# How to measure renal blood flow? SUMMARY

By measuring renal plasma flow using the concept of clearance

But first we have to choose a substance that is freely filtered, not reabsorbed and completely secreted

active process that takes place in the nephrone

filteration is a passive process that takes place in the glomerulus

And this substance is PAH

C PAH * P PAH = U PAH * UF

C PAH = U PAH / P PAH * UF

C PAH = effective RPF

True (total) RPF = effective RPF / 0.9

RBF = RPF / (1- Hct)

This is not a routine clinical test because PAH is not endogenous and we have to infuse it and stabilize its concentration in the blood using a pump which requires several hours

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T max = 80 mg/ min

If P PAH < Tmax
20% will be filtered
80% secreted
No reabsorption
All the amount is cleared
C PAH = RPF (effective)

If P PAH > T max
20% will be filtered
Less than 80% will be secreted [we will secrete only the amount that equals T max => the remaining amount will continue to renal vein]
Not all the amount is cleared
C PAH doesn't equal RPF (effective)

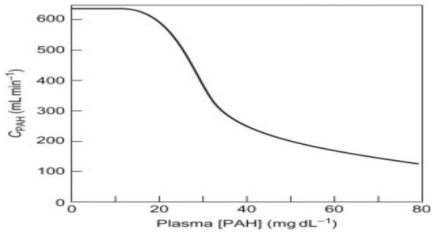
And whenever P PAH become very large
20% will be filtered
Secretion will be very small and negligible as a percentage
C PAH = GFR

**clearance**

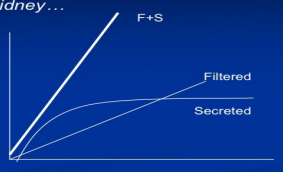
**Clearance is the volume of plasma that provides X for excretion per minute**. (it's volume/min and not amount)
ex: protein in urine is zero, plasma that entered is 650ml and carries protein. how much volume of plasma that provide protein for excretion? Clearance of proteins is zero because none of it gets cleaned from the plasma.

Clearance of PAH ($C_{PAH}$) = Volume of plasma cleaned from PAH / min

**$C_{PAH}$ = RPF** because all the plasma that entered through the renal artery has been cleared from PAH.
Let's suppose that the $T_{max}$=80mg/min and you provided 100 mg of PAH then 80mg will be transported and 20mg will continue through the renal vein, that means that the plasma will not be completely cleared from PAH and the clearance in this case **underestimates RPF**.
(RPF will not equal clearance because not all the plasma was cleared)
If you greatly increased the concentration of PAH provided to 8000mg for example, then the amount secreted will be 80mg which is negligible compared to the 8000mg provided and what appears in the urine will be what was coming through filtration (20%) in this case this substance becomes GFR marker rather than RPF marker.
The clearance of PAH will equal 650ml/min until it reaches the $T_{max}$ it will start decreasing gradually but it will never decrease below 125ml/min because filtration is passive, and it is guaranteed.
so basically
1) below Tmax works as RPF marker
2) above Tmax works as GFR marker




***Remember***:
*PAH is completely cleared (cleaned) from plasma in the kidney…*
*But only under one condition…name it……*
- When we increase the PAH in the plasma, the filtration will increase proportionally (because filtration is a passive process).
(remember: 20% of the PAH is filtered)




- But in the case of secretion (which is an active process) after reaching Tmax…. No more increase in secretion…plateau phase

- So at a certain concentration the kidney will not be able to clear the whole plasma from that substance (Cr).

**- If PAH delivered to the peritubular capillaries exceeds Tmax (80 mg/min) →→ PAH clearance becomes less than RPF (underestimation of RPF)**

- The difference between predicted excretion rate for PAH (assuming all PAH molecules bind to their transporter) and actual excretion rate is called splay. It is high at high PAH concentrations (i.e., just less than $T_{max}$) and approaches zero at lower concentrations.
- **Note:**the last two points will be further explained when glucose reabsorption is discussed.

