxtamedullary glomeruli)
Interlobular Vein → Arcuate Vein → Interlobar Vein → Renal Vein

Figure 15 (Chapter 1) Diagram Showing Two Different Capillary Systems Arising From Different Nephrons (Peritubular and Vasa Recta) After Efferent Arteriole
P. L. Williams and R. Warwick (Eds.): "Gray's Anatomy", 4th Edition,
Figure 16 (Chapter 1): Another Diagram Showing Two Different Capillary Systems Arising From Different Nephrons (Peritubular and Vas Recta) After Different Arteriole

Figure 17 (Chapter 1): Diagram of Kidney Lobule and Lobst
WATER IN THE BODY
(Lectures 2 and 3a)

- Compartments
- Composition
- Movement of solutes and water between compartments

IMPORTANCE OF BODY WATER

1) Abundance - 60% of body weight

2) Medium in which all metabolic reactions take place
WATER COMPARTMENTS IN BODY

1) **Intracellular Fluid (ICW or ICF)**  
   a) 25 Liters, 2/3 of total body water

2) **Extracellular Fluid (ECW or ECF)**  
   a) 15 Liters, 1/3 of total body water  
      - Plasma: 3 Liters  
      - Interstitial Fluid (ISF): 12 Liters

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**Figure 1 Percentage of water in various compartments in the body**  
Figure 2  Diagram of circulatory system

Figure 3  Diagram of small vasculature structures in tissues
Figure 4  Diagram of plasma, interstitial fluid, and intracellular water

Figure 5  Structure of the interstitium
INTERSTITIUM

1) **Solid structures**
   a) Collagen fiber bundles
      - provides tension strength
   b) Proteoglycan filaments
      - Very thin, forms fine mat, consists of 98%
        hyaluronic acid and 2% protein
      - Resistance to fluid flow

2) **Water**
   a) Entrapped in proteoglycan
   b) Pockets of free fluid
      - Expands tremendously with edema

3) **Mechanism of fluid movement - Diffusion**

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Figure 6  Drainage of water from ISF into lymphatics
FUNCTION OF LYMPHATICS

1) Returns remaining 1/10 of liquid to blood that entered interstitium through the capillary network

2) Remove proteins and large particulate matter from tissue spaces

3) Major route of absorption of fats from GI tract
CHARACTERISTICS OF LYMPHATICS

1) Lymph is part of ISF

2) Composition of lymph at a particular location is the same composition as tissues ISF at that location

3) All tissues are drained by lymphatics
   - Exceptions: superficial portion of skin, central nervous system (CNS), deep portion of peripheral nerves, endomysium of muscles, and bones

LYMPH NODES

1) Large particles such as bacteria are removed from lymph in lymph nodes

2) Extensive amount of water in lymph is removed by lymph nodes (protein concentration increased in efferent lymph)
TRANSCELLULAR WATER

1) Although it is ECF in strictest sense, not conventionally considered as ECF

2) Most Important
   - Gastrointestinal
   - Genitourinary (fluid and urine present in kidneys and urinary tract)

3) Others
   - Cerebrospinal Fluid (CSF)
   - Naso-respiratory
   - Aqueous humor of eye

FLUID FROM BODY SPACES

1) Examples of Body Spaces
   - Pericardial (surrounding heart)
   - Pleural (surrounding lungs)
   - Peritoneal (abdominal cavity)
   - Synovial [fluid of joint cavities, bursae (sac in places in tissue where friction occurs), and tendon sheets]

2) Cavities are normally empty, containing a few mL of viscous lubricating fluid

3) Considered ISF
Figure 8  Electrolyte composition of plasma, ISF, and ICF

Table I  Composition of water in various body compartments
ANIONS IN ECF

1) Principle anions are chloride and bicarbonate
   - Principal anion accounting for plasma osmolarity is chloride
   - Bicarbonate has buffering role in ECF

2) Proteins
3) Others

CATIONS IN ECF

1) Sodium
   - Main cation in ECF
   - Principal cation accounting for plasma osmolarity
   - Very important in the regulation of body water volume

2) Potassium
   - Low concentration in ECF (compared to ICF)
   - Important because concentration in ECF is major determiner of cell potential

3) Calcium
   - Effects neuromuscular excitability

4) Magnesium
PLASMA WATER

1) 93% of plasma is aqueous, with remaining 7% being lipid

2) Concentration of constituents in plasma water (not plasma) is the physiologically important concentration

3) Cases of increased lipids or proteins in plasma leads to a change in concentration of ions in plasma, but not in plasma water

COMPOSITION DIFFERENCES BETWEEN PLASMA AND ISF

1) Higher concentration of protein in plasma

2) Slight differences in ion concentrations
   a) Greater concentration for monovalent cations for plasma water
   b) Lesser concentration for anions for plasma water
   c) Greater concentration of divalent cations plasma

3) Reasons for ion differences
   a) Gibbs-Donnan equilibrium for a and b
   b) Binding to plasma proteins for C
INTRACELLULAR FLUID

1) **Principle cation is potassium**
   - Plays osmotic role in ICF

2) **Magnesium is far more concentrated than ECF**

3) **Major anions are organic phosphate and proteins**

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**Figure 9** Effect of hypo- and hyper-osmotic solutions on cell size

Figure 10  Osmotic pressure

Figure 11  Effect of osmotic pressure
Figure 12  Explanation of mechanism of cell potential generation (A)

Figure 13  Explanation of mechanism of cell potential generation (B)
Figure 14  Explanation of mechanism of cell potential generation (C)

Figure 15  Explanation of mechanism of Gibbs-Donnan equilibrium effect (A)

Figure 16  Explanation of mechanism of Gibbs-Donnan equilibrium effect (B)

Goldman-Hodgkin-Katz equation

\[ EMF(mV) = -61 \log \frac{C_{Na^+} P_{Na^+} + C_{K^+} P_{K^+} + C_{Cl^-} P_{Cl^-}}{C_{Na^+} P_{Na^+} + C_{K^+} P_{K^+} + C_{Cl^-} P_{Cl^-}} \]

<table>
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<tr>
<th>Ion</th>
<th>ECF (mEq/L)</th>
<th>ICF (mEq/L)</th>
<th>Permeability</th>
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<tr>
<td>Na⁺</td>
<td>142</td>
<td>10</td>
<td>0.05</td>
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<tr>
<td>K⁺</td>
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<tr>
<td>Cl⁻</td>
<td>103</td>
<td>2</td>
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</table>
CONTROL OF BLOOD FLOW AND BLOOD PRESSURE
(Lectures 3b and 4)

1) REASON: Body needs different levels of nutrient delivery and metabolic removal for differing levels of activities

   High Activity $\rightarrow$ High blood Flow
   Low Activity $\rightarrow$ Low Blood Flow

2) PRINCIPLE: Blood flow is regulated to minimal level to just meet needs
HOW BLOOD FLOW IS CONTROLLED

1) Local Control in Tissue (Intrinsic)

2) Nervous System (Extrinsic)

3) Hormonal (Extrinsic)

Figure 1  Structure of local vascular bed
ANATOMY OF MICROCIRCULATION

1) ARTERIOLE
   - Vessel through which blood enters capillaries
   - Dense smooth muscle coat

2) METARTERIOLE
   - Vessels which branch out from arteriole
   - More sparse, but highly active smooth muscle coat

3) PRECAPILLARY SPHINCTER
   - Point where capillaries leave metarteriole
   - Consists of single smooth muscle strand surrounding entrance to capillaries

ANATOMY OF MICROCIRCULATION (cont.)

