Sheet ○ Slide ○ Handout

Number

3

Subject

GFR

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Price:

This sheet was written according to section 1 records with a different arrangement.
Main topics; revision, GFR, Autoregulation and Nephrotic syndrome.

❀ *Revision*

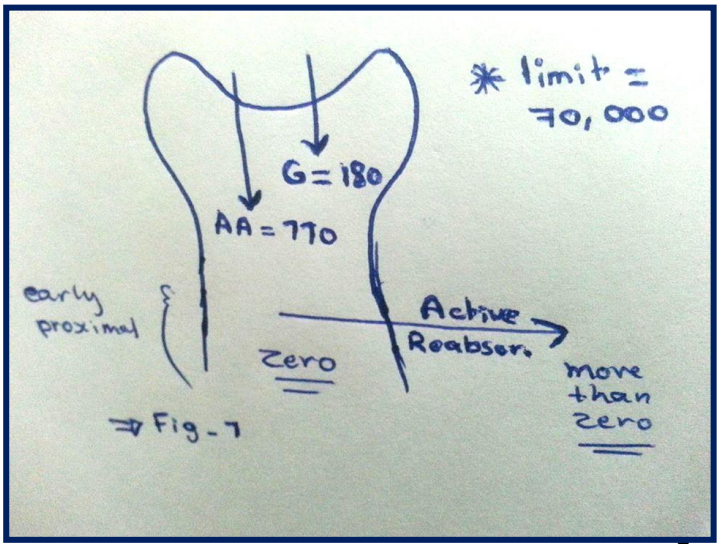
* Remember that **Filtration** is the main function of the kidney.
last time we talked about ways to measure the **GFR**, there is what's called **true GFR;** the **problem** with it is → it requires **24 hour urine collection**, so we estimate the GFR (**eGFR**) using 2 equations; **Schwartz equation for children** and **adult equation**.
There are other equations, each for certain purpose→if the kidney is normally functioning there is an equation , if there is late stage renal failure there is another one **(**we don't care which equation for which purpose-it's a waste of time & effort-, just know that **we have different equations, and these equations are used for different situations/conditions.)**
In end stage renal failure the **Creatinine overestimates the GFR**.

***Not mentioned in the lecture**
Creatinine is removed from plasma by Glomerular filtration into the urine without being reabsorbed by the tubules to any significant extent. Renal tubular secretion also contributes a small quantity of Creatinine to the urine. As a result, Creatinine clearance often overestimates the true Glomerular filtration rate (GFR) by 10% to >20%. (It's not only filtered, it's also secreted).
In renal failure there is no Creatinine filtration but there is secretion that overestimates the GFR.

We don't like too much GFR neither too little GFR,why?

Fig-1→ This is the tubule, glucose **(G)** is freely filtered **(**its molecular weight **= 180)**and amino acids **(AA)** are freely filtered **(**the average molecular weight of the 20 AA in our body **= 110**; some AA are small others are big**)**.We need both **G** and **AA**, so we are going to **reabsorb them from the early proximal tubule**→ reabsorbing them *totally*, so there concentration in the proximal tubule become **zero**, and outside it will be **more than zero**→it has to be **active transport**.

*Our limit of molecular weight **= 70,000**



Any active transport (primary active or secondary active**) has T max**(transport maximum); it means if you deliver too much glucose (because you have too much GFR) some of this glucose might escape the receptors & not be reabsorbed, it will be excreted in the urine causing **glucosuria**(glucose in the urine),or you deliver too much amino acids causing **aminoaciduria** (amino acid in the urine). AA is the building block for the proteins we cannot tolerate losing it.

So, too much **GFR** means too much **filtered load** of the substance, and roughly it's **beyond the capacity of the reabsorbing receptors** to take care of this.

Too little GFR is bad, because waste products (like urea, Creatinine, uric acid) are going to stay in the blood and accumulate in the body.

➔ ***GFR must remain relatively constant; not too much high losing valuable substances, and not too much low retaining waste products.***

❀ *What is **GFR**?*

It's the volume of plasma filtered moving from the glomerular capillaries to bowman space.