✞ **Example:** If the plasma concentration of a substance is **2500 mg/ml** and **60%**of the substance passing through the kidneys is filtered and **10%** secreted while **20%** reabsorbed. Assuming infinitive $T_{max}$ for the substance transporters, calculate the clearance and the RPF (per minute) given that during the next 24 hours, **720 ml** of urine were collected, and the substance concentration in urine was **100 mg/ml**.

- V = 720 ml/day = 0.5 ml/min  Us = 100 mg/ml  Pc = 2500 mg/ml
- Cs = (V x U) / Ps = 0.5 x 100 / 2500 = 0.02 ml/min
- Excreted = 60 + 10 -20 = 50%
- Since $T_{max}$ is much higher than the concentration of the substance reaching peritubular capillaries, the splay phenomenon does not affect the accuracy of the calculated RPF. Thus, RPF = 0.02 / 0.50 = 0.04 ml/min. (half of the RPF was cleared)

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## Lecture (2 and 3)

## Glomerular Filtration Rate

Is the first step in urine formation.

By the way: Filtered load of a substance "x" : is how much of "x" is being filtered/minute.

Large amounts of plasma diffusing passively into Bowman's capsule.

✞ What is the difference between filtration and diffusion?

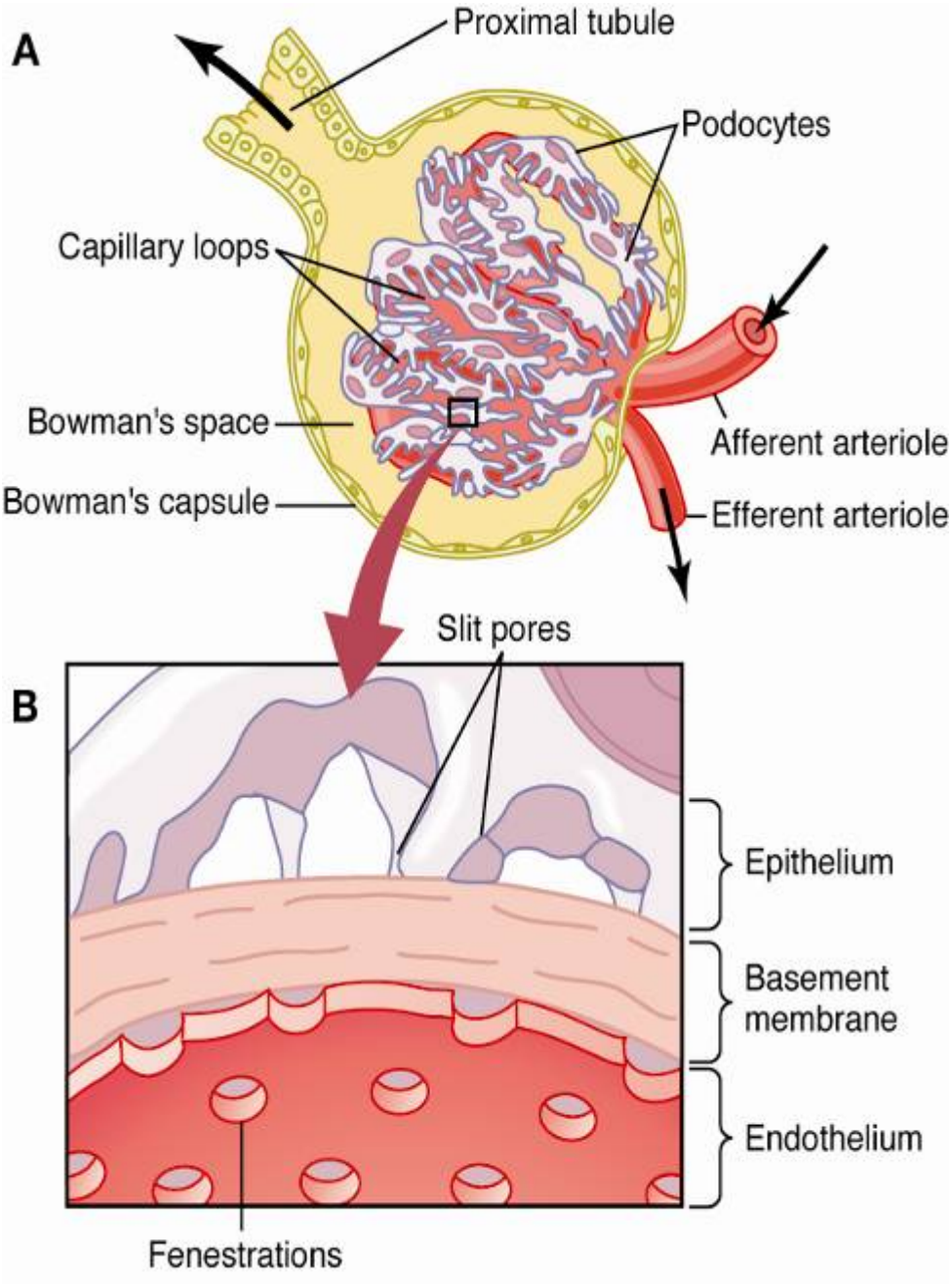
✞ Filtration is a bulk flow of fluids with the dissolved solutes. It is driven by the pressure gradient across the membrane.