4) TRUE CAPILLARIES
   - Exchange of nutrients and metabolic wastes
   - No muscle coat

5) VENULE
   - Vessel through which blood leaves capillaries
   - Has smooth muscle coat, not as extensive as arterioles

6) PREFERENTIAL CHANNEL
   - Vessel large capillary which goes directly to the venule
ROLE OF MUSCLES SURROUNDING VASCULATURE IN THE CONTROL OF BLOOD FLOW

CONSTRICITION → DECREASES BLOOD FLOW

DILATION → INCREASES BLOOD FLOW

LOCAL CONTROL IN TISSUE

A) SHORT TERM

1) CHARACTERISTICS
   a) Timing: minutes
   b) Extent of correction: 75% of requirement

2) THEORIES
   a) Oxygen Demand Theory
      - Oxygen is required to maintain muscle contraction. With increased activity, there is a decrease in oxygen which causes blood vessels to dilate.

   b) Vasodilator Theory
      - Some metabolic product acts as a vasodilator causing relaxation of muscles surrounding the vasculature
      (Candidates: carbon dioxide, lactic acid, adenosine)
Figure 2  Effect of increasing rate of metabolism on tissue blood flow


Figure 3  Effect of arterial oxygen saturation on blood flow

LOCAL CONTROL IN TISSUE

B) LONG TERM

1) MECHANISM
   - With extended oxygen depletion there is increase in number of capillary blood vessels

2) EXAMPLES
   - Animals at high altitudes
   - Premature infants: Retrolental Fibroplasia without gradual adjustment to normal atmosphere after oxygen tent

NERVOUS SYSTEM CONTROL

1) Blood vessels: Controls extent of constriction

2) Heart: Controls rate and strength of contractability

3) Adrenal Glands: Stimulates adrenal medulla to produce the vasoconstrictors epinephrine and norepinephrine
NERVES 101

1) **Autonomic:** Controls involuntary body functions
   a) Parasympathetic – energy conserving processes
   b) Sympathetic - energy expending processes

2) **Somatic Motor:** Voluntary skeletal muscles

VASOMOTOR CENTER
COMMAND CONTROL FOR BLOOD FLOW CONTROL

1) Controls sympathetic vasoconstrictor fibers innervating blood vessels
   - Arterioles are extensively innervated
   - Venules are innervated to a lesser extent
   - Metarterioles, precapillary sphincter are not innervated
   - Lateral portion of center stimulates vasoconstrictor fibers while medial portion inhibits vasoconstriction

2) Control of heart activity
   a) One location within the vasomotor center controls sympathetic nerves
      - Increased heart rate and strength of contractability
   b) Another location with in the vasomotor center controls parasympathetic nerves
      - Decreased heart rate and strength of contractability
**Figure 4**
*Nervous system regulation of circulation through vasomotor system*


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**Figure 5 Innervation of vasculature**

3) Stimulates adrenal medulla to produce the vasoconstrictors epinephrine and norepinephrine

A) Baroreceptors

1) Pressure receptors on arteries (sensitive to blood pressure)
   - Particularly abundant on internal carotid and aortic arch
   - Stimulated with increase of pressure

2) Mechanism when baroreceptor is stretched (incr. pressure)
   a) Signals are sent to the vasomotor center that inhibit the vasoconstrictor location
      - Causes vasodilation throughout the periphery
   b) Signals are sent that excite the vagal center
      - Causes decreased heart rate and decreased strength of contraction
SIGNALS SENT TO VASOMOTOR CENTER (cont.)

B) **Stretch Receptors**

1) Sensitive to blood volume (volume receptors)

2) Located in central veins, pulmonary vessels and right and left atria of heart

3) Receptors send signal to vasomotor center and hypothalamus when stretched by high blood volume

4) Signals sent to increase urinary output
   - signal from stretch receptors sent **directly** to kidney to increase urinary output
   - signal from stretch receptor sent to hypothalamus to decrease ADH, which also increases urinary output
SIGNALS SENT TO VASOMOTOR CENTER

C) Chemoreceptors

1) Sensitive to chemical changes in blood when flow is diminished
   - Activated with decrease oxygen, increased carbon dioxide, increased

2) Present in aorta and carotid arteries

3) Signal excites vasomotor center causing vasoconstriction

4) Active only when blood pressure drops below 80 mm Hg

Blood Flow

Arterial Pressure  \[ \rightarrow \] Tissue (R)  \[ \rightarrow \] Venous Pressure

Analogy to electronics  \[ \Delta V = IR \]

Equation for blood flow through tissue:
\[ \Delta P \text{ (Arterial - Venous)} \ll (\text{Blood Flow}) \times \text{(Resistance)} \]
\[ \Delta P/\text{Resistance} \ll \text{Blood Flow} \]
Body’s Maintenance of Constant Arterial Pressure

1) **Mean Arterial Pressure**
   - 95 – 100 mm Hg

2) **Systolic Pressure** (pressure after contraction of left ventricle)
   - 120 mm Hg

3) **Diastolic Pressure** (pressure with blood filling chambers)
   - 80 mm Hg

GENERAL MECHANISMS OF ARTERIAL PRESSURE CONTROL

1) **Short Term General Mechanisms:**
   - Constriction of blood vessels
   - Change in heart contractability
   - Change in heart rate

2) **Long Term General Mechanism:**
   - Regulating the volume of the blood by changing urinary output
Body’s Maintenance of Constant Arterial Pressure

1) Fundamental Relationship
   Arterial Pressure is proportional to:
   Cardiac Output x Total Peripheral Resistance

2) Illustration of Relationship
   With a momentary decrease in arterial pressure:
   a) Cardiac output is increased:
      - Increased strength and/or rate of contraction
      - Increased volume of blood delivered to heart
   b) Peripheral resistance is increased:
      - Constriction of vasculature

SHORT TERM ARTERIAL PRESSURE REGULATION

1) Speed of action
   - Fast: acts within seconds to minutes

2) Acts as a high frequency filter
   - Reduces high frequency fluctuation of pressure variation

3) Effectiveness of Control
   - Loses capability for pressure control after few hours or few days

4) Extent of control
   - Does not return pressure all the way back to normal

5) Mechanism
   - Hormonal, nervous system, local factors
LONG TERM ARTERIAL PRESSURE REGULATION

1) **Speed of action**
   - Slow: acts in hours to days

2) **Control over period of days, weeks, and months**
   - Reduces high frequency fluctuation of pressure variation

3) **Effectiveness of Control**
   - Becomes more effective as time increases

4) **Extent of control**
   - Ability to return pressure all the way back to normal

5) **Mechanism**
   - Acts through the kidneys adjusting the blood volume

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**Figure 8** Various controls of blood pressure showing effectiveness and response speed

SPECIFIC MECHANISMS OF SHORT TERM ARTERIAL PRESSURE CONTROL

1) **Constriction of vasculature (arteries, arterioles, veins, venules) through nervous system**
   a) Baroreceptors (Also affects heart rate and contractability)
   b) Chemoreceptors
   c) CNS Ischemia

2) **Hormonal**
   a) Norepinephrine and epinephrine
   b) Vasopressin (anti diuretic hormone; ADH)
   c) Angiotensin II

3) **Capillary Fluid Shift**

4) **Stress Relaxation**

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*Figure 11  Baroreceptors, chemoreceptors, CNS Ischemic Response effect on vasomotor center which controls vasoconstrictor nerves connected to systemic circulation (shown above)*

1) Mechanism

Receptors respond to pressure, sending inhibitory signals to vasomotor center (resulting in vasodilation of peripheral vessels) and stimulating signals to vagal center (resulting in decreased heart rate and decreased strength of contraction).

Figure 6

The baroreceptor system

BARORECEPTORS (cont.)