So, it's a **Flow**→*because itsvolume per unit time* and it follows **ohms law.**

Flow = GFR = DF * K (**DF**: Driving Force, **K**: permeability or filtration coefficient)
→ **GFR can increase or decrease by changing DF or K or both.**

Again, too much GFR is bad & too little GFR is bad -الفضيلة تقع بين رذيلتين- so we must maintain **normal GFR**, to do that we should know the 2 factors that manipulatethe GFR; **DF** and **K.**

❀ *Driving force is **thestarling forces**, what are these forces (fig-2)?*

1) **P_{GC}**= Glomerular capillary hydrostatic pressure = **60** mmHg (very high)
✓ **Hydrostatic pressure in systemic capillary = 30 mmHg**
(At the arterial end = 40, at the venous end= 20)
✓ **In lung it's from 7-10 mmHg**

This force is favoring filtration.

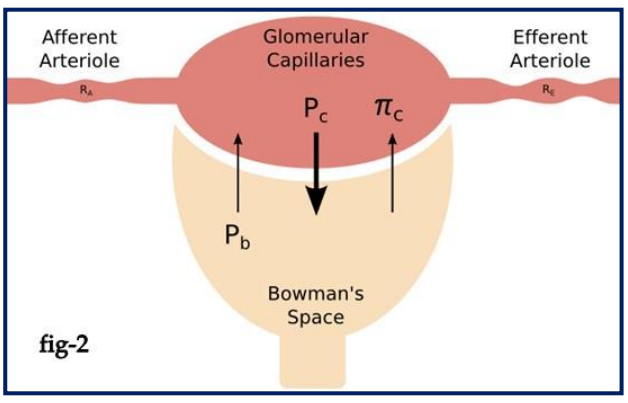
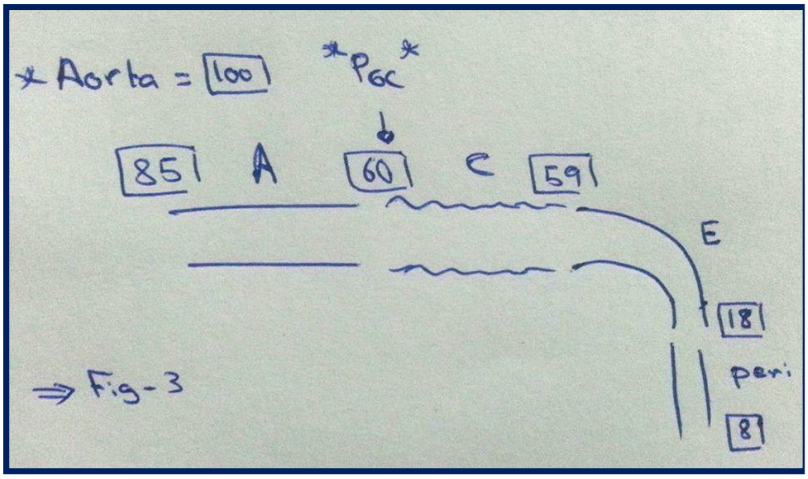


fig-2

Fig-3→ in the major artery (**aorta**) P=**100**, reaching the **beginning** of the **afferent** arteriole P=**85**, at the **end** of the afferent P=**60** (which is the Glomerular) in **capillary** from 60 to 59; only 1 mmHg difference, to the efferent from 59 to 18 (too much drop).

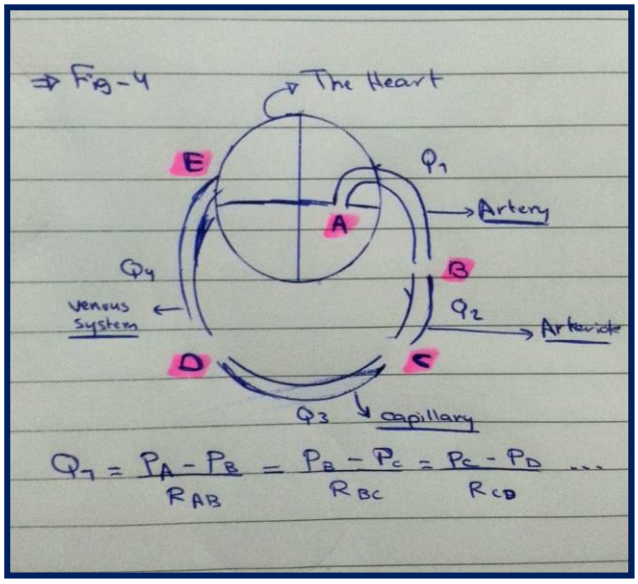


❀ Important recap from CVS:

Most of the total peripheral resistance resides in the **arteriole**, why?