✞ Diffusion is the movement of molecule by molecule. They cross the membrane based on concentration gradient (glucose) or down their electrochemical gradient (electrolytes). The composition of the filtrate is essentially similar to that of the plasma. However,

glomerular capillaries, like most other capillaries are not permeable to proteins. Also, calcium and fatty acids are not freely filtered since they are partially bound to plasma proteins. Ultrfiltrate is plasma minus proteins

- How do we know that for sure?
- By using the micropuncture technique (taking a sample from Bowman's capsule in vivo and analyze it. Due to the current circumstances, I'm not going to touch topics related to micropuncture technique.

  **Note:** Most systemic capillaries have an arterial end where plasma is filtered and a venous end where most filtered plasma is reabsorbed. Plasma in glomerular capillaries *is only filtered and not reabsorbed*. Another exception is gastrointestinal capillaries which function only to reabsorb nutrients.




## •Glomerular Filtration Rate (GFR)

The volume of plasma filtered from the glomerular capillaries to Bowman's capsules per unit time (125 ml/min or 180 lit/day).

Ohm's law $F \propto \frac{\Delta P}{R}$ — filteration is flow ↘ — $GFR \propto \Delta P \times K$ (Starling forces, permeability)

- You may notice that Plasma volume (3 lit) is filtered 60 times per day
  - Determined by the balance between starling forces and the capillary filtration coefficient **($K_f$)**, which and is the product of the permeability of the capillary for the substance and the surface area/thickness of the filtration barrier provided for filtration.

- The permeability of the capillary for a substance, in turn, is determined by the molecular weight and the charge of the substance.

| Substance | Molecular Weight | Filterability |
|---|---|---|
| Water | 18 | 1.0 |
| Sodium | 23 | 1.0 |
| Glucose | 180 | 1.0 |
| Inulin | 5,500 | 1.0 |
| Myoglobin | 17,000 | 0.75 |
| Albumin | 69,000 | 0.005 |