2) Characteristics
   a) Greatest sensitivity in normal range
   b) No response in 0 – 60 mm Hg range
   c) Greater response the faster the rate of pressure change
   d) Primary purpose is to reduce daily variation in arterial pressure by ½ to ⅓: with long term abnormal pressure the baroreceptors adapt

Figure 9  Response of the baroreceptors at different levels of arterial pressure
CHEMORECEPTORS

1) Location
   In aorta and carotid arteries

2) Mechanism
   a) Responds to chemical content of blood
      - Decreased oxygen, increased carbon dioxide, increased H+ causes excitation of chemoreceptor
      - Above chemical changes occurs with a decrease in blood flow
   b) Signal from chemoreceptor causes excitation of vasomotor center causing vasoconstriction
   c) Mechanism only active below 80 mm Hg
CNS ISCHEMIA

1) Mechanism

Results when blood pressure falls so low that vasomotor center itself responds to nutritionally deficient blood (increased CO$_2$ is possible agent)

2) Characteristics

a) Arterial pressure at which mechanism is operational
   - At 60 mm Hg and below CNS Ischemic response is initiated
   - Greatest degree of activation is 15-20 mm Hg
b) Most powerful mechanism for correction of arterial pressure
   - Causes nearly total occlusion of peripheral vessels
   - Can elevate pressure to 270 mm Hg
   - Ceases urine production by the kidney
CNS ISCHEMIA

c) Time limit for the CNS response
- Within 3-10 minutes neuronal cells will die
- Vasomotor center control of arterial pressure will be lost
- Pressure will fall to 40-50 mm Hg

SPECIFIC MECHANISMS OF SHORT TERM ARTERIAL PRESSURE CONTROL

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3) Capillary Fluid Shift

4) Stress Relaxation
Figure 8 Various Controls of Blood Pressure Showing Effectiveness and Response Speed

Figure 12 The renin-angiotensin vasoconstrictor mechanism for arterial pressure control
Figure 13  Structure of capillary wall showing endothelial cells and intercellular clefts between these cells

Table 1
Figure 15  Pressures controlling water movement into and out of the capillary

SPECIFIC MECHANISMS OF SHORT TERM ARTERIAL PRESSURE CONTROL

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Figure 8  Various Controls of Blood Pressure Showing Effectiveness and Response Speed

Figure 16 How kidneys control blood pressure longterm
Figure 17 How increased blood volume increases arterial pressure

I. Glomerular Filtration Rate (GFR) and Autoregulation
   (Lecture 5)

II. Plasma Clearance, Measurement of GFR and RBF
   (Lecture 6a)

Figure 1  Filtration Process from Glomerulus to Bowman’s Space
Pressure Terms in Glomerular Filtration

\[ P_{GC} \] - hydrostatic pressure of Glomerular Capillaries
(+ value is force out of capillaries)

\[ P_{BC} \] - hydrostatic pressure of Bowman’s Capsule
(+ value is force out of Bowman’s Capsule)

\[ \Pi_{GC} \] - Colloid osmotic pressure of Glomerular Capillaries
(+ value force into capillaries)

\[ \Pi_{BC} \] - Colloid osmotic pressure of Bowman’s Space
(+ value force into Bowman’s Space)
Net Filtration Pressure (NFP) Equation

\[ NFP = \sum \text{Pressures inducing filtration} - \sum \text{Pressures opposing filtration} \]

Table 1 Glomerular filtration forces in man

Definitions/Normal Values

The below rates are the total normal rate for both kidneys combined

Renal blood flow (RBF) - total blood flow through kidneys
1100 mL/min

Renal plasma flow (RPF) – total plasma flow through kidneys
= (fraction of blood that is plasma) x RBF
= 0.55 x 1100 mL/min =
605 mL/min

Glomerular Filtration Rate (GFR) – rate of filtrate that is formed in all the renal corpuscles of both kidneys
125 mL/min

Filtration Fraction (FF) – fraction of renal plasma flow that becomes filtrate
FF = RPF/RBF = [125 mL/min]/[605 mL/min] = 0.20

A proposal for the kidney’s regulation of arterial pressure.
Is it correct?
Autoregulation in Kidneys

- Maintains constant RBF and GFR with changing arterial pressure

- Only operable $\geq 70$ mm Hg

- **Reason:**
  Maintain constant urine output even when blood pressure changes
The Three “Hows” to Understand of Kidney Autoregulation

1) How is the GFR maintained constant?

2) How is the RBF maintained constant?

3) How is the FF maintained constant?

GFR is maintained by keeping NFP constant.

But what really controls NFP?
\[ \text{NFP} = \text{P}_{\text{GC}} - (\text{P}_{\text{BC}} + \text{\pi}_{\text{GC}}) \]

NFP is maintained by keeping \( \text{P}_{\text{GC}} \) constant.

Since \( \text{P}_{\text{BC}} \) and \( \text{\pi}_{\text{GC}} \) do not normally change

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Figure 4  How \( \text{P}_{\text{GC}} \) is maintained constant — controlling the constriction of the afferent and efferent arteriole

Derivation of Equation for the Effect of Arteriole Resistances on $P_{GC}$

$P_{aff} - P_{GC} = k^*BF^*R_{aff}$

$P_{GC} - O = k^*(BF - GFR) R_{eff}$

Equation for the Effect of Arteriole Resistances on $P_{GC}$

$$\left[P_{Aff} - k^*(GFR)^*R_{Aff}\right] \left(\frac{R_{Eff}}{R_{Aff} + R_{Eff}}\right) = P_{GC}$$

Above equation shows that if $P_{GC}$ has a temporary decrease because the $P_{Aff}$ decreases (due to decreased blood pressure) it can be corrected upward (that is increased) by:

a) Decreasing $R_{Aff}$

b) Increasing $R_{Eff}$
Figure 6 Diagram of changes in pressure in different place in the kidney circulation before, including and after the glomerulus

Figure 7 Diagram showing how control of afferent and efferent diameter affects GFR and RBF
Summary

Question: How does the body maintain a constant GFR?

Answer: By maintaining a constant glomerular hydrostatic pressure.

Question: How is a constant glomerular hydrostatic pressure maintained?

Answer: By adjusting the resistances (by dilation or constriction) in the efferent and afferent arterioles.

Figure 8  Juxtaglomerular apparatus control of efferent arteriole constriction
Molecular Mechanism of GFR Autoregulation

Overview

GFR is controlled by the macula densa cells in the distal tubule monitoring the tubular fluid sodium concentration.

Molecular Mechanism of GFR Autoregulation
Specifics for Decrease AP

\[
\downarrow \text{Arterial Pressure} \rightarrow \downarrow P_{GC} \text{ (transient)} \rightarrow \downarrow \text{GFR (transient)} \rightarrow \\
\uparrow \text{Na reabsorption in Loop of Henle} \rightarrow \\
\downarrow [\text{Na}^+] \text{ in tubular fluid entering distal tubule} \rightarrow \\
\uparrow \text{MDC secretion signal to JGC} \rightarrow \uparrow \text{Renin released into blood} \rightarrow \\
\uparrow \text{Ang II} \rightarrow \uparrow \text{vasoconstriction of efferent arteriole} \rightarrow \\
\uparrow P_{GC} \text{ (back to normal)} \rightarrow \uparrow \text{GFR (back to normal)}
\]
Use of GFR in Clinical Lab

GFR provides the most useful general index in the assessment of the severity and progress of renal damage. Used for following the course of chronic renal disease.

GFR is decreased as chronic renal disease progresses and kidney function worsens.

Plasma Clearance

**Definition:** Plasma clearance is the measure of the kidneys’ ability to clean or clear the plasma of various substances. It is given in terms of (mL plasma)/min.

**Example:** A clearance of urea of 70 mL/min means that 70 mL of plasma is completely cleared of urea in one minute by the kidneys.
Plasma Clearance

Does the kidney really completely clear a substance from the plasma?

- Not for most substances:
  Remember only 20% of the plasma is filtered, the rest of the plasma still has the substance in it as it passes out of the glomerulus. So unless it is completely secreted into the tubule system after the glomerulus, the plasma is not “completely cleared” of the substance.

- This is an artificial quantitative measure of how effective the kidneys are in clearing a substance, it is not reality.

**Corrected Plasma Clearance \( (C_x)_{Cor} \)**

Equation

\[
(C_x)_{Cor} = \frac{(UFR) \times [X]_{urine}}{[X]_{plasma}} \times \frac{1.73}{A}
\]

- **UFR** – urine flow rate (mL/min) = 24 hour urine volume/1440
- **[X]_{urine}** – concentration of substance X in the urine (moles/mL)
- **[X]_{plasma}** – concentration of substance X in the urine (moles/mL)
- **A** – surface area of individual (m²)
How Plasma Clearance is Measured in the Clinical Lab

- Substance X is continuously infused into patient (either externally or endogenously)
- Concentration of infused substance X is measured in the plasma and urine
- The urine flow rate is determined by collecting 24 hour urine sample and measuring the volume

Laboratory Determination of GFR

When infused substance X has the following characteristics:

1) Freely filtered (permeability = 1)
2) Not reabsorbed in the tubular system
3) Not secreted into the tubular system

THEN

Plasma Clearance of X ($C_x$) = GFR
Substances X for Determination of GFR

**Externally Infused Substances**
- Inulin
- Mannitol
- Radioactive iothalamate

**Endogenous Substance**
- Creatinine

Determination of GFR using creatinine

1) **Convenient** – no external infusion needed

2) **Problem** – Creatinine is secreted into the proximal tubule.