Because the **major drop in arterial pressure** (BP) is across the arteriolar end, what does that mean?

Fig-4→the circle is the heart, arteries are coming out of it, followed by the arteriole, capillary and vein. From A-B all cardiac output will pass (5L) = Q_1, same 5L pass from B-C (Q_2), from C-D (Q_3)and from D-E (Q_4)



→$\mathbf{Q_1}$ = $(P_A-P_B)/R_{AB}$ = $\mathbf{Q_2}$ = $(P_B-P_C)/R_{BC}$ and so on … (rem. Q=flow=P/R)

If the **pressure** is low somewhere → it's because the **resistance** is low there, and if the pressure is high → it's because the resistance is high, take this example: how to know the strength of contraction in the biceps (the tone of the muscle)? Well, if the muscle is holding a heavy object, it will be more tensed (more tone) and vice versa. So you will need **so much force if you're facing so much resistance** because you're transporting the same volume of blood (5L).

So, because we need too much pressure difference, it means we are facing too much resistance. We will apply the same principle here.

Back to **fig-3**→in **peri**tubular capillary, pressure will drop from 18 to **8** mmHg. Now, we can tell that **most resistance** occurs at the level of **afferent** arteriole and **efferent** arteriole, because there is **25** mmHg drop in the pressure (at the level of afferent) and **42** mmHgdrop (at the level efferent).

So, most of the vascular resistance in the kidney resides in the afferent and the efferent arterioles.

❀ *cont. starling forces*

2) π_{GC}: thecolloid osmotic pressure of the glomerular capillary blood = **32** mmHg

✓ It equals **28** mmHg in systemic capillary (at **both** arterial and venous end).***why?***

Fig-5→In ***systemic circulation***-at the level of the capillary- there is **20L** that are **filtered** per day, **17L** are reabsorbed per day and **3L** are retained through the lymphatic (numbers are important).

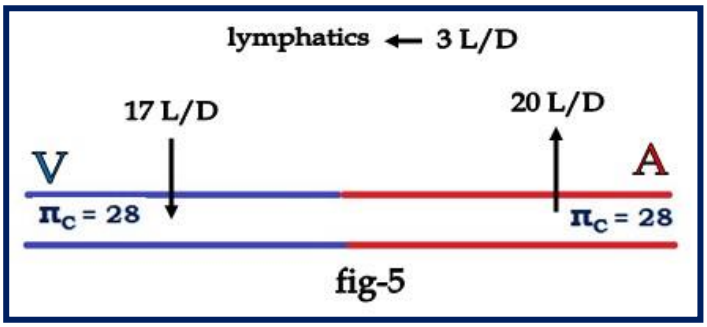


fig-5

- In proteins, π_C is directly proportional to ΔC (osmotic pressure∝concentration**).** (Δ**C**is measured by molar or osmolar as we care about **number** of particles not the size).
- There is **more filtration** than reabsorption at the capillary two ends, so the protein should me **more concentrated**, and subsequently π_C **should be higher** (**π_C**and**Δ**C**aredirectly proportional to each other**)**.Although this, π_C **remains 28**, ***how come?!***

➔ well, we have3 facts:

✓ There is more filtration than reabsorption

✓ π_C is directly proportional to ΔC (osmotic pressure ∝ concentration)

✓ $\pi_C$remain the same (doesn't fit with the previous facts) 🤔

ANS: filtration didn't affect the concentration; the amount filtered is so small and have no effect! More explanation:

Amount of ***plasma*** *that reach the capillary* ***per day=***
*2L/min (out of the 5L/min cardiac output) * **60** min/h * **24** h/day = 2280 L/D.*
You are talking about almost 3000 L/D passing the capillary, what is the significance of20L filtered? Its only **0.5**% change in volume (this 0.5% is called **filtration fraction**) that will not affect the concentration. (**Π_C** might change from **28** to **28.1**→ not a significant change so we say *it* ***remains 28*** *because concentration remains the same*).

