YU - Medicine Passion Academic Team

The Urogenital System

Sheet# 1 - Physiology (Part 1)

Lec. Title : Glomerular Filtration

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Glomerular filtration

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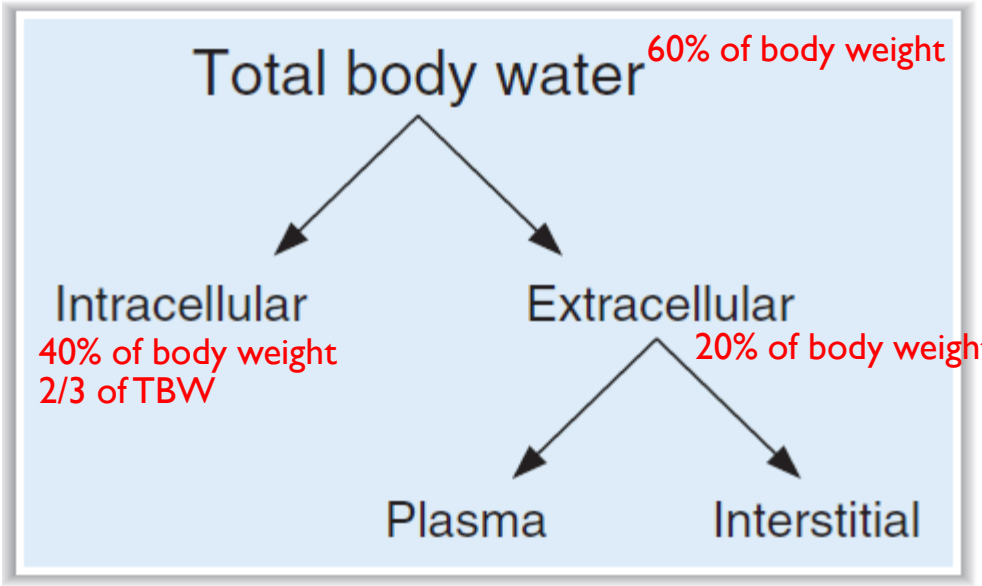
دعواتكم ، كل الحُبّ...

Body fluids

- Total body water (TBW) is approximately **60% of body weight.**
- The percentage of TBW varies, depending on the amount of adipose tissue in the body (**inversely).** So, it's **highest in newborns and thin adult males and lowest in obese adult females**.
- Changes in body weight can be used to estimate changes in body water contents.

Distribution of water

- Total body water is distributed between two major compartments: **intracellular fluid (ICF)** and **extracellular fluid (ECF).**
- **60-40-20 rule..** Shown in the Fig.



Body fluid compartments.

Distribution of water

- the volumes of the body fluid compartments are measured by the **dilution method.**
- The basic principle is that a marker substance will be distributed in the body fluid compartments according to its physical characteristics.

E.g. a large molecular weight sugar such as **mannitol** cannot cross cell membranes and it will be distributed in ECF but not in ICF. Thus mannitol is a **marker for ECF volume.**

In contrast, **isotopic water** (e.g., deuterium oxide [D2O]) will be distributed **everywhere** that it is used as a marker for total body water.

table Body Water and Body Fluid Compartments

Body Fluid Compartment	Fraction of TBW*	Markers Used to Measure Volume	Major Cations	Major Anions
TBW	1.0	Tritiated H_2O D_2O Antipyrene		
ECF	1/3	Sulfate Inulin Mannitol	Na^+	Cl^- HCO_3^-
Plasma	1/12 (1/4 of ECF)	RISA Evans blue	Na^+	Cl^- HCO_3^- Plasma protein
Interstitial	1/4 (3/4 of ECF)	ECF–plasma volume (indirect)	Na^+	Cl^- HCO_3^-
ICF	2/3	TBW–ECF (indirect)	K^+	Organic phosphates Protein

* Total body water (TBW) is approximately 60% of total body weight, or 42 L in a 70-kg man. ECF = extracellular fluid; ICF = intracellular fluid; RISA = radioiodinated serum albumin.