Will this lead to a positive or negative error in GFR?
How does secretion affect the calculated clearance?

\[ C_x = \frac{(UFR) \times [X]_{\text{urine}}}{[X]_{\text{plasma}}} \]

Jaffé Reaction for Determining Creatinine

1. Colorimetric reaction using alkaline picrate
2. Monitor product at 510-520 nm
3. Interfering compounds in plasma
   a) Compounds that reduce picrate to picramate
      (absorbs at 482 nm)
      glucose, uric acid, ascorbic acid
   b) Other interferences
      acetone, acetoacetic acid, fructose, hippuric acid, urea, indole, histidine, asparagine, resorcinol, glycocyamidine hydantoin, and cephalosporin antibiotics
4. Overestimates creatinine in plasma due to interfering compounds – which counter balances positive error in GFR due to secretion. Thus Jaffé reaction gives “accurate” GFR determination (in normal range)
5. Overestimates GFR at low levels GFR (because creatinine is larger fraction of Jaffé chromagens at low GFR)
Laboratory Determination of RPF

When infused substance X has the following characteristic:

It is totally cleared (through a combination of filtration and secretion) in one passage through the kidneys

THEN

Plasma Clearance of X ($C_x$) = RPF
Substances X for Determination of RPF

Externally Infused Substance

- Para-aminohippurate (PAH) (90% cleared)

Equations for RPF and RBF with PAH Infusion Experiments

\[ \text{RPF} = \frac{C_{PAH}}{0.90} \]

\[ \text{RBF} = \frac{C_{PAH}}{0.90 \times 0.55} \]

Fraction of blood that is plasma
Calculation of Filtration Fraction (FF)

\[ FF = \frac{GFR}{RPF} \]
Mechanisms of Sodium and Water Reabsorption by the Kidneys
(Lectures 6b, 7, and 8a)

Control of ECF Volume

1. Control Water Output of Body
   - Kidney controlling urine volume

2. Control Water Input to Body
   - Thirst response
Kidneys’ Control of Volume of ECF Water

\[
\downarrow
\]

Regulation of ECF’s Sodium Amount

Relationship of ECF Volume to ECF Sodium Amount

\[
\downarrow \text{ECF Na amount} \quad \rightarrow \quad \downarrow \text{ECF Water Volume}
\]

\[
\uparrow \text{ECF Na amount} \quad \rightarrow \quad \uparrow \text{ECF Water Volume}
\]
The Sodium relationship to ECF volume:

Is **NOT** a concentration effect:
- ECF Volume Expansion can have low, normal, high [Na\(^+\)] in serum
- ECF Volume Depletion can have low, normal, high [Na\(^+\)] in serum

It **IS** a total sodium amount effect

---

**General Principle**

Water follows Na\(^+\)

Water goes where-ever sodium goes
If body retains sodium, it will retain water
If body releases sodium, it will release water
Kidneys Control Na\(^+\) Excretion Rate to Control ECF Volume

\[ E_{Na^+} = F_{Na^+} - R_{Na^+} \]

\( E_{Na^+} \) is the amount of sodium excreted per unit time
\( F_{Na^+} \) is the amount of sodium filtered per unit time
\( R_{Na^+} \) is the amount of sodium reabsorbed per unit time

---

Kidney’s Control of Na Excretion

\[ E_{Na^+} = F_{Na^+} - R_{Na^+} \]

\[ E_{Na^+} = GFR[Na^+]_{filtrate} - R_{Na^+} \]
Overview of fluid osmolarity in the various tubules of the kidney

a) Proximal Tubule - isoosmotic with plasma (i.e., tubular fluid has the same osmolarity as the plasma).

b) Thin Descending Limb of the Loop of Henle - hyperosmotic

c) Thin and Thick Ascending Limb of the Loop of Henle - osmolarity decreases progressively to the point that the fluid is hypoosmotic at the start of the distal tubule.

d) Distal Convoluted Tubule - osmolarity decreases further

e) Cortical Collecting Tubule and Medullary Collecting Duct - osmolarity depends on the presence of ADH (hyperosmotic with ADH present, further decrease in osmolarity with ADH absent).

Figure 1A Percentage of filtered sodium reabsorbed in different tubular sections

Percent Substance Reabsorbed in Proximal Tubule

Water 60%-65%
Sodium 60%-65%
Potassium 80%
Bicarbonate 80%-90%
Glucose 100%
Amino Acids 100%
Phosphate 80-95%
Proteins 100%
Mechanisms of Sodium Reabsorption in the Proximal Tubule

1) Electrochemical Gradient
2) Electrogenic
3) Passive NaCl
4) Solvent Drag
5) Other factors (see chapter notes)

Figure 2 Diagram of proximal tubule cell showing the electrochemical gradient forces driving Na\(^+\) reabsorption into the cell

Electrochemical Gradient Mechanism (Proximal Tubule)

1) “Electro-“ negative charge of tubular cell drives Na+ into cell from lumen

2) “-chemical” – concentration gradient in Na+ between lumen and cell drives Na+ into the tubular cell from lumen

3) Transport proteins on lumen membrane of cell needed to carry Na+ into cell
   - Na+/H+ counter-transport protein
   - Na+/glucose co-transport protein
   - Na+/ amino acid co-transport protein

Figure 3 Mechanism of sodium reabsorption in proximal tubule cell via Na+/H+ counter-transport protein

Electrogenic Mechanism (Proximal Tubule)

Positive potential of lumen drives Na+ into (through Na+ channels) and between (through junction) the tubular cells

Figure 4  Lumen potential at various points in the proximal tubule

Figure 5  Anion concentration differences between lumen and pertubular space in the late proximal tubule sections. Which concentration gradient is establishing the potential (i.e. which ion is the junction more permeable to)?


---

Passive NaCl Reabsorption (Proximal Tubule)

NaCl is driven through the junction by the Cl- concentration difference between the lumen and the ISF
Figure 7 Reabsorption of sodium draws water with it due to sodium’s osmotic pull on the water


Solvent Drag (Proximal Tubule)

As Na+ pulls water with it in the reabsorption process, the solute in the water (including Na+) is pulled with it
Water and sodium reabsorption are linked in the proximal tubule

Proximal tubule is permeable to both Na\(^+\) and H\(_2\)O

Water follows sodium in the proximal tubule by its “osmotic pull”

Diabetes

What is a major symptom of diabetes?

Can this symptom be explained from what we have learned so far?
Figure 8 Difference in predominant anions in proximal tubule lumen and ISF space on the other side of the proximal tubule cell


Glomerular Tubular Balance

1) Process by which any change in GFR is responded to by an appropriate change in Na\(^+\) and water reabsorption

\[ \uparrow \text{GFR} \rightarrow ? \text{Na}^+ \text{ (water) reabsorption} \]

2) Happens in proximal tubule, as well as other tubule sections

3) Second line of correction for correcting a change in GFR (first is autoregulation)
Glomerular Tubular Balance
Mechanisms in the Proximal Tubule

- Starling Forces

\[ \uparrow P_{GC} \rightarrow \uparrow GFR \rightarrow \uparrow FF \rightarrow \text{?} \ P_{\text{peritubular capillaries}} \]

How will this affect water movement?
From where and to where will it move?

