Physiology
Lecture 2

Too much blood is received by the glomerular capillaries, this blood contains plasma, once this plasma enters the glomerular capillaries it will be filtered to bowman's space. The volume of plasma filtered per minute is called GFR (glomerular filtration rate).

The normal GFR in a 70 kilogram male equals 125 ml /min/1.73 m^2 surface area

What controls GFR ?

GFR is controlled by the **starling forces**, the same principles as in the systemic capillaries but we have three forces instead of four since proteins can't be filtered to bowman's space.

1. ***Glomerular capillary hydrostatic pressure.*** (favors filtration)
2. ***Glomerular capillary colloid osmotic pressure.*** (opposes filtration)
3. ***Capsular hydrostatic pressure .***(opposes filtration)

* The first force (normally under physiological regulation) which is the glomerular capillary hydrostatic pressure has been estimated to be about 60 mmHg under normal conditions.

Changes in glomerular hydrostatic pressure serve as the primary means for physiological regulation of GFR. An increase in the glomerular hydrostatic pressure raises GFR, whereas a decrease in the glomerular hydrostatic pressure reduces GFR.

This force is generated from the difference in the pressure between the afferent and efferent arterioles. At the beginning of the afferent arteriole the pressure is 85, while at the end of it the pressure is 60, in the glomerular capillaries the pressure changes from 60 to 59, In the efferent arteriole from 59 to 18, In the peri-tubular capillaries from 18 to 8, So there is a difference in the pressure within the renal vascular system.

This results from the resistance within the system, which is equal 25 (efferent), 1(capillaries ,41 (efferent) respectively. So most of the resistance which is found within the renal vascular system resides in the afferent and efferent arterioles, If we control the resistance there we can control the blood flow and the blood pressure in the glomerular capillaries.

***Glomerular hydrostatic pressure is determined by three variables:**

1. Arterial pressure 2. Afferent arteriolar resistance 3. Efferent arteriolar resistance

*** Arterial pressure:**

increase the arterial pressure ⟶ increase glomerular hydrostatic pressure ⟶ increase the GFR

***Afferent arteriolar resistance:**

If we have afferent arteriole dilatation this means a decrease in the resistance, more blood flow (more blood is entering), more glomerular hydrostatic pressure is generated, more GFR.

An Increase in the resistance of afferent arterioles reduces the glomerular hydrostatic pressure and reduces GFR.

***Efferent arteriolar resistance:**

constriction of the efferent arterioles increases the pressure in the glomerular capillaries as if we are constricting a vein.

> Note :
> the increase in the resistance of the **A**fferent arteriole results in a decrease in the pressure whereas the increase in the resistance of the **E**fferent arteriole increases the pressure .

The resistance is inversely proportional to the fourth power of the radius.

$$R \propto \frac{\eta \cdot L}{r^4}$$

20-25 % decrease in radius results in a 3 times increase in the resistance, so the constriction in the efferent arteriole increases the pressure in the glomerular capillary.

But if the constriction was more than the mentioned, and the resistance increased more than 3 times, we will have a decrease in the blood flow and accumulation of proteins (their concentration will increase), the colloid osmotic pressure will overcome the increase in the hydrostatic pressure, when this occurs the net force for filtration actually decreases causing a reduction in the GFR.

So the constriction of the efferent arteriole up to certain point will increase the GFR, after that point any further constriction will result in a decrease in the GFR.

The ultra-filtrate contains all substances like amino acids, glucose, Also it contains waste products such as urea and creatinine.

The amino acids and glucose that are filtered are going to be reabsorbed by the epithelium.

* Creatinine is a waste product and should not be reabsorbed, so whatever filtered should be excreted. Urea, although it's a waste product too, it will be partially reabsorbed .

The increase in the GFR results in the loss of some valuable substances like amino acids and glucose .

<u>The decrease in the GFR results in</u> the accumulation of the waste products, so we don't like the increase in the GFR nor the decrease in it.