Fig-6→In ***kidney***, filtration fraction = **20**%(650 ml enter, 125 ml is filtered → 125/650=20%), this **20% is significant** as π_{GC}at the beginning = 28, and at the end= 36 so on average π_{GC} **= 32**.

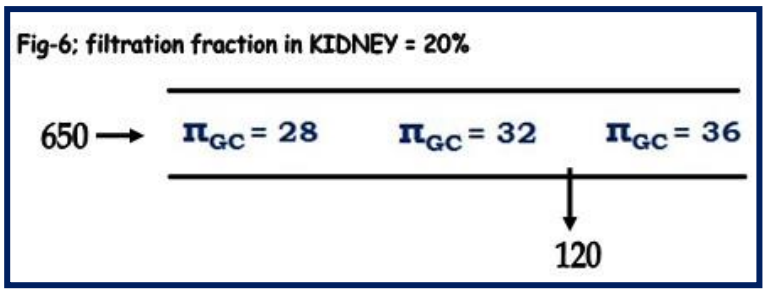
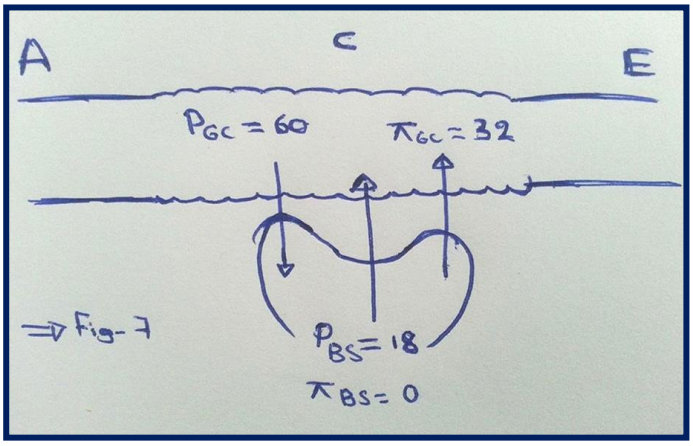


Fig-7 → Again, one force favoring **filtration** which is the **hydrostatic pressure** =60 and the second force opposing filtration which is the **colloid osmotic pressure** due to **albumin**, ***why albumin?***

- ✓ Because 2 grams of albumin contain **more number of molecules**than 2 grams of globulin, we don't care about the size of the molecule, we care about the **number**; the size influence the movement, large particles have slow movement and small particles have fast movement → eventually movement is the same. (They attract the same number of both molecules; the big ones and the small ones). So we care about the albumin mainly because it have **smaller molecular weight** (70 kDa in comparison with the 250 kDa molecular weight of globulin)
- ✓ In addition albumin is almost double **concentrated** (all plasma proteins are 6-8g/dl, albumin alone accounts for 3.5-5.5 g/dl).

P_{GC} and π_{GC} are forces inside the capillary, what about the forces outside?

- ➔ **Bowman's space hydrostatic pressure (P_{BS})=18**
- ➔ **Bowman's space colloid osmotic pressure (π_{BS}) = zero** because proteins are not filtered.



So we are dealing with **3 forces** instead of four:
GFR = DF * K = (60 – (32+18))* K = **10 mmHg**

- ➔ This 10 mmHg is what we depend on to have **filtration.**

If the arterial pressure = 100 and we have this 10 mmHg as the effective pressure (P_{eff}), does it mean that if the arterial pressure **declines** to 90, 80, 70… (As while sleeping) **P_{eff} will become zero**?? We have a problem, **the arterial blood pressure fluctuates** during

the day ups and downs, so **GFR should fluctuate ups and downs** and that's bad! If I have a small increase in arterial pressurethat lead to small increase in GFR (↑Pc ↑DF ↑**GFR)** I might lose amino acids, glucose or small proteins/peptides for example.

- This takes us to **the concept ofAutoregulation** (fig-8)

If the blood pressure was changed, we notice that **between 70-150 mmHg GFR is constant,** beyond that; any change in **P above 150, GFR will increase** and any change in **P below 70, GFR will decrease**.