Shifts of water between compartments

- The **volume** of a body fluid compartment depends on the amount of solute it contains (shown in the previous table.) e.g. volume of ECF determined by *amount* of NaCl and sodium bicarbonate (NaHCO3) it contains
- **Osmolarity** is is the concentration of osmotically active particles.
- **Plasma osmolarity (P_{osm})** is estimated from the plasma [Na+], plasma [glucose] and blood urea nitrogen (BUN), as these are the major solutes of ECF and plasma:

$$P_{osm} = 2 \times Na^{+} + Glucose/18 + BUN/2.8$$

- *where:*

P_{osm} = plasma osmolarity (mOsm/L)

Na^{+} = plasma Na^{+} concentration (mEq/L)

Glucose = plasma glucose concentration (mg/dL)

BUN = blood urea nitrogen concentration (mg/dL)

- The Na+ concentration is multiplied by 2 because Na+ must be balanced by an equal concentration ofanions. (In plasma, these anions are Cl− and HCO)
- The glucose concentration in mg/dL is converted to mOsm/L when it is divided by 18.
- The BUN in mg/dL is converted to mOsm/L when it is divided by 2.8.

- At steady state, **ECF osmolarity and ICF osmolarity are equal.(**osmolarity is the same throughout the body fluids)
- To achieve this equality, **water shifts freely** between the ECF and ICF compartments.
- if a disturbance occurs to change the ECF osmolarity, water will shift across cell membranes to make the ICF osmolarity equal to the new ECF osmolarity
- Solutes such as NaCl, $NaHCO_3$ and mannitol do not cross cell membranes readily and are assumed to be confined to ECF.
- if a person ingests a large quantity of NaCl, that NaCl will be added only to the ECF compartment and the total solute content of the ECF will be increased.

Six disturbances of body fluids

before u study the next 3 slides, u should know these things:

- **Volume contraction** means **a *decrease*** in **ECF** volume.
- **Volume expansion** means an **increase** in ECF volume.
- **isosmotic** disturbance means that there is **no change in ECF osmolarity**
- **hyperosmotic** disturbance means that there has been an **increase in ECF osmolarity**
- **hyposmotic** disturbance means that there has been a **decrease in ECF** osmolarity.

- In *Isosmotic Volume Expansion—Infusion of NaCl:*

- Because NaCl is an extracellular solute, all of the **isotonic NaCl solution is added to the ECF,** causing an increase in ECF volume but **no change in ECF osmolarity** (**no shift** of water between ICF and ECF.). Both plasma protein concentration and hematocrit will decrease (the increase in blood volume, which is one of ECF compartments.)

- In *Isosmotic Volume Contraction—Diarrhea:*

- The osmolarity of the fluid lost from GIT is approximately equal to that of the ECF. (loss **of isosmotic fluid** from ECF), ECF volume decreases, no change in ECF osmolarity, no fluid shift. Both plasma protein concentration and hematocrit will increase (the decrease in blood volume)

- In *Hyperosmotic Volume Expansion _ High-NaCl Intake:*

- Increase the total amount of solute in the ECF, **ECF osmolarity increases**, (**Transiently**, ECF osmolarity **is higher** than ICF osmolarity, which causes **water to shift from ICF to ECF**), **In the new steady state**, **both** ECF and ICF osmolarities will be **higher** than normal and **equal to each other**. ICF volume will decrease and **ECF volume will increase**, both plasma protein concentration and hematocrit will decrease.

- In *Hyperosmotic Volume Contraction _ Water Deprivation, sweat & heat:*

- **sweat is hypoosmotic** relative to ECF (contains more water), Because **hypoosmotic fluid is lost** from the ECF, **ECF volume decreases** and ECF **osmolarity increases** (the same as previous point). But, **hematocrit is unchanged** (Loss of fluid from ECF alone would cause an increase in the "concentration" of red blood cells, but with the presence of water shift toward the ECF, the net result will be unchanged).