If the glomerular hydrostatic pressure was 60, the colloid osmotic pressure is 32 and the hydrostatic pressure in bowman's space is 18:

The net filtration pressure equals = 60 – (32 + 18)

Net filtration pressure = 10, this is the effective filtration pressure.

GFR = net filtration pressure * filtration coefficient

GFR = 10 * KF

If the pressure in the arterial system was 100, by the time it reaches the glomerular capillaries, the pressure would have dropped to 60. So if it was 90, it will become 50 when it reaches the capillaries, there will be no force for filtration (the 10 mmHg difference –the driving force- is gone).

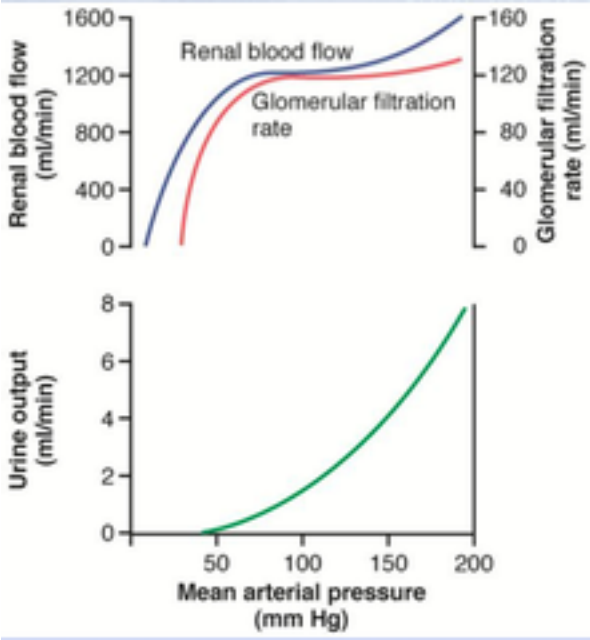
The problem here is that the source which provides the force for the filtration (<u>blood pressure</u>) is not constant during the day, it is fluctuating (going up and down), if It goes up to 130(the mean blood pressure not the systolic blood pressure nor the diastolic) the GFR will increase resulting in the loss of valuable substances such as amino acids and glucose. If it goes down to 90 , this means that there will be no more driving force for the filtration, no more filtration means that the kidney is no longer working and that may result in irreversible kidney damage since there is some sort of blockage in the nephron . While we are sleeping the pressure might decrease to 90 or 85 too.

So the kidney must separate its own function from the systemic arterial blood pressure.

The kidney must *uncouple* the GFR from the systemic arterial blood pressure, this uncoupling is called autoregulation of GFR.

<u>The relative constancy of GFR and renal blood flow is referred to as autoregulation</u>

SO autoregulation of GFR means that when the pressure fluctuates from 70 to 150 the autoregulation in the kidney maintains a relatively constant GFR .
*Graphic presentation of autoregulation .



If the blood pressure drops to below 70 the kidney cannot handle the change and the GFR will decrease , above 150 or sometimes 170, GFR is going to increase .

The Q is how does the kidney achieve this auto regulation?

Example : In bleeding there will be a decrease in the cardiac output resulting in a decrease in the renal blood flow resulting in a decrease of the GFR, when the GFR decreases, the amount of Na and Cl ions that reaches the distal tubule is going to decrease too , the decrease in the NaCl can be sensed by special cells –that are dark in color- in the distal tubules called the macula densa cells.

So the macula densa -at any time the NaCl decreases- sends two signals; One to the afferent arterioles causing their dilatation, and one to the neighboring cells in efferent and afferent arterioles called granular cells or juxtaglomerular cells that secrete rennin.

So, a decrease in the blood flow due to any reason results in a signal to juxtaglomerular cells to secrete rennin.

Now rennin is secreted from the kidney, then it leaves the kidney through the renal vein to the systemic circulation, In the systemic circulation it will look for a small peptide produced by the liver and this peptide is composed of 14 amino acids called angiotensinogen.