- Cations are more readily filtered than anions because the endothelium and the basement membrane are negatively charged and thus, repel anions. Cations with a molecular weight less than 70,000 kDa are readily filtered. In contrast, anions need to be much smaller in order to pass through the capillaries. Albumin, for example, despite its relatively low molecular weight (70,000 kDa), does not cross due to its highly negative net charge. However, $Cl^-$, yet negatively charged, readily crosses due to its very small size.
- In nephrotic syndrome, loss of negative charge causes albumin loss and edema.
- (Remember the four cause of hypoalbuminemia: malnutrition, malabsorption, malproduction, and increased loss from the kidney).
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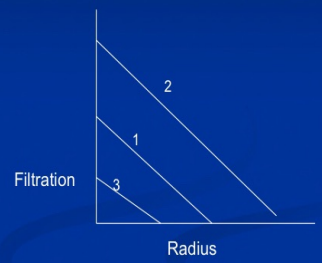
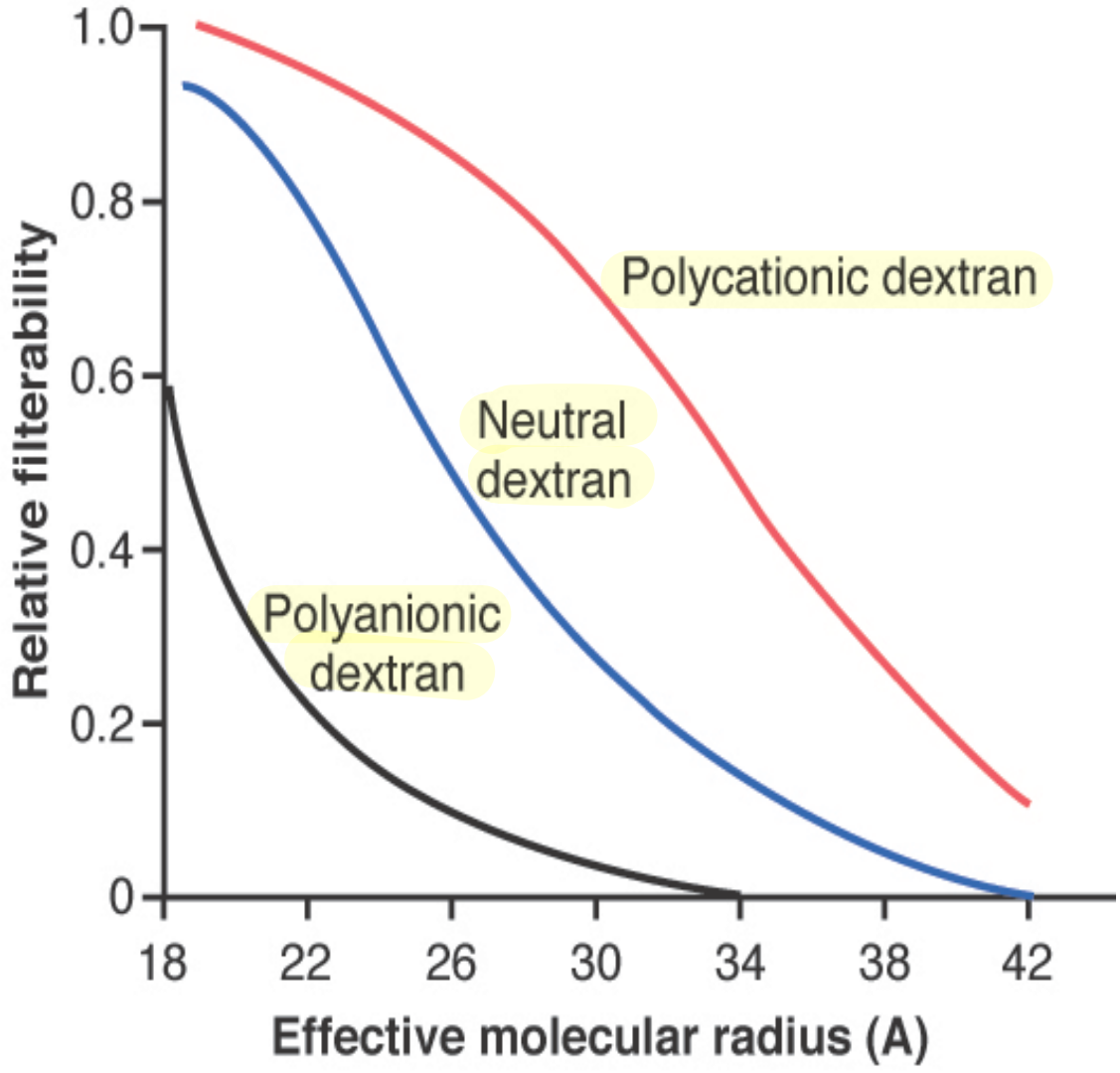
- Any substance with a MW less than 70 K can be filtered, and the filtration is inversely related with the radius:
(Mω)

(1) a neutral substance
(2) Is a cation substance: because it'll attach to the –ve basement membrane, more filtration.
(3) Anion: less filtration




***Note:***

Hemoglobin MW is less than 70 K. However, it is not filtered because Hb is bounded to protein: in hemolysis we can see Hb in the urine (pink urine).