Glomerular Tubular Balance
Mechanisms in the Proximal Tubule

2) Stimulation of Na\(^+\)/H\(^+\) Counter Transport Protein

a) The increased filtration rate leads to less reabsorption of bicarbonate.

b) The higher concentration of bicarbonate in the tubular fluid stimulates the Na\(^+\)/H\(^+\) counter-transport protein.

c) There is an increased reabsorption of Na\(^+\) by the proximal tubule cell.
Sodium Reabsorption in Loop of Henle
General Comments Applying to the Whole

1) 25% of sodium load is reabsorbed
2) Sodium and water are uncoupled in their reabsorption. Tubule cells permeable to one but not the other, differing what it is permeable to depending on the segment
3) Reabsorption is passive

Order and Classification of Tubular System

A) Proximal Tubule (starts after Bowman’s Space)
   1) Early Proximal Convoluted Tubule
   2) Late Proximal Convoluted Tubule
   3) Proximal Straight Segment (Pars Recta)

B) Loop of Henle (starts at medulla)
   1) Descending Thin Segment
   2) Ascending Thin Segment
   3) Ascending Thick Segment

C) Distal Tubule (starts at point where tubular system passes by renal corpuscle)

D) Connecting Segment

E) Collecting Tubules
   1) Cortical Collecting Tubule (starts at end of distal tubule)
   2) Medullary Collecting Duct (starts at medulla ends at papilla)
Reabsorption in the Thin Descending Limb of the Loop of Henle

Tubular cells has HIGH permeability to water but low permeability to solutes (including Na$^+$). Concentrating segment

- This causes what to happen with the exposure to the medulla?

- What will happen to the Na concentration in the tubular fluid?
Reabsorption in the Thin Ascending Limb of the Loop of Henle

Tubular cells have high permeability to solutes but low permeability to water. Diluting segment.

➢ This causes what to happen? Why?
(Hint: what is the relative concentration of Na⁺ in the tubular fluid compared to the medulla)?
Reabsorption in the Thick Ascending Limb of the Loop of Henle (TALH)

1) Tubular cells impermeable to water
2) Na reabsorbed into tubular cell via secondary active process involving a protein carrier (Na+, K+, 2Cl- carrier) down a concentration gradient
3) Na also reabsorbed paracellular due to positive lumen potential (How is this generated?)
4) Diluting segment. Tubular fluid is hyposmotic at the end of TALH

Figure 11
Diagram showing the sodium reabsorption mechanisms in the thick ascending limb of the loop of Henle tubular cell

Table 7-1 Hormone responsiveness of distal nephron segments

<table>
<thead>
<tr>
<th>Segment</th>
<th>Antidiuretic hormone</th>
<th>Aldosterone</th>
<th>Parathyroid hormone</th>
<th>Calcitriol</th>
<th>Atrial natriuretic peptide</th>
</tr>
</thead>
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<tr>
<td>Distal convoluted tubule</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Connecting segment</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Cortical collecting tubule</td>
<td>+</td>
<td>?</td>
<td>±</td>
<td>±</td>
<td>0</td>
</tr>
<tr>
<td>Principal cells</td>
<td></td>
<td>0</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Intercalated cells</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Medullary collecting tubule</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Outer</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inner</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
</tbody>
</table>


Figure 14 Diagram showing the sodium reabsorption mechanism in the distal tubule cell

Reabsorption in the Connecting Segment

a) absorbs roughly 10% of the filtered sodium load
b) Shares characteristics common to both the distal tubule and cortical collecting tubule.
c) Impermeable to water
d) Reabsorption of Na+
   1') Via Na+/Cl- co-transporter
   2') Reabsorbs Na+ (via Na+ channels) and secretes K+ in response to aldosterone.
e) Diluting segment

Figure 15 Diagram showing the sodium reabsorption mechanism in the principal cell in the cortical collecting duct tubule cell
Figure 16 Diagram showing the effect of aldosterone on the sodium channels in the connecting segment and cortical collecting tubule cells


Figure 17 Diagram showing the sodium reabsorption mechanism in the papillary collecting duct tubule cell

Figure 18 Summary of solute changes in tubular fluid at various points in the tubular system.


Regulation of Extracellular Fluid Volume
(Lectures 8b, 9a)

Figure 1 Pathophysiological effects of changes in ECF volume.
Figure 2 Distribution of sodium in the body. The amount of exchangeable sodium controls ECF volume.

Non-Renal Output Mechanisms for Body Water

1) **Insensible Perspiration**
   - loss from skin and lungs

2) **Sweat**

3) **GI Losses**
   - Health – Only small amounts
   - Pathologic – can be large
     a) Vomiting
     b) Diarrhea

Two Major Ways Kidneys Have Influence on Na⁺ Excretion

1) R (Na⁺) (in health and disease)

2) GFR (in disease)

\[ E_{Na^+} = GFR \times [Na^+]_{Plasma} - R_{Na^+} \]
Mechanisms of GFR Response to Decreased ECF Volume

1) $\pi_{\text{Plasma}} \rightarrow \downarrow \text{GFR}$
2) $\downarrow \text{Arterial Pressure} \rightarrow \downarrow \text{GFR}$
3) Stretch Receptor Signal $\rightarrow$ Inhibitory Nerve Signal $\rightarrow$ Vasoconstriction of Afferent Arteriole $\rightarrow \downarrow \text{GFR}$

Ways in Which Kidneys Regulate Sodium Reabsorption

I. Hormonal Factors
   - Aldosterone
   - Renin/Angiotensin
   - Atrial Natriuretic Peptide
   - Prostaglandins
   - Kallikrein-Kinin System

II. Physical and Hemodynamic Factors
   - Starling Forces
   - Medullary Blood Flow
   - Interstitial Pressures
   - Pressure Natriuresis

III. Renal Nerve Activity
Factors that Increase Aldosterone Release from Adrenal Cortex

1) Angiotensin II

2) Low $[\text{Na}^+]_{\text{plasma}}$

3) High $[\text{K}^+]_{\text{plasma}}$

ACTH (released from anterior pituitary gland) is necessary for aldosterone secretion

How does Aldosterone increase sodium reabsorption?

What tubular segments does it act on?
Mechanisms of Renin Release

1) Stimulation of Juxtaglomerular Cells of Afferent Arteriole

↓ECF Volume → ↓renal arterial pressure → ↑renin

Note: cells of afferent arteriole (juxtaglomerular cells) respond to renal arterial pressure directly
Mechanisms of Renin Release (cont.)

2) **Stimulation of Macula Densa Cells**

\[
\downarrow \text{ECF volume} \rightarrow \downarrow \text{P}_{\text{GC}} \rightarrow \downarrow \text{GFR} \\
\downarrow \text{Na+ load at macula densa cells} \\
\uparrow \text{Renin}
\]

Mechanisms of Renin Release (cont.)

3) **Renal Nerve Stimulation**
   a) Renin released with decreased ECF volume

\[
\uparrow \text{Renal Nerve Firing} \rightarrow \uparrow \text{Renin} \\
\downarrow \text{ECF Volume}
\]

No stretch receptor
inhibition of renal nerve

No stretch receptor firing
Mechanisms of Renin Release (cont.)

3) **Renal Nerve Stimulation**
   b) No Renin released with increased ECF volume

   ![Diagram showing Renal Nerve Firing inhibiting Renin release with stretch receptor firing leading to increased ECF volume.]

   - Renal Nerve Firing → Renin released
   - Inhibits above pathway
   - (inhibition indicated by cross-out)
   - Stretch Receptor Firing
   - ↑ ECF Volume

What hormone does Renin directly produce?
Angiotensin II Causes Na\(^+\) Reabsorption

1) Affects renal hemodynamics

2) Increases aldosterone secretion from adrenal glands

3) Directly affects the proximal tubule to increase Na\(^+\) reabsorption

1) Angiotensin II Effect on Renal Hemodynamics

a) Effect on GFR

- Constriction of Efferent Arteriole
- GFR
- FF
- Sodium and water reabsorption

- Ang II
- Renin
- (via mechanisms on previous slides)

- ECF Volume

\(\Pi_{\text{plasma (efferent)}}\)
\(\Pi_{\text{plasma (efferent)}}\)
\(P_{\text{plasma (efferent)}}\)
2) Angiotensin II Effect on Renal Hemodynamics (cont.)

b) Effect on Medullary Blood Flow

- Medullary Blood Flow
  - ↓
  - Ang II
  - ↑
  - Renin
  - (via mechanisms on previous slides)
  - ↓ ECF Volume

- Medullary Washout
  - ↓
  - Osmolarity of Medulla
  - ↑
  - Na+ reabsorption in thin ascending limb of loop of Henle

Less urea carried out of medulla

2) Angiotensin II Effect on Aldosterone Secretion from Adrenals

- Production of aldosterone from adrenal glands
  - ↑
  - Ang II
  - ↑
  - Renin
  - (via mechanisms on previous slides)
  - ↓ ECF Volume