Rennin works as a scissor and cuts 4 amino acids resulting in a 10 amino acid peptide called angiotensin 1 which will reach the lung and will further be converted by angiotensin Converting enzyme (ACE) into a smaller peptide with 8 AAs called angiotensin 2 (octa-peptide). So, the end result of the decrease in the renal blood flow is the decrease in the GFR and eventually the production angiotensin 2.

***Angiotensin 2:**

1. It's a very potent vasoconstrictor ,by constricting the arteries you will raise the pressure and thus you increase the perfusion of the kidney .

2.It has a receptor in the efferent arteriole but not in the afferent arteriole and this will result in an increase in the glomerular pressure.

3.Goes to the adrenal gland and stimulates the release of aldosterone (adrenal gland is composed of medulla and cortex ,the cortex is composed of 3 zones; the outer zone is called zona glomerulosa, it secretes aldosterone) .
Aldosterone goes to the kidney, to the distal tubules, to increase Na reabsorption and the excretion of both potassium (by principal cells) and hydrogen ions

4. increases Na reabsorption in the proximal tubule. (Directly by itself)

*note: the afferent arteriole is not affected by angiotensin 2.

So the two signals that came from macula densa cells resulted in the dilation of the afferent arteriole and the constriction of the efferent arteriole, these two changes is increase the glomerular hydrostatic pressure which increases GFR to maintain the kidney function. That's how the kidney maintains its normal GFR regardless of the systemic arterial pressure.

In bleeding we have two opposing problem

First, we need to conserve the water (we don't want to lose water in the urine). Second, we want to get rid of the waste products such as urea and creatinine. They oppose each other because in order to get rid of the waste products we need a normal GFR, while in order to conserve water we need less GFR. Angiotensin 2 does this by constricting the efferent arteriole resulting in an increase in the GFR so that we get rid of the waste products; urea and creatinine.

The constriction of the efferent arteriole also makes the hydrostatic pressure in the peritubular capillaries less so the pressure there decreases and this leads to an increase in the force of reabsorption, which leads to conservation of water.

*note: If we dilate the afferent arterioles by prostaglandins, nitric oxide or bradykinin we will increase the blood delivery to the capillaries, increasing the pressure then increasing GFR.
if you constrict the afferent the blood delivery to the capillary decrease , the GFR also decrease

EX : if a patient is taking aspirin -which inhibits the synthesis of prostaglandins (NSAID) ,this is dangerous due to the constriction of the afferent arteriole and this may result in a decrease in the GFR which is very dangerous ,so for any patient to take NSAIDs we must first measure the GFR before we

give the patient the drug , also it should be measured as long as the patient takes the drug.
<u>If GFR decreases we should stop the medication</u> .

A decrease in the GFR may result in blockage of the nephrons (by crystallization of the Na, Ca, etc.) *especially* in the thin loop of henle since it has a very thin diameter of 11-12 micrometer.

The diameter of the proximal tubule is around 60 micrometer ,The diameter of the corpuscle is around 200 micrometer , So in general, we don't have much space in the nephron , that's why sometimes the blockage of these spaces can't be flushed .

So we should never allow the decrease in GFR (whether by hypotension or NSAIDs) to occur even for a very short period of time, since you can't tell how much the kidney can take and because any damage will be irreversible. (You can't reopen the nephron).

We should make sure that all the drugs that we are going to deal with don't affect the afferent arteriole and don't affect prostaglandins, bradykinin or nitric oxide.

The afferent arterioles under normal conditions are not subjected to autonomic sympathetic system control; so the sympathetic system does not affect the afferent arteriole, but during severe bleeding it will affect it causing constriction of the afferent arteriole, decreasing the GFR. But normally, what overcomes the sympathetic (catecholamine) control are the prostaglandins so if we remove the prostaglandins the sympathetic system will work resulting in the constriction of the afferent arterioles leading to a decrease in the GFR.

* proteins :

As we increase the intake of proteins we might think that this we will increase the colloid pressure inside so we are opposing the filtration process, but actually the proteins are going to be degraded into amino acids and the amino acids are freely filtered, the average molecular weight of the amino acid is approximately 110 and we said that the limit for the filtration is 70000 so they are very small.