- Water is filtered freely across glomerular capillaries and thus, the filterability of water is said to be 1. The filterability of other substances ranges from 0 to 1 and is determined relative to that of water. It is estimated according to its Bowman's space concentration/its plasma concentration

  - The RPF averages 625ml/min; the glomerular filtration rate is 125 ml/min. Dividing these numbers yields 0.2, which is the filtration fraction.

- **Starling Forces**

1. **$P_{GC}$**: the blood hydrostatic pressure in the glomerular

| 85 | 60 | 59 | 18 |
|---|---|---|---|
| Affarent arteriole | Glomerular capillary | Efferent arteriole | |

capillaries which is generated by the pumping force of the heart. It averages 60 mm Hg in the glomerular capillaries. # 18 is the pressure at the beginning of the peritubular capillaries.

**Table 26-3. Approximate Pressure and Vascular Resistances in the Circulation of Normal Kidney**

Afferent + efferent contribute to about 70% of the intrarenal vascular resistance (mainly efferent).

| | Pressure mmHg | | % Total Vascular R |
|---|---|---|---|
| | Beginning | End | |
| Renal Artery | 100 | 100 | 0 |
| Interlobar, arcuate and interlolbular arteries | 100 | 85 | 15 |
| Afferent | 85 | 60 | 25 |
| Glomerular capillaries | 60 | 59 | 1 only 1mmHg which means little resistance |
| Efferent | 59 | 18 | 43 resistance mainly resides her |
| Peritubular Capillaries | 18 | 8 | 10 |
| Interlobar, arcuate and interlolbular veins | 8 | 4 | 4 |
| Renal vein | 4 | ≈4 | 0 |

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# Note that $P_{GC}$ decreases markedly as blood passes through the arterioles (afferent and efferent), indicating high blood flow resistance in these vessels.

- $P_{GC}$ is the determinant of GFR and is subject to physiological control
- Factors that influence $P_{GC}$
  - arterial pressure (effect is buffered by autoregulation of GFR)
  - afferent arteriolar resistance
  - efferent arteriolar resistance

**Autoregulation of GFR is to be discussed with the regulation of $P_{GC}$**

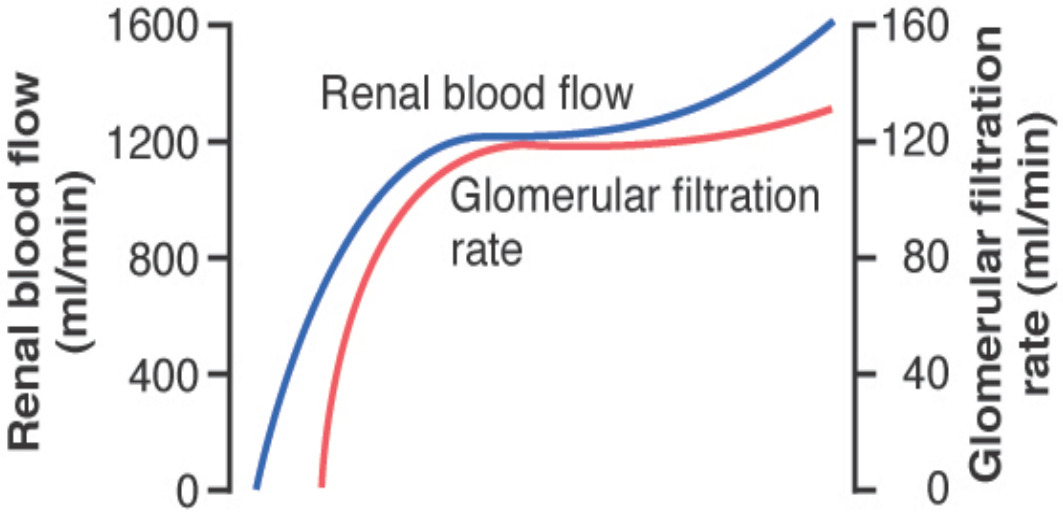
Simply: Autoregulation of GFR means the kidney (auto) can separate its GFR from the systemic ABP