So when we work with a patient in a surgery where we open the abdomen and bleeding is everywhere; the surgeon ask to decrease the bleeding by decreasing the pressure, but **never below 70 mmHg**, or else the patient will not urinate after surgery → acute renal failure**.**

So the kidney can tolerate this fluctuation in blood pressure between 70-150 mmHg, i.e. the kidney can manage this problem by itself, and this is called **Autoregulation of GFR.**

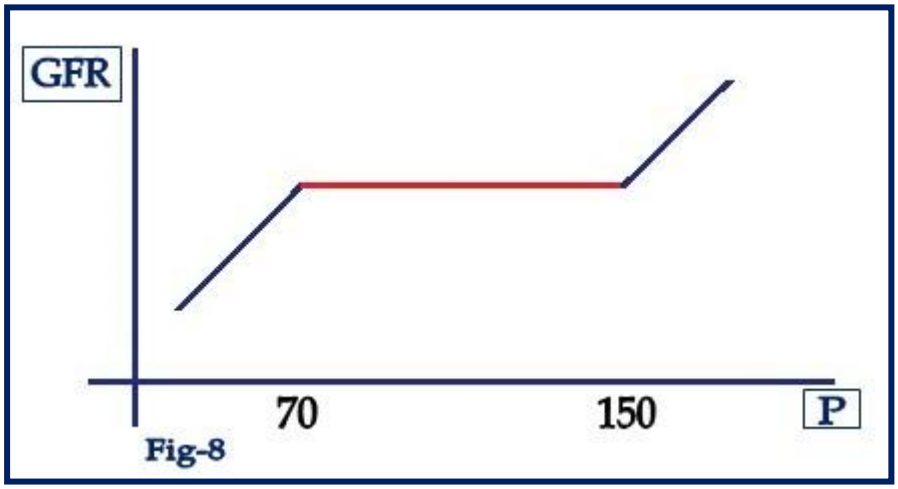


Fig-8

- **Mechanisms of Autoregulation**

Now, how the kidney auto regulate its GFR? We have 2 mechanisms:

1. **Through Afferent and Efferent**
   - ✓ if we **constrict** the efferent then the pressure in the capillary will increase
   - ✓ If we **dilate** the afferent , pressure will increase and if we **constrict** it the pressure will decrease (constriction→↓amount of blood→↓P).

Any **drug** results in **afferent constriction**, it might affect the GFR badly. Prostaglandin dilate the afferent; so any **drug** which **inhibit the production of prostaglandin** like Aspirin, voltaren **(NSAIDs)**are somehow dangerous to the kidney, **before** taking NSAIDs the patient should **test his plasma Creatinine**, and repeat the test after a week, then each 2 weeks, 6 weeks, 3 months if he takes the voltaren for ever (to treat rheumatoid arthritis or bone problem or disc for example). Even if the voltaren had no effect for a year or two, it **doesn't mean** that it will never cause a bad effect; the patient should keep on testing his Pcr as you will never know when the problem will occur.

After age of 40, GFR will decrease 1 ml each year; 80 year old man might have a **normal** GFR of **60-50**. So; **GFR declines with age**. If a patient is taking NSAIDs and his GFR is already declining because of aging, sometimes a small decrease in prostaglandin is enough to decrease GFR significantly. So **we should test Pcr periodically**.

If a patient **Pcr =0.6**, and after taking NSAIDs **Pcr** becomes **1 -**although it still in the normal range (0.6-1.4); but this increase indicate a problem, that's why you should take the baseline **before** the beginning of drug administration, to avoid chronic renal failure.

2. Rennin - AngiotensinSystem

Note: Bleeding will decrease the **GFR**, decrease Na^+ ,K^+ ,CL^- ,Ca^{+2}**filtration** and will decrease **NaCl delivery** to distal tubules.

Fig-9→In the distal tubules we have **specialized cells (sensory cells)** that sense how much Na^+ is being delivered to that part, these are dark cells called **macula densa** cells , they sense **the GFR** and send impulses to their neighboring cells; afferent and efferent, where they have what's called **juxtaglomerular cells**→granular cells that secrete **rennin**.