- In *Hyposmotic Volume Expansion—SIADH*

- A person with **syndrome of inappropriate antidiuretic hormone (SIADH)** secretes high levels of (ADH), promotes water reabsorption, the excess water is distributed throughout (TBW), **ECF & ICF volumes increase** (follow the consequences). But **hematocrit is unchanged** as a result of two offsetting effects (dilution & water shifts into red blood cells)

- In Hyposmotic Volume Contraction _ Adrenal Insufficiency:

- Comes with **aldosterone difficiency**, excess NaCl is excreted in the urine, **ICF osmolarity decrease** (follow the consequences)

Examples of shifts of water between compartments

table Changes in Volume and Osmolarity of Body Fluids

Type	Key Examples	ECF Volume	ICF Volume	ECF Osmolarity	Hct and Serum [Na^+]
Isosmotic volume expansion	Isotonic NaCl infusion	↑	No change	No change	↓ Hct –[Na^+]
Isosmotic volume contraction	Diarrhea	↓	No change	No change	↑ Hct –[Na^+]
Hyperosmotic volume expansion	High NaCl intake	↑	↓	↑	↓ Hct ↑ [Na^+]
Hyperosmotic volume contraction	Sweating Fever Diabetes insipidus	↓	↓	↑	–Hct ↑ [Na^+]
Hyposmotic volume expansion	SIADH	↑	↑	↓	–Hct ↓ [Na^+]
Hyposmotic volume contraction	Adrenal insufficiency	↓	↑	↓	↑ Hct ↓ [Na^+]

– = no change; ECF = extracellular fluid; Hct = hematocrit; ICF = intracellular fluid; SIADH = syndrome of inappropriate antidiuretic hormone