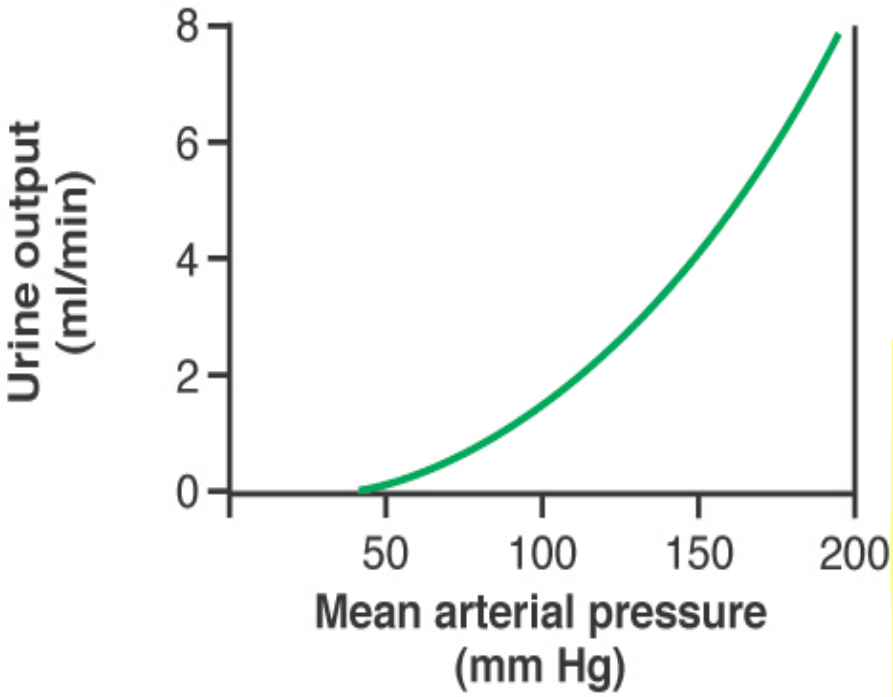
GFR fluctuates slightly in relation to changes in arterial blood pressure but this translates in a large increase in urine output… why is that?

GFR = 125ml/min and UOP is only = 1ml/min = 1.5L/day which means 124ml/min is reabsorbed (99.4% of the filtered water is reabsorbed and only 0.8% is excreted) so a little change in GFR changed the urine output a lot.

Therefore, GFR must be regulated and this is achieved mainly by the renal vascular system (glomerular capillary hydrostatic pressure) and this is controlled by afferent and efferent arterioles by the following mechanism:

next page




**Auto regulation of renal blood flow and glomerular filtration rate but lack of auto regulation of urine flow during changes in renal arterial pressure**