Amino acids are reabsorbed from the proximal tubule along with sodium and this is called secondary active transport (co-transport).

The mechanism: In the lumen and the luminal brush border of the proximal tubule we have amino acids along with sodium ,Sodium concentration in the lumen is approximately 140 ,In the cell its 14, there is a ten times gradient, So sodium is reabsorbed from high concentration to low concentration and at the same time amino acids are going to be reabsorbed from low to high concentration (against its gradient so it's an active process). The concentration gradient of the sodium is maintained by the Na/k pump that is found on the baso-lateral membrane of the cells of the lumen, it pumps 3 sodium outside for 2 potassium inside. That's why we called this mechanism secondary active, since we use the energy that is generated from the NA/K pump. We are not utilizing any ATP from the luminal side, we are utilizing it from the basolateral side . That's why the basolateral side is full of mitochondria .

More amino acid delivery to the kidney means more AA filtration and more reabsorption, so, more sodium will be reabsorbed and less sodium chloride will reach the macula densa , the macula densa doesn't understand the cause behind this ,It just understands that less Na is present in the distal tubules, so it will do the same process as mentioned before (sending two signals).

Giving the patient amino acids is a way to increase GFR, if there was a decrease in it, for example, post-operatively.

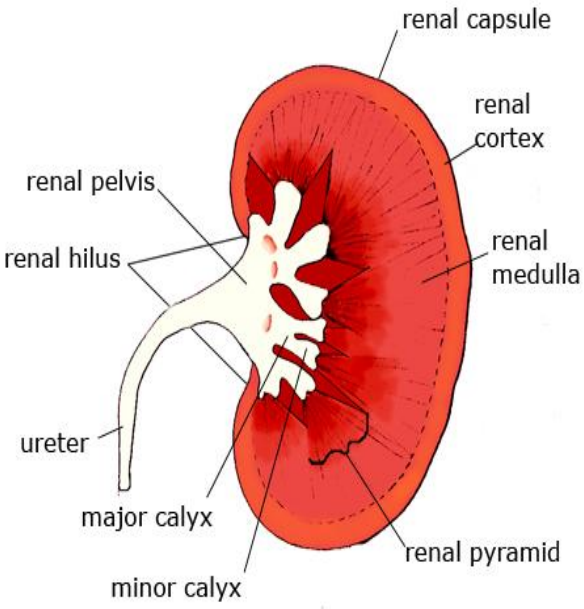
Another factor which is very imp but not under the physiological control, the **bowman's space hydrostatic pressure** which equals 18.

If we have a kidney stone, it will block the flow of the tubular fluid, if the pressure due to the blockage reaches 28 there will be no more filtration.

A Stone in the upper major calyx cancels only a part of the kidney, while a stone in the renal pelvis for example, may destroy the whole kidney, a Stone also might destroy both kidneys.

Prostate enlargement overtime will affect and destroy both kidneys that's why we remove this obstruction, in order to preserve the kidney s, this is not under physiological control but eventually it might result in kidney damage.

*Note: 90% of the causes of chronic renal failure are due to pre-renal or intra-renal causes and only 10 % is due to post -renal causes (stones).



Measuring GFR:

GFR can be used as a tool to determine how many functioning nephrons are left so we need to measure the GFR, HOW?
We are going to use a substance which is freely filtered, not reabsorbed nor secreted, meaning that the filtered load of this substance equals the excretion rate.

* Note: filtered load is how much of it is being filtered per minute (mg/min).

If 10 mg is filtered per min, 10 mg will be excreted per min, As long as this substance is not metabolized in the kidney and doesn't affect the function of the kidney, this substance is called **glomerular marker.**

So the criteria For the glomerular marker (which is used to measure the GFR) is to be freely filter , not reabsorbed ,not secreted, does not affect the kidney function , not metabolized , not produced by the kidney, etc.