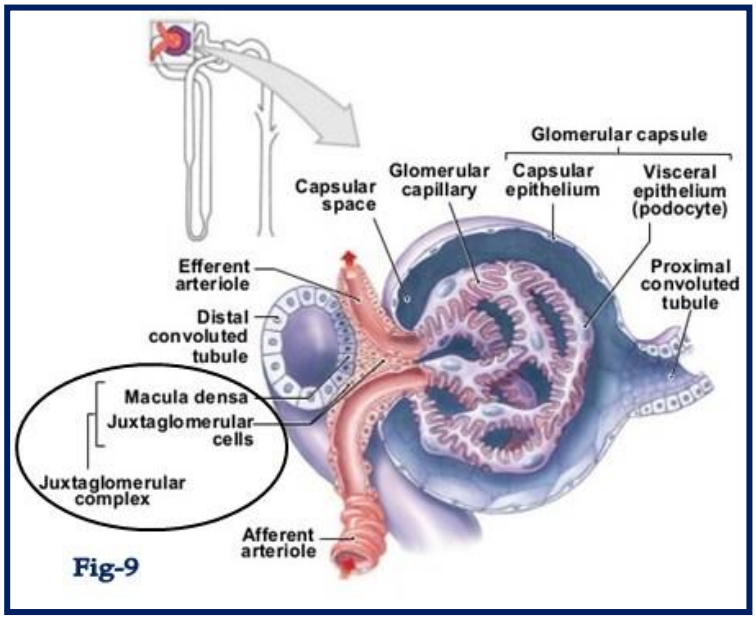


Fig-10→Rennin now is secreted from the kidney then it leaves the kidney and goes to the systemic circulation,in **the systemic circulation**; Rennin will work on **angiotensinogen**(secreted from the **liver** and contain **14** amino acids) and cut 4 amino acids out of it forming **angiotensin I** (decapeptide, contain **10** amino acids), then in the **lung**, another scissors called **angiotensin converting enzyme** (ACE) will form **angiotensin II** (octapeptide, contain 8 amino acids).