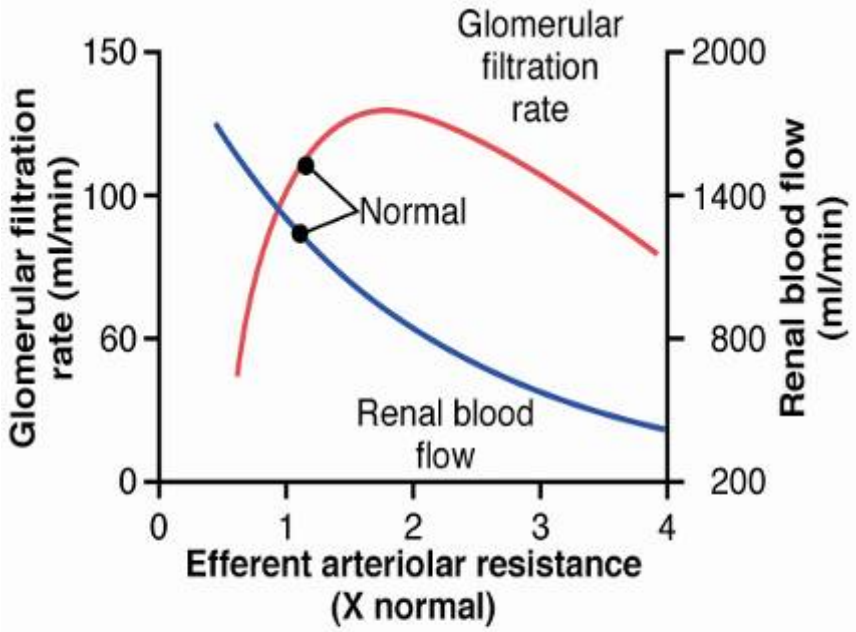
***Extra***

Normally, GFR is about 180 L/day and tubular reab-sorption is 178.5 L/day, leaving 1.5 L/day of fluid to be excreted in the urine. In the absence of autoregulation, a relatively small increase in blood pressure (from 100 to 125 mm Hg) would cause a similar 25 per cent increase in GFR (from about 180 to 225 L/day). If tubular reabsorption remained constant at 178.5 L/ day, this would increase the urine flow to 46.5 L/day (the difference between GFR and tubular reabsorp-tion)—a total increase in urine of more than 30-fold. Because the total plasma volume is only about 3 liters, such a change would quickly deplete the blood volume.

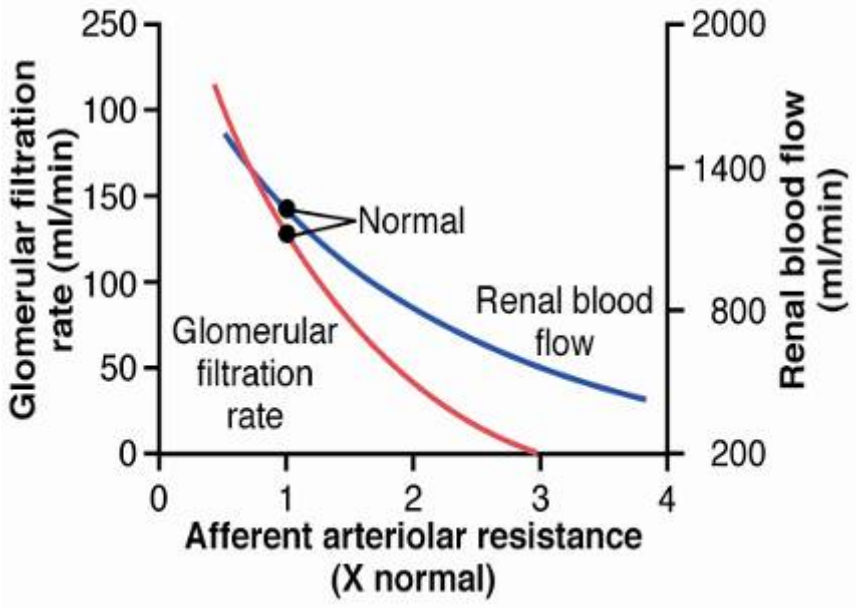
But in reality, such a change in arterial pressure exerts much less of an effect on urine volume for two reasons: (1) renal autoregulation prevents large changes in GFR that would otherwise occur, and (2) there are additional adaptive mechanisms in the renal tubules that allow them to increase their reabsorption rate when GFR rises, a phenomenon referred to as *glomerulotubular balance*.

Even with these special control mechanisms, changes in arterial pressure still have significant effects on renal excretion of water and sodium; this is referred to as *pressure diuresis* or *pressure natriuresis,* and it is crucial in the regulation of body fluid volumes and arterial pressure.

Will be discussed in more details in page 30, 31, 32, 33, 34, 35 (paragraphs highlighted in blue)




efferent arteriolar constriction has a biphasic effect on GFR. At moderate levels of constriction, there is a slight increase in GFR, but with severe con-striction, there is a decrease in GFR. The primary cause of the eventual decrease in GFR is as follows: As efferent constriction becomes severe and as plasma protein concentration increases, there is a rapid, non-linear increase in colloid osmotic pressure caused by the Donnan effect; the higher the protein concentra-tion, the more rapidly the colloid osmotic pressure rises because of the interaction of ions bound to the plasma proteins, which also exert an osmotic effect.