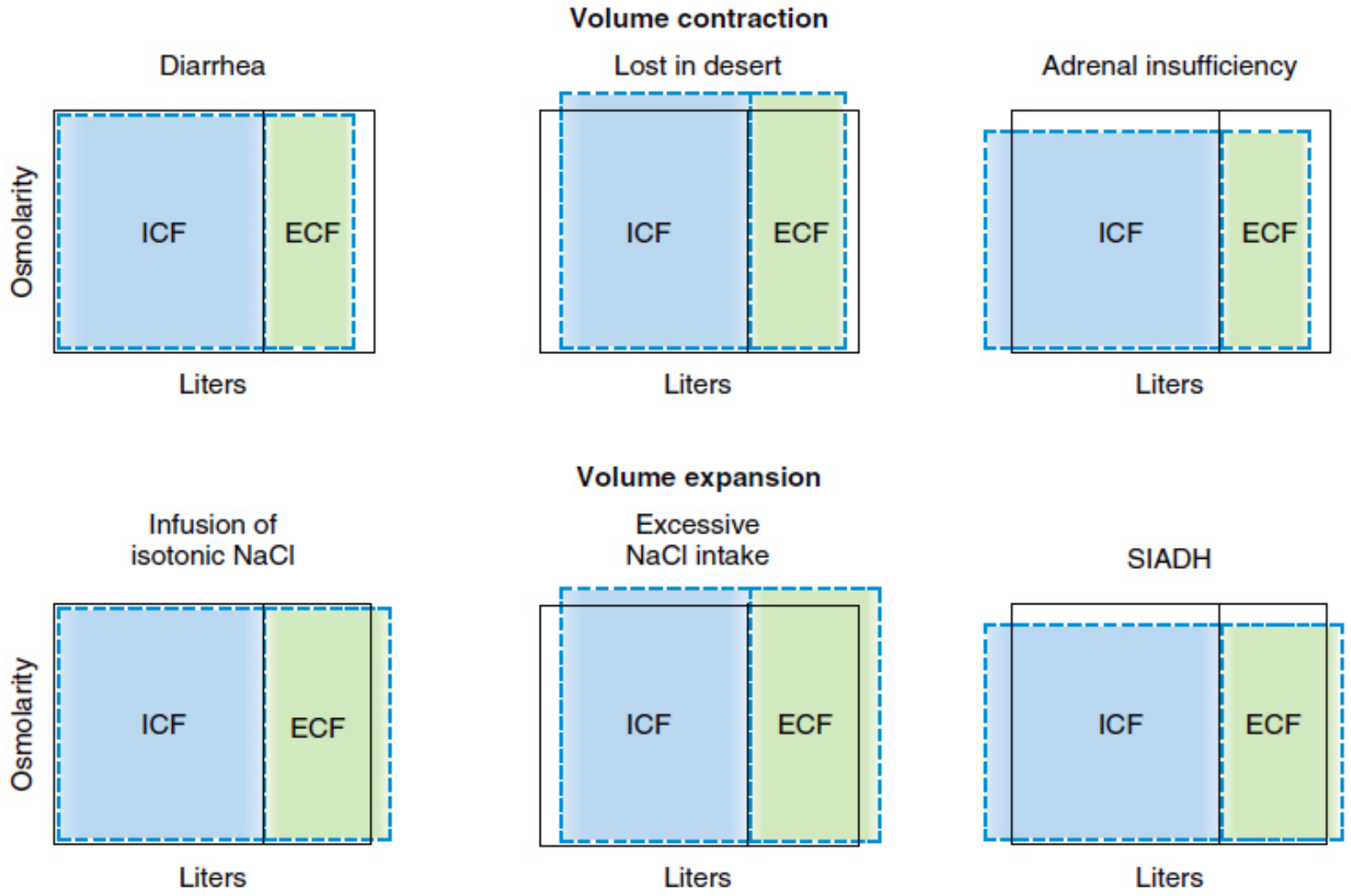