Inulin is an ideal substance, it's an exogenous polysaccharide (MW= 5000, much less 70000) which is not produced inside the body so we must infuse it into the patient.

It is freely filtered, neither reabsorbed nor secreted. When inulin is filtered it's going to be excreted, the amount which is excreted per min is equal to the amount provided for the excretion (filtered) per min.

The amount excreted per min (mg/min) = urine output * concentration of inulin in the urine

If we have 1 ml/min urine output and the inulin concentration in the urine is 1 mg/ml, this means that 1mg/min is being excreted.

The amount provided for excretion (filtered load) (mg/min) = GFR (how much fluid is filtered (ml) per minute) x the concentration of inulin in the GFR (plasma).

20 % of the inulin filtered and 80% of it leave through the efferent arteriole.

*note: To measure inulin plasma concentration we don't need to use a micropipette to take a sample from the afferent arteriole, we can we can take a sample from any venous blood.

GFR (ml/min) *plasma inulin concentration (mg/ml) = urine output (ml/min) *inulin concentration in the urine (mg/ml)

GFR = (urine output *inulin concentration in the urine) / plasma inulin concentration

For example :
if the urine concentration of inulin is 100 ,the plasma inulin is 1 and the urine output equal 1.1 ml per min , The GFR equals 110 .

The problem here is that when we want to measure inulin's concentration in the plasma, we should make sure that the plasma inulin concentration is at the Plateau phase (constant). So, while we are infusing inulin in the circulation we should measure the urine output of inulin until it reaches a certain value that indicates that the plasma concentration is now constant, that's when we measure the concentration. This is very hard to do; you may do it for an experiment or for research purposes.

But for clinical purposes we need a substance which is produced by our body and its concentration in the plasma is constant and doesn't fluctuate due to the physical exercise or daily food intake etc., so we use creatinine instead of inulin.

1) Creatinine is freely filtered with a molecular weight of 114 which is very small.

It's produced by our muscles in a constant rate. (It's a breakdown product of creatine phosphate in muscles)

Our muscles make 1.5 to 2 grams of creatinine per day, our urine must contain this amount of creatinine, so we should remove about 2 grams of creatinine everyday from our body in order to make the creatinine plasma concentration constant.

2) it's not reabsorbed

3) Slightly secreted and this is a problem.

10% of creatinine in the urine comes from secretion and 90% come from the part that was filtered and not reabsorbed. Therefore creatinine in the urine overestimates GFR by 10%; creatinine's concentration in the urine is higher than what we expected, so GFR becomes higher that its true value according to the equation GFR= (urine output x concentration in urine)/ plasma concentration).

** inulin clearance*

Clearance of X: **volume** of plasma that provides X (substance) for excretion per min **(ml/min)**

In case of inulin: volume of plasma that provides X for excretion is equal GFR.

If we bring substance X, it will be carried by 650 ml of plasma, if the plasma concentration of X became zero in the renal vein, this means that the entire amount that entered the kidney was filtered (and not reabsorbed) and secreted; 20 % of X is filtered and not reabsorbed, and 80% is secreted, so the entire 650 ml have been cleaned totally from X, and this substance can be used to measure the renal plasma flow. So, in order to measure renal plasma flow, we need a substance that once it enters the kidney it will be completely removed from the blood; Zero concentration in the renal vein.

*If the concentration of X in the plasma was 1mg/ml:

How much x has been delivered to the kidney per min? 650 mg/min has been delivered
(650 ml/min x 1 mg/ml)

How much urine is excreted per minute? 1 ml/min, This one ml contains the whole amount of the X that was delivered, so its concentration is equal 650 mg\ml in the urine.

So the clearance of the para-aminohippuric acid (pah) equals:
(the concentration in the urine /concentration in the plasma) * urine output

So the clearance = (585 /1) * 1 so, Clearance = 585 , this is the effective renal plasma flow. (the dr. said that this will be explained later on).

*para-aminohippuric acid (pah) is a substance that is freely filtered and used as a test for plasma clearance.