- Na+ reabsorption
  - ↑

Tubules acted upon by aldosterone: [connecting segment and collecting ducts (principal cells)]
3) Angiotensin II Action on Proximal Tubule

ECF Volume ↓

(Renin ↑)

(Ang II ↑)

↑ Na+ reabsorption in proximal tubule

(via mechanisms on previous slides)

Ways in Which Kidneys Regulate Sodium Reabsorption

I. **Hormonal Factors**
   - Aldosterone
   - Renin/Angiotensin
   - Artial Natriuretic Peptide
   - Prostaglandins
   - Kallikrein-Kinin System

II. **Physical and Hemodynamic Factors**
   - Starling Forces
   - Medullary Blood Flow
   - Interstitial Pressures
   - Pressure Natriuresis

III. **Renal Nerve Activity**
Atrial Natriuretic Peptide (ANP)

- ANP is a peptide hormone synthesized and stored in the atria of the heart.
- Leads to increased sodium excretion.
- Acts on:
  a.) Proximal Tubule
  b.) Medullary Collecting Duct

Prostaglandin PGE$_2$

- $\uparrow$ PGE$_2$ leads to:
  - $\downarrow$ Na$^+$ Reabsorption ($\uparrow$ Na$^+$ excretion)
  - $\uparrow$ Vasodilation
Figure 6  Kinin generation pathway

Physical and Hemodynamic Factors Leading to Na⁺ Excretion

1. Pressure Natriuresis

2. Renal Interstitial Hydrostatic Pressure

3. Medullary Blood Flow

4. Starling Forces
   (The invoking of Starling Forces in the renin-angiotensin II mechanism can be considered in this category)

Figure 7  Pressure Natriuresis mechanisms
Effect on Medullary Blood Flow on Na+ Reabsorption

- ECF Volume
- Medullary Blood Flow
- Medullary Washout
- Osmolarity of Medulla
- Na+ reabsorption in thin ascending limb of loop of Henle

More urea carried out of medulla

Figure 9 Diagram of the vasa recta showing the carrying out of solutes from the medulla by the vasa recta capillary system

Figure 8  Medullary washout mechanism

Figure 10  Diagram of reabsorption characteristics of the thin descending and thin ascending limb of the Loop of Henle
Role of Renal Nerve in Sodium Reabsorption/Excretion

1. ↑ Stimulation → ↑ Renin Release → ↓ Na⁺ Reabsorption

2. ↑↑ Stimulation → ↓ GFR and ↓ RBF → ↓ Na⁺ Excretion (Since filtered load decreases)

3. ↑ Stimulation (Low level) → ↑ Na⁺ reabsorption in proximal convoluted tubule and Loop of Henle
Regulation ECF Osmolarity
(Lecture 9b)

1) Control Intake
   Thirst Mechanism

2) Control Water Excretion
   Action of ADH on collecting tubules

3) Shift of water between ECF and ICF compartments
Control of ECF Osmolarity

Control of water movement into or out of ECF

Figure showing thirst center osmoreceptors and antidiuretic center in hypothalamus and the pituitary gland

Mechanisms of Thirst Stimulation

1. **Thirst receptors in hypothalamus sense ECF osmolarity**
   Stimulated by ECF osmolarity (which cause water to move out of thirst receptor cells) (Note respond only to change in concentration of solutes that are impermeable to cell membrane, such as sodium, mannitol, sucrose but NOT urea or glucose).

2. **Receptors stimulated by profound loss of blood volume (10%)**
   Receptors located in left atrium, pulmonary veins. Arterial baroreceptors also involved in thirst stimulation.

Mechanisms of Thirst Stimulation (cont.)

3. **Angiotensin II**
   Angiotensin II has been shown to stimulate thirst when placed in third ventricle

4. **Excessive loss of potassium from body**
   Causes water to move out of thirst receptor cells.
Chemical structure of antidiuretic hormone (vasopressin)


Figure showing the various factors affecting ADH release

ADH Release Mechanism

1. **ECF Osmolarity Response**
   ADH release most responsive to ECF osmolarity

2. **ECF Volume Response**
   - Volume loss must be > 10%
   - Overrides osmolarity control

---

**Mechanism of Osmolarity Control of ADH Release**

- ECF osmolarity
- Water moves ______ osmoreceptor cells (in hypothalamus)
- ▀ ICF volume in osmoreceptors
- ▀ osmoreceptor cell size
- ▀ rate of signal discharge of osmoreceptors to pituitary gland
- ▀ release of ADH from pituitary gland
- ▀ water reabsorption in collecting tubules
- ▀ ECF osmolarity (back to normal)
Mechanism of ECF Volume Control of ADH Release

1. Stretch Receptors
   - Located in left and right atria of the heart
   - If stretched inhibits the secretion of ADH by the posterior pituitary gland

2. Baroreceptors

---

Figure showing mechanism of ADH action on collecting tubule cell causing water reabsorption

Mechanism of ADH

ADH increases epithelial cell water permeability in the cortical collecting tubule and medullary collecting duct by the following mechanism:

1) Binds to peritubular side of the collecting duct
2) Activates adenylate cyclase

\[
\text{ATP} \xrightarrow{\text{adenylate cyclase}} \text{cAMP}
\]

3) Camp activates (ultimately) protein kinase which causes increased H\textsubscript{2}O permeability of the luminal cell wall (presumably through a phosphorylation of the luminal membrane)

Figure showing the two controls of ADH release and thirst response

Disorders of Sodium (Water): Depletion and Excess (Lectures 9b and 10a)

Pathologic Conditions of Total Exchangeable Body Sodium

1) Sodium depletion conditions
   ECF volume contraction

2) Sodium expansion conditions
   ECF volume expansion
Figure shows sodium balance maintained by the kidneys excreting same amount of sodium as is ingested


This figure (day 1) and succeeding figure (days 2 and 3) shows what happens to sodium excretion by the kidneys over a 3 day period when sodium intake is reduced from 150 mEq/day (days previous) to 30 mEq/day (days 1 – 3)

Figure shows what happens to sodium excretion by the kidneys over a 3 day period (days 2 and 3 shown) when sodium intake is reduced from 150 mEq/day (days previous) to 30 mEq/day (days 1–3).


Response to Change in Sodium Intake

1) **Usual Priority**

Body prioritizes maintaining ECF osmolarity over ECF water volume

What is the response to ↓ sodium intake?

What is the response to ↑ sodium intake?
Response to Change in Sodium Intake (cont.)

2) Priority in chronic sodium deprivation conditions
Priority changes in that body will now retain water at expense of trying to maintain osmolarity

What is the response to ↓ sodium intake?

What is the response to ↑ sodium intake?

Negative Sodium Balance

1. Extra-renal losses

2. Renal losses
Extrarenal Losses of Sodium

1) Gastrointestinal (GI)
   a) No change in ECF osmolarity since most GI fluids are isotonic
   b) Leads to hypokalemia
   c) Acid/base consequences
      Loss of gastric fluid (vomiting) → metabolic alkalosis
      Loss of intestinal fluid (diarrhea) → metabolic acidosis

Table II. Volume and Electrolyte Concentrations* of Gastrointestinal Fluids

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Mean volume (ml/day)</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Cl⁻</th>
<th>HCO₃⁻</th>
<th>H⁺</th>
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<tr>
<td>Saliva</td>
<td>1300</td>
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<td>Bile</td>
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<td>Pancreatic secretion</td>
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<td>Jejunal secretion</td>
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<td>Ileal secretion</td>
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<td></td>
</tr>
</tbody>
</table>

*Concentrations in mEq/liter. H⁺ concentration in all fluids but gastric secretion is negligible as compared to other electrolytes.

S.Klahr (Ed.) "The Kidney and Body Fluids in Health and Disease" Plenum Medical Book Company: New York, 1984
Extrarenal Losses of Sodium
(cont.)