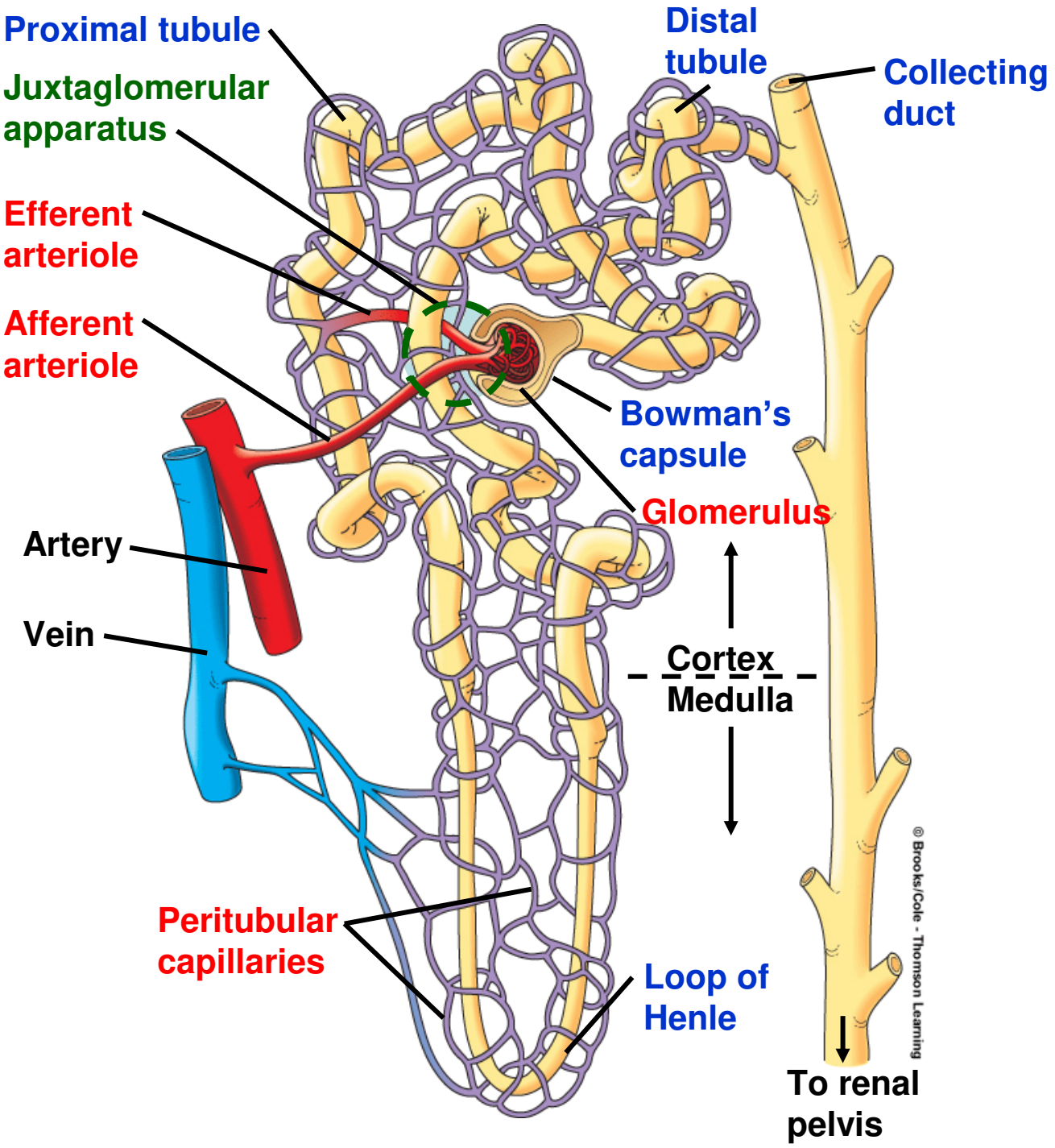