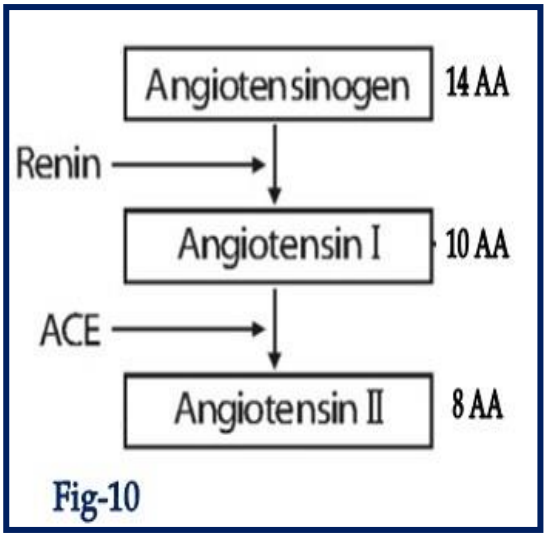


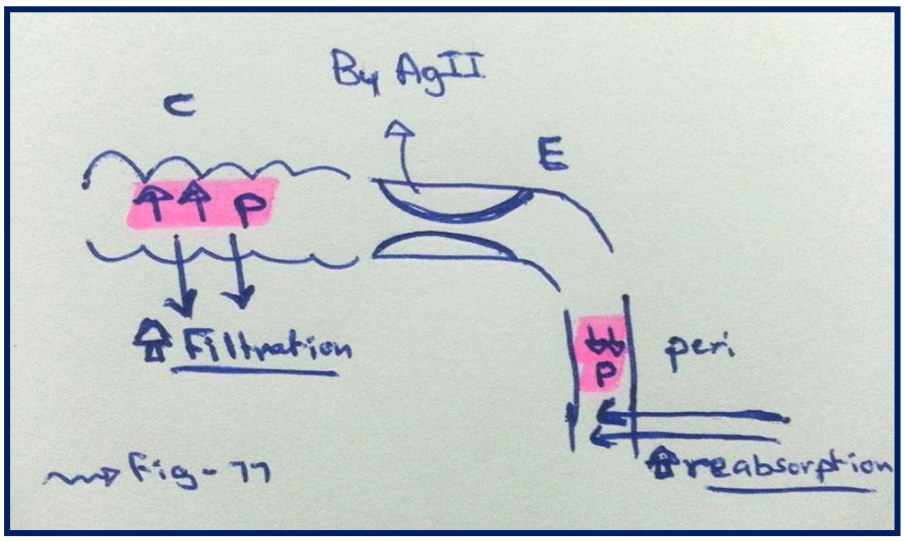
Fig-10

➔ Functions of angiotensin II

- ✓ It's a **vasoconstrictor** so it will **increase the systemic arterial pressure**andthusincrease the blood that goes to the kidney.
- ✓ It will **stimulate** the production of**aldosterone**form the adrenal gland (from the most superficial layer of the **adrenalcortex**; **glomerulosa**). Aldosterone goes to the kidney and **increase reabsorption of sodium** in exchange for potassium secretion. So, more sodium reabsorbed→ more water reabsorbed → hypervolemia → increase blood pressure again.
- ✓ It **increases sodium reabsorptiondirectly** from the proximal tubules (by itself not through aldosterone).
- ✓ Most imp. Function →**angiotensin II**has receptors in the **e**fferent arteriole (not the afferent), the efferent arteriole is **narrower** than the afferent; that's why the pressure is high in the capillary (as if the blood is locked there), **angiotensin II cause constriction in the efferent so it will raise the pressure in the glomerular capillaries and bring the filtration back to normal.**

Again, we have bleeding →we are facing 2 challenges:
1. We want to make little urine **(make the urine output the minimum)**because we want to conserve water.
2. We want -at the same time- to **get rid of waste products** (urea, Creatinine, uric acid).
→***Angiotensin II can achieve these two goals.***
How? Follow (fig-11).

- By **constricting the efferent arteriole**, angiotensin IIwill **raise the pressure in the glomerular capillary and increase GFR**, also when you constrict the efferent you make the **hydrostatic pressure in the peritubular capillariesless** (you make P_{GC}**more** proximally and **less** distally). So you give chance for **more reabsorption**, you're not going to reabsorb Creatinine; you will reabsorb sodium, water, etc.
- By that you made **GFR normal and get rid of waste product** and at the same time you did something to **reabsorb water**.
- Again (Fig-11),**efferent** is preceded by the **glomerular capillaries**(C) and followed by the **peritubular capillaries** (peri).If we **constrict the efferent;** pressure will **rise** before it (in **C**) and will **decrease** after it (in **peri**). The increased pressure allow for **more filtration** (at C), and the decreased pressure allow for **more reabsorption** (at peri) and that's what you aim to do. (All of this is done **by angiotensin II**).



Purposes of Autoregulation

The **purpose** of Autoregulation of GFR is **to uncouple the GFR from the systemic arterial blood pressure.**→ not to have too much GFR & not to have too little.

Some say that Autoregulation is **totally** done in the kidney, but we take angiotensinogen from the liver (from outside), so we say it's **mostly** in the kidney.Again, **autoregulation**:

- **Decreased blood flow**→ decreased GFR → this is sensed by juxtaglomerular apparatus → secret rennin → rennin brings angiotensin II → angiotensin II comes back to the kidney causing **constriction of the efferentarteriole** brining GFR back to normal.
- Therefore, systemic arterial pressure goes up or down but **GFR remains constant**.

❀ Nephrotic syndrome

- It's more common in children.
- The basement membrane **loses its negative charge**, losing the negative charge makes the **albumin** (which is negatively charged) **able to cross the membrane** and be **filtered**, so we start losing the albumin in the urine →**Albuminuria**.
- Also, albumin in the blood will decrease, when it decrease **below 3.5 g/dl** we call this →**hypoalbuminemia**
- Hypoalbuminemia results in **generalized edema** (eyelid edema or face edema in the morning, or lower limb edema, or edema in the lung i.e. **anywhere**)
- So each time you see edema – specially in children- you should **test** for 2 things:
  - ✓ Albumin (or proteins) in the **urine**; look for proteinuria (its reported as +1, +2 ,+3,+4 , each mean certain concentration)
  - ✓ Albumin in the **blood**.

Then send your patient to a nephrologist :)

The End :)

"فَاصْبِرْ صَبْرًا جَمِيلا, إِنَّهُمْ يَرَوْنَهُ بَعِيدًا وَنَرَاهُ قَرِيبًا"❤