2) Cutaneous
   a) Sweating
      Leads to ECF osmolarity since water loss is greater than electrolyte loss
   b) Burns
      - Causes loss of water through skin
      - Also causes increased capillary permeability
        (which causes loss of plasma sodium, plasma water, and plasma protein from vascular space.
         The loss of plasma protein leads to a disproportional loss of vascular volume
disproportional to magnitude of Na⁺ loss)

Renal Losses of Sodium

1) Factors acting on normal kidney causing Na⁺ excretion

2) Increased Na⁺ excretion due to diseased kidney
### Osmotic Diuresis

- **Conditions of excess solute in proximal tubule keeps water in tubule**

- **Examples:**
  - Excess excess glucose in diabetes
  - Excess excess bicarbonate in metabolic alkalosis
Mechanism by which Osmotic Diuresis Increases Na⁺ Excretion

1. ↓[Na⁺] entering Loop of Henle  
   Why?

2. ↓Na⁺ reabsorption in ascending thin and thick limb of the Loop of Henle  
   Why?

3. ↑Na⁺ load to distal tubule segments – exceeding reabsorptive capabilities of these segments for Na⁺

4. ↑Na⁺ excretion

Note: Anion diuresis has this osmotic diuresis mechanism and also an electrostatic mechanism for explaining sodium excretion (anion carries positive Na⁺ with it). This occurs when excess solute is HCO₃⁻.
**Primary Adrenal Insufficiency (Addison’s Disease)**

1. **↓** Aldosterone secretion leads to modest excretion of Na⁺

2. Loss of Na⁺ normally compensated by increased dietary NaCl, thus water status normally minimally affected

3. **LARGE** depletions of ECF volume seen in these patients upon extrarenal loss of Na⁺

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**Sodium Losses from Various Kidney Diseases** (Listed in Previous Table)

Common to these diseases is the tubular cells are unable to reabsorb sodium with normal efficiency.
Non-Renal Losses of Na⁺ will have Renal Compensation (Sodium Reabsorbed)

![Diagram]

Lab Tests Distinguishing Extrarenal and Renal Loss of Sodium

**Extrarenal Loss of Na⁺**
- Urine Analysis
  - [Na⁺] < 10 mEq/L
  - __ urinary volume
  - __ [K⁺]

**Renal Loss of Na⁺**
- Urine Analysis
  - [Na⁺] ≥ 20 mEq/L
  - __ urinary volume

**Exceptions to extrarenal loss urine analysis:**
1. Loss of gastric fluid leads to increased bicarbonate, leading Na⁺ and K⁺ excretion [i.e., Na⁺ and K⁺ increased in the urine (due to anion counter ion carry down)]
2. Diabetics have Na⁺ and K⁺ excretion because of generation of ketoacids [i.e., Na⁺ and K⁺ increased in the urine (due to anion counter ion carry down)]
Positive Sodium Balance Disorders

1. Certain renal diseases

2. Persistent stimulation of sodium reabsorption and water retention
Renal Disease Causes of Positive Sodium Balance Disorders

1. Acute nephrotic syndrome
2. Acute renal failure (oliguric phase)
3. Terminal chronic renal failure
4. Iatrogenic overload in following conditions:
   - obstructive uropathy
   - tubular necrosis

Mechanism (except for nephrotic syndrome) –
*decreased sodium excretion due to decreased GFR*

Conditions Leading to a Persistent Stimulation of Sodium Reabsorption

1. Congestive heart failure (CHF)
2. Hepatic cirrhosis
3. Protein deficiency states
4. Lymphatic obstructions
5. Conditions of increased aldosterone
Common Mechanisms in Conditions of Persistent Stimulation of Sodium/Water Reabsorption

ADH release and thirst response (volume response mechanisms)

Water Reabsorbed (due to ADH)

Water intake

Arterial Blood Volume

Cardiac Output

Arterial Pressure

Renin

Angiotensin II

Sodium Reabsorption

GFR

Renal Water/Na+ Excreted

How Decreased ECF Volume Leads to Renin Release

1. Cells in afferent arteriole sense decrease in arterial pressure
2. Decreased sodium concentration at macula densa cells
   \[ \text{ECF volume leads to } \downarrow \text{GFR which leads to } \uparrow \text{Na+ reabsorption in Loop of Henle} \]
3. Increased renal nerve stimulation
Potassium: Control Mechanisms and Pathology
(Lectures 11, 12, and 13a)

Function of Potassium

a) Major determinant of cell potential

b) Major determinant of intracellular ionic strength and affects the cell’s chemical environment
Effect of Extracellular \([K^+]\)

Alterations in E cell most often occur clinically with alteration of \([K^+]\) in ECF

\[
\begin{align*}
E_{\text{ECF}} &= \frac{[K^+]}{5} \text{ mEq/L} \\
E_{\text{cell}} &= -62 \log \left( \frac{[K^+]}{[K^+]_{\text{ICF}}} \right) \\
-90 \text{ mV} &= -62 \log \left( \frac{150}{5} \right)
\end{align*}
\]
Effect of Intracellular [K⁺]

a) Major determinant of cell volume

b) Effects cell’s acidity

Figure 1. Dietary intake, excretion, and distribution of potassium.
Daily $K^+$ Losses from Body

1) Renal (90 mE /day)

2) Extrarenal
   a) Feces (10m E/day)

   b) Sweat (Negligible)

Reabsorption and Secretion of $K^+$ by/into tubules

1) Proximal Convoluted Tubule
   $K^+$ reabsorbed

2) Proximal Straight and descending thin limb of LH
   $K^+$ secreted

3) Thick ascending limb of LH
   $K^+$ reabsorbed
Reabsorption and Secretion of K⁺ by/into tubules (cont.)

3) Distal Convoluted Tubule
   Nothing

4) Connecting Tubule and Cortical Collecting Duct and outer Medullary Collecting Duct
   K⁺ Secretion

5) Inner strip of outer Medullary Collecting Duct
   K⁺ Secretion and Reabsorption

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K⁺ Excretion of Kidneys

1. Case of increased K⁺ in body

   ➢ Mechanism of control mainly through increased secretion in connecting tubule and cortical collecting duct

   ➢ Timing of control: Within hours
K⁺ Excretion of Kidneys (cont.)

2. Case of reduced K⁺
   - Kidney decreases K⁺ excretion rate within days (Not very effective in its control)
   - In diseased patients K⁺ conversation is less complete

Maintenance of [K⁺] in Blood

1) Factors that affect renal excretion

2) Factors that affect cellular uptake/release
General Mechanisms of Increased $K^+$ Secretion into the Tubule Lumen

A. Increased $[K^+]_{\text{tubular cell}}$

**Mechanism 1**:  
$\uparrow [Na^+]_{\text{tubular cell}} \rightarrow \uparrow \text{Na,K ATPase Activity} \rightarrow \uparrow [K^+]_{\text{tubular cell}}$

**Mechanism 2**:  
$\uparrow [K^+]_{\text{ECF}} \rightarrow \uparrow \text{Na,K ATPase Activity} \rightarrow \uparrow [K^+]_{\text{tubular cell}}$

**Mechanism 3**:  
$\uparrow \text{pH}_{\text{ECF}} \rightarrow \text{Transfer of H}^+_{\text{ICF}} \text{ into ECF with K}^+_{\text{ECF}} \text{ going into ICF}$  
$\downarrow \uparrow [K^+]_{\text{all cells (including tubular cells)}}$
General Mechanisms of Increased K⁺ Secretion into the Tubule Lumen (cont.)

B. Decreased $[K^+]_{\text{lumen}}$

Mechanism 4
$\downarrow [K^+]_{\text{lumen}} \rightarrow$ greater $[K^+]$ gradient, driving $K^+$ from tubular cell to lumen through $K^+$ channels

C. Electrostatic Mechanisms

Mechanism 5
$\uparrow$ Non-reabsorbed anion $\rightarrow$ drives $K^+$ from tubular cell to lumen through $K^+$ channels via electrostatic force

Mechanism 6
$\uparrow$ $[Na^+]_{\text{tubular cell}} \rightarrow$ increased positivity (less negativity) of the tubular cell, leading to $K^+$ being driven out of the tubular cell into the lumen through the $K^+$ channels

Factors that affect cellular uptake/release of $K^+$

a) $\uparrow$ Insulin in plasma $\rightarrow$ $\uparrow$ $K^+$ into cell

b) $\uparrow$ $H^+$ in ECF $\rightarrow$ $\uparrow$ $K^+$ in ECF

c) $\uparrow$ Osmolarity in ECF $\rightarrow$ $\uparrow$ $K^+$ in ECF

(Due to solvent drag mechanism)
Mechanism of Insulin’s Effect on $K^+$ Movement into cell

1) Stimulates Na, K  ATPase
2) Stimulates glycogen synthesis
3) Stimulates Glycolysis
   (Which increases phosphorylated intermediates of glucose which must be electrically balanced by $K^+$)

Potassium also stimulates insulin release

$K^+$ in Plasma \[\rightarrow\] Insulin Produced

284  285
Figure showing serum potassium concentrations versus body potassium content at various ECF pHs.