FIGURE 5.2 Shifts of water between body fluid compartments. Volume and osmolarity of normal extracellular fluid (ECF) and intracellular fluid (ICF) are indicated by the *solid lines*. Changes in volume and osmolarity in response to various situations are indicated by the *dashed lines*. SIADH = syndrome of inappropriate antidiuretic hormone.

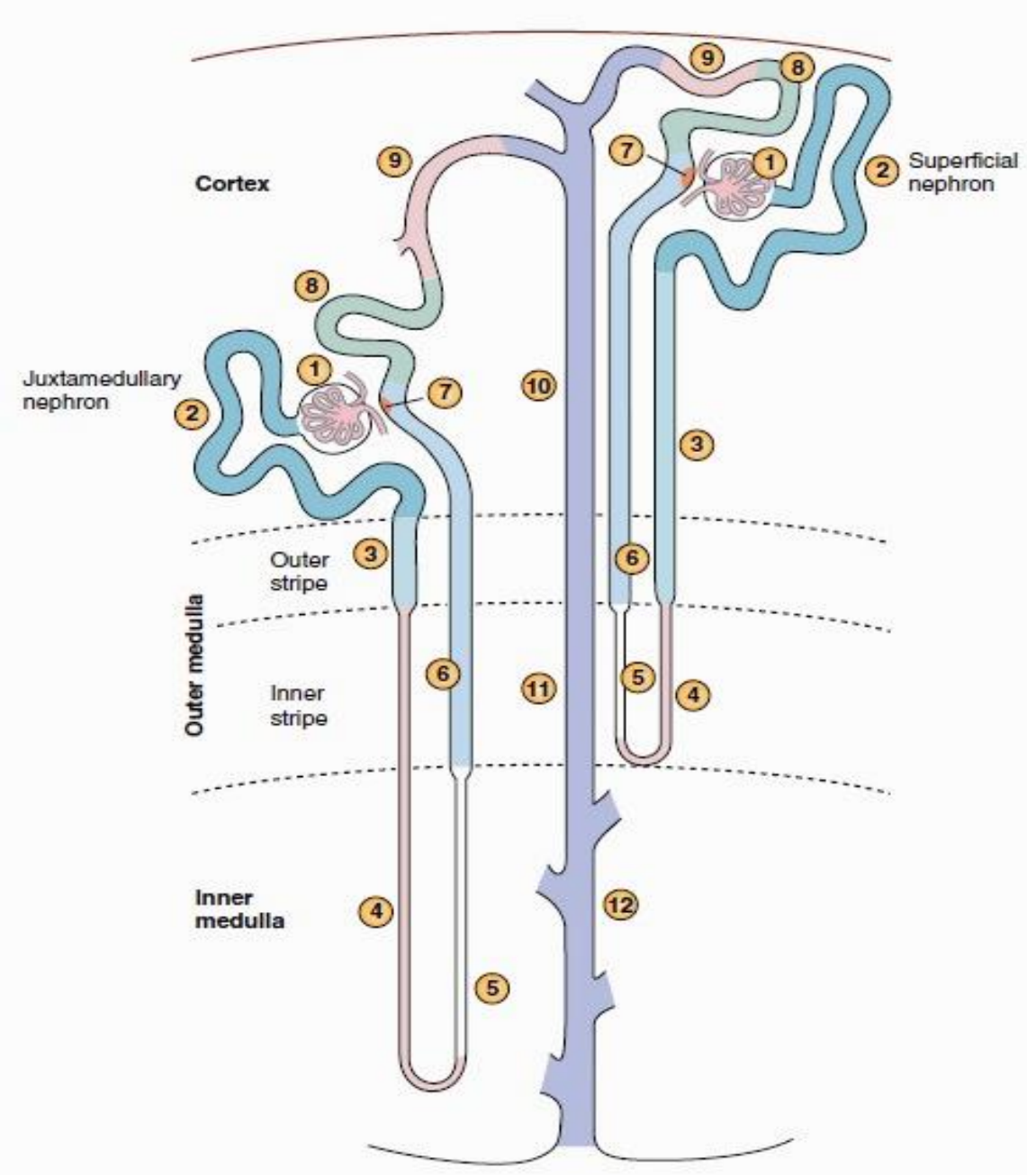
Renal Clearance,

Renal Blood Flow (RBF) and

Glomerular Filtration Rate (GFR)


Proximal tubule
Juxtaglomerular apparatus
Efferent arteriole
Afferent arteriole
Artery
Vein
Peritubular capillaries
Distal tubule
Collecting duct
Bowman's capsule
Glomerulus
Cortex
Medulla
Loop of Henle
To renal pelvis
© Brooks/Cole - Thomson Learning

You need to know this details…



Segments of the Nephron

1. Glomerular capillaries and Bowman's space
2. Proximal convoluted tubule
3. Proximal straight tubule
4. Thin descending limb
5. Thin ascending limb
6. Thick ascending limb
7. Macula densa
8. Distal convoluted tubule
9. Connecting tubule
10. Cortical collecting duct
11. Outer medullary collecting duct
12. Inner medullary collecting duct

- Three **basic processes** occur in the nephrons and they are:

1. glomerular filtration
2. tubular reabsorption
3. tubular secretion.