Figure showing mechanisms involved in maintenance of normal serum potassium when potassium intake is increased.
Hypokalemia

Serum K+ Value < 3.5 mEq/L

Clinical Manifestations of Hypokalemia

a) Neuromuscular
   Decrease excitability of muscles and nerves
   Weak → Paralysis
   (Mild hypokalemia ~ 2.5 meQ/L) → (Severe hypokalemia < 2.0 meQ/L)

b) GI Symptoms
   Nausea, vomiting, and anorexia due to impaired GI motility
Clinical Manifestations of Hypokalemia

c) **Renal manifestation**

Polyuria
- Mild (with loss of 200 mEq K⁺)
- Severe (with loss of 400-600 mEq K⁺)
  (Urine osmolarity does not rise above isotonicity in severe condition)

Mechanism speculated as either decrease medullary interstitial tonicity or decreased ADH effectiveness

d) **Cardiac**

Decreased excitability of heart muscle cells leading to various arrhythmias

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**Figure 14–5.** Transmission of the cardiac impulse through the heart, showing the time of appearance (in fractions of a second) of the impulse in different parts of the heart.
Figure showing the essential event – SA node cell switching polarity from negative to positive: generation of an action potential

Diagram of how action potential is generated in SA node cell and then how the SA node cell reverts to its starting negative potential.
Summary of mechanism by which the SA node cell goes through a perpetual cycle of generating an action potential and then reverting to its starting potential.

1) $\text{Na}^+$ leaks into cell causing cell to go steadily from $-60 \text{ mV}$ to $-40 \text{ mV}$.
2) At $-40 \text{ mV}$ calcium, sodium gates open causing a surge of $\text{Ca}^{2+}$ and $\text{Na}^+$ to enter cell - cell above $0 \text{ mV}$.
3) Also at $-40 \text{ mV}$ there is a slow closing of the calcium, sodium gates and a slow opening of potassium gates.
4) After a short period of time, the $\text{Na}^+$ flow is cutoff to the interior of the cell and $\text{K}^+$ pours to the outside of the cell. Potential is at $-60 \text{ mV}$.
5) $\text{Na}^+$ leaks into the cell perpetuating the cycle.

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**Figure 10-12.** Propagation of action potentials in both directions along a conductive fiber.
How ECF potassium concentration affects heart rate

Causes of Hypokalemia

1. **Diuretics**  
   Loop diuretics and thiazide

2. **GI Loses**  
   a) Vomiting and gastric suction  
   b) Diarrheal (less severe K\(^+\) deficiency than gastric loss)  
   ➢ laxative and enema abuse

3. **Primary Hyperaldosteronism**  
   Adrenal glands autonomous secretion of aldosterone due to an adenoma (benign tumor), hyperplasia (increase in number of cells, normally arranged) or tumor of the adrenal gland.
Causes of Hypokalemia (cont.)

4. Hyperrenism
   a) Renovascular hypertension (renal artery stenosis, malignant hypertension, vasculitis, scleroderma) lead to renal ischemia
   b) Renin secreting tumors in the juxtaglomerular apparatus (rare)
   c) Bartter’s Syndrome – hyperplasia of juxtaglomerular cells
Causes of Hypokalemia (cont.)

5. Increased ACTH (Adrenocorticotropic Hormone) Production

ACTH in addition to causing the increased synthesis and release of deoxycorticosterone, corticosterone, and aldosterone, all of which have mineralocorticoid activity (i.e. leads of increased Na reabsorption by the kidneys)

a) Cushing’s Disease
b) Ectopic ACTH production
c) Enzymatic deficiencies in cortisol synthesis
   11 beta-Hydroxylase Deficiency
   17 α-Hydroxylase Deficiency

Hypothalamic release of CRF, which causes the pituitary gland to release ACTH, which causes the adrenal glands to release cortisol, which then has a negative feedback effect on the hypothalamus, shutting down CRF release, which ultimately shuts off further production of cortisol.
Causes of Hypokalemia (cont.)

6. **Shift of potassium into the cell**
   a) Insulin therapy for diabetics
   b) Alkalosis

7. **Decreased Potassium intake**
Causes of Hypokalemia (cont.)

8. Other
   a) Renal Tubular Acidosis
      (condition of impaired distal H+ secretion)
   b) Hypokalemic Periodic Paralysis
      (shift of K+ into cell - unknown mechanism)
   c) Excessive Licorice
      (contains glycyrrhizic acid which has mineralocorticiod activity)
   d) Hypomagnesemia (mechanism not understood)
   e) Losses of potassium through skin
      - Excessive sweating
      - Burns

Treatment of Hypokalemia

Mild Cases
   Oral dose  40 mEq  2-3x daily
   Note: Only given if patient’s renal excretion is intact
         (at least 1400 mL/day)

Severe Cases
   Infuse  10-20 mEq/hr
   Note: - In extreme cases can go up to 80mEq/15min
         - Gradually replete and stop infusion and replace
           with oral treatment as soon as symptoms abate
Hyperkalemia

Serum $[K^+] > 5$ mEq/L

Clinical Manifestations of Hyperkalemia

a) **Neuromuscular** (non-specific, may or may not be present)
   - Lassitude, fatigue, weakness
   - Mental confusion, paresthesia
   - Paralysis (in very severe cases)

b) **Heart**

Hyperexcitability of heart muscle leads to various arrhythmias

$[K^+] > 7.5$ mEq/L is life threatening
### Causes of Hyperkalemia

1) Renal Failure (Acute usually not Chronic)
   - In chronic renal failure hyperkalemia is uncommon because $K^+$ is excreted by secretion and not dependent on GFR
   - Hyperkalemia can result from additional factors in addition to chronic renal failure
     a) Substantial dietary $K^+$
     b) Aldosterone decreased
     c) Certain drugs (spironolactone, triamterene, amiloride)
     d) End stage chronic renal failure

### Causes of Hyperkalemia (cont.)

2) Adrenal Insufficiency
   a) Addison’s disease (Primary Adrenal Insufficiency)
   b) 21–hydroxylase deficiency
   c) Hypopituitarism
   d) Bilateral adrenalectomy
Causes of Hyperkalemia (cont.)

3) Hyporeninemic hypoaldosteronism
   - Caused by damage to cells of juxtaglomerular apparatus and/or damage to tubular cells engaged in K⁺ secretion
   - Most common causes are diabetic nephropathy or tubulo-interstitial disease

4) Other selective aldosterone deficiencies

5) Acidosis

6) Rapid release of cellular K⁺
   a) Massive tissue injury
   b) Chemotherapy of lymphoma, leukemia, multiple myeloma
   c) Arginine or other cationic infusion (uptake causes cell to release K⁺)
   d) Familial periodic paralysis (muscular paralysis resulting from shift of K⁺ out of muscle cells)
      Precipitated by muscular exercise, cold, high K⁺ intake

7) Excessive K⁺ intake (Hyperkalemia occurs only with compromised kidney function)

8) Blood transfusions: if aged or red blood cells are not washed effectively
Causes of Hyperkalemia (cont.)

9) Drugs
   Spironolactone
   Triamterene
   Amiloride
   K+ sparing diuretics

10) Pseudohypaldosteronism (unresponsive to aldosterone)

Pseudohyperkalemia

1) Hemolysis after sample collection

2) Thrombocytosis (Increased number of platelets in blood) or Leukocytosis (Increased number of leukocytes in blood)
   - Released during blood clotting
   - Plasma should thus be run

3) Use of tourniquet with vigorous fist action