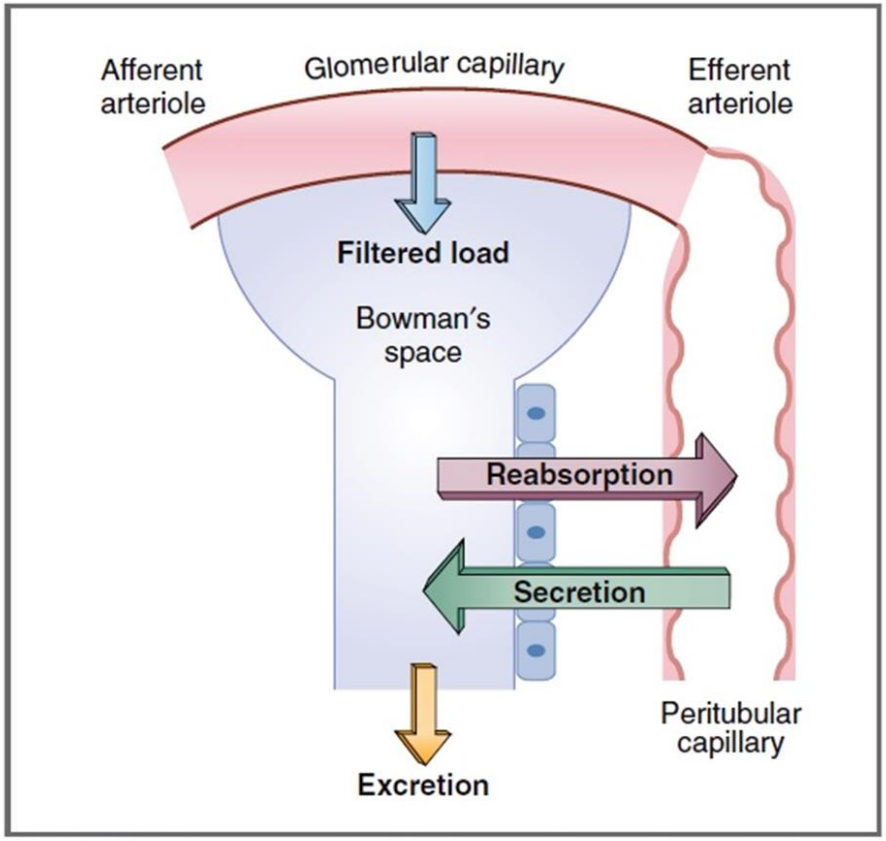


Fig. 6.12 Processes of filtration, reabsorption, and secretion in a nephron. The sum of the three processes is excretion.

Renal clearance

- Indicates the volume of plasma cleared of a substance per unit time.
- The units of clearance are **mL/min or mL/24 hour.**

$$C = \frac{UV}{P}$$

where:

C = clearance (mL/min or mL/24 hour)
U = urine concentration (mg/mL)
V = urine volume/time (mL/min)
P = plasma concentration (mg/mL)

- Substances with the **highest renal clearances may be completely removed** on a single pass of blood through the kidneys;
- substances with **the lowest renal clearances are not removed at all.**

Renal blood flow (RBF)

- Is 25% of the cardiac output. (if the cardiac output equals 5 liters, then 1.25 liters will be the RBF)
- RBF is **directly proportional to the pressure difference** between the renal artery and the renal vein, and **is inversely proportional to the resistance** of the renal vasculature.
- The major mechanism for changing blood flow (in kidney) is by changing afferent arteriolar resistance and/or efferent arteriolar resistance.

Factors affecting RBF

1. **Sympathetic nervous system and circulating catecholamines.**

- Both afferent and efferent arterioles are innervated by sympathetic nerve fibers that produce **vasoconstriction by activating α_1 receptors.**
- **α_1 receptors are more on *afferent* arterioles**, increased sympathetic nerve activity causes a decrease in the blood that enters the nephrone, as a result **decreasing in both RBF and glomerular filtration rate (GFR)**.
- Example: response to haemorrhage (our bodies do that to save the blood for brain mainly, but raise arterial pressure even at the expense of blood flow to the kidneys save the nephrons.)

2. Angiotensin II

- Angiotensin II is a potent **vasoconstrictor** of **both** afferent and efferent arterioles → **increases resistance** → **decreases RBF.**
- However, *efferent* arterioles are more sensitive to angiotensin II than *afferent* arterioles, so:
  - **low levels** of angiotensin II produce an ***increase in GFR*** (by preferentially constricting sensitive efferent arterioles),
  - **high levels** of angiotensin II produce a ***decrease in GFR*** (by constricting both afferent and efferent arterioles).

Angiotensin II levels are increased in haemorrhage, causing further decrease in RBF & GFR.

3. Atrial natriuretic peptide (ANP)

- ANP and related substances such as brain natriuretic peptide (BNP) **cause dilation of afferent arterioles (more blood to the nephron)** and **constriction of efferent arterioles (less resistance)**.
- **Dilatory** effect of ANP on *afferent* arterioles is **greater** than the constrictor effect on *efferent* arterioles → overall decrease in renal vascular resistance → **increase in RBF.**

- Dilation of afferent arterioles and constriction of efferent arterioles both lead to **increased GFR**.

4. Prostaglandins

- Several prostaglandins (e.g., prostaglandin E_2 and prostaglandin I_2) are produced locally in the kidneys and cause **vasodilation of** both afferent and efferent arterioles.
- The vasodilatory effects of prostaglandins are clearly protective for RBF.
  - Prostaglandins **attenuate** the vasoconstriction produced by the sympathetic nervous system and angiotensin II. Unopposed, this vasoconstriction can cause a profound reduction in RBF, resulting in renal failure.
- **Nonsteroidal antiinflammatory drugs (NSAIDs)** inhibit synthesis of prostaglandins and therefore interfere with the protective effects of prostaglandins on renal function following a hemorrhage.

5. Dopamine

- Dopamine, a precursor of norepinephrine, has selective actions on arterioles in several vascular beds.
- At low levels, dopamine *dilates* cerebral, cardiac, splanchnic, and renal arterioles, and it *constricts* skeletal muscle and cutaneous arterioles.
  - ➢ protective (vasodilatory) effect on blood flow in several critical organs including the kidneys.

- **Bradykinin** and **nitric oxide** also causes vasodilation of renal arterioles.
- ACE drugs increase bradykinin so they can regulate PB & protect the kidney… so it's the best for diabetic patients.

Autoregulation of RBF

- Is accomplished by **changing renal vascular resistance**. If arterial pressure changes, a proportional change occurs in renal vascular resistance to maintain a constant RBF.
- RBF remains constant over the range of arterial pressures from **80 to 200** mm Hg **(autoregulation).**
- **The mech. Is not cleare and not related to ANS! (**transplanted kidney can do that!)
- **We have 2 hypothesis:**

1. **Myogenic** mechanisms: renal afferent arterioles contract in responce to **stretch** (opening of stretch-activated calcium (Ca2+) channels in the smooth muscle cell membranes)→ ↑ resistance
2. **Tubuloglomerular** feedback: ↑ renal arterial pressure → ↑ **fluid delivery to macula densa** → constriction of the nearby afferent arteriole → ↑ resistance.

- Of clinical importance is the effect of a **high-protein diet** to increase GFR by: increasing Na+ and Cl− reabsorption **proximal** to the macula densa, thus **decreasing** Na+ and Cl− delivery to the macula densa and, via tubuloglomerular feedback, causes an decrease in risistance, as a result increasing in GFR.

Measurement of RBF

- Measurement of RBF depends on the measurement of clearance of **para-aminohippuric acid (PAH)** → filtered and secreted by renal tubules, but not reabsorbed → almost all of the PAH entering the kidney via the renal artery is excreted in urine.

- First, renal plasma flow (RPF) is calculated as follows:

$$\text{Effective RPF} = \frac{[U]_{PAH} \times \dot{V}}{[P]_{PAH}} = C_{PAH}$$

where

Effective RPF = Effective renal plasma flow (mL/min)

$[U]_{PAH}$ = Urine concentration of PAH (mg/mL)

$\dot{V}$ = Urine flow rate (mL/min)

$[P]_{PAH}$ = Plasma concentration of PAH (mg/mL)

C_{PAH} = Clearance of PAH (mL/min)

- Then, RBF is calculated using the hematocrit (Hct) as follows:

$$RBF = \frac{RPF}{1 - Hct}$$

where

RBF = Renal blood flow (mL/min)

RPF = Renal plasma flow (mL/min)

Hct = Hematocrit

SAMPLE PROBLEM. A man with a urine flow rate of 1 mL/min has a plasma concentration of PAH of 1 mg%, a urine concentration of PAH of 600 mg%, and a hematocrit of 0.45. *What is his RBF?*

SOLUTION. Because values are not given for renal artery and renal vein concentrations of PAH, *true* RPF (and true RBF) cannot be calculated. However, *effective* RPF can be calculated from the clearance of PAH. Effective RBF can then be calculated by using the hematocrit. Remember, *mg%* means mg/100 mL.

$$\text{Effective RPF} = C_{PAH}$$

$$= \frac{[U]_{PAH} \times \dot{V}}{[P]_{PAH}}$$

$$= \frac{600 \text{ mg/100 mL} \times 1 \text{ mL/min}}{1 \text{ mg/100 mL}}$$

$$= 600 \text{ mL/min}$$

$$\text{Effective RBF} = \frac{\text{Effective RPF}}{1 - \text{Hct}}$$

$$= \frac{600 \text{ mL/min}}{1 - 0.45}$$

$$= \frac{600 \text{ mL/min}}{0.55}$$

$$= 1091 \text{ mL/min}$$