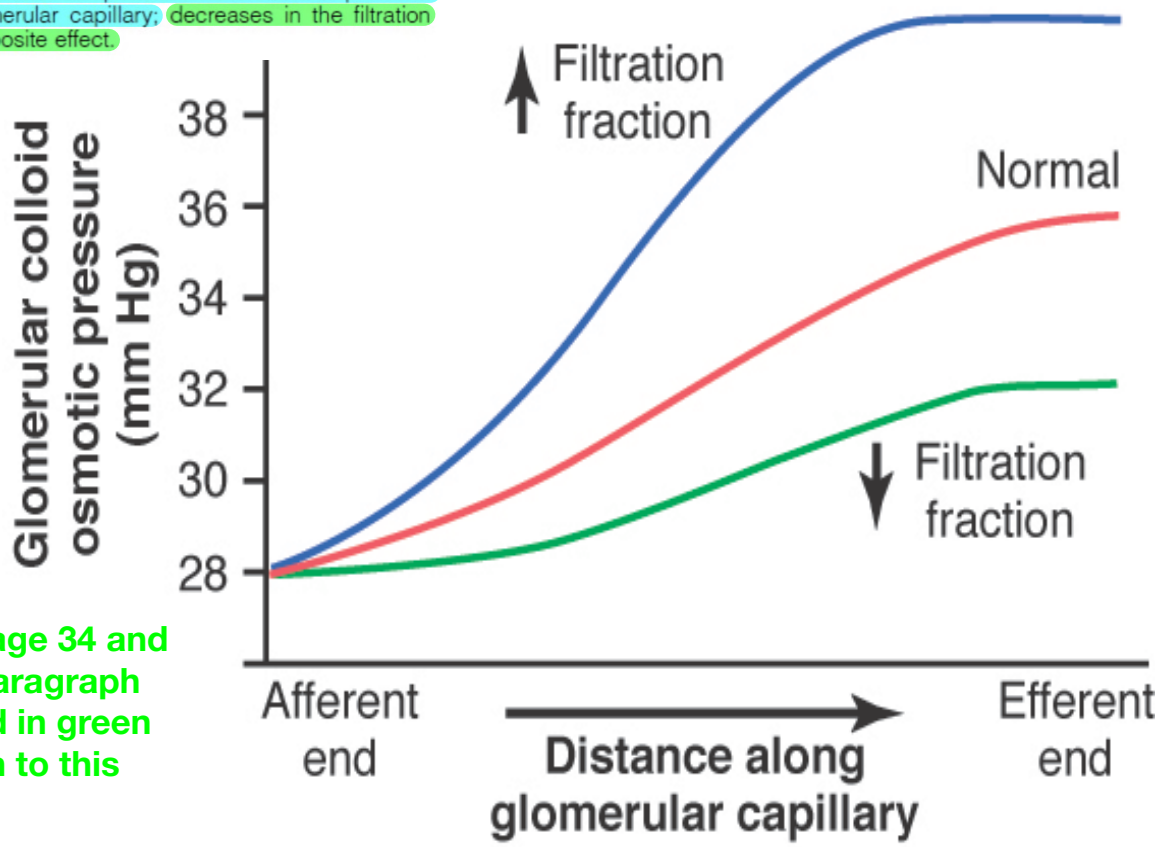



Increased resistance of afferent arterioles reduces glomerular hydrostatic pressure and decreases GFR. Conversely, dilation of the afferent arterioles increases both glomerular hydrostatic pressure and GFR

**Will be discussed in more details in page 30 (paragraphs highlighted in orange)**

2. $\pi_c$: the colloid osmotic pressure generated by the impermeable proteins in the plasma. Since 20% of plasma passing through the capillary is filtered, impermeable proteins concentration increases as they pass along the length of the capillaries from 28 mmHg to 36 mm Hg. Thus, the average $\pi_c$ is approximately 32 mm Hg.

Increase in colloid osmotic pressure in plasma flowing through the glomerular capillary. Normally, about one fifth of the fluid in the glomerular capillaries filters into Bowman's capsule, thereby concentrating the plasma proteins that are not filtered. Increases in the filtration fraction (glomerular filtration rate/renal plasma flow) increase the rate at which the plasma colloid osmotic pressure rises along the glomerular capillary; decreases in the filtration fraction have the opposite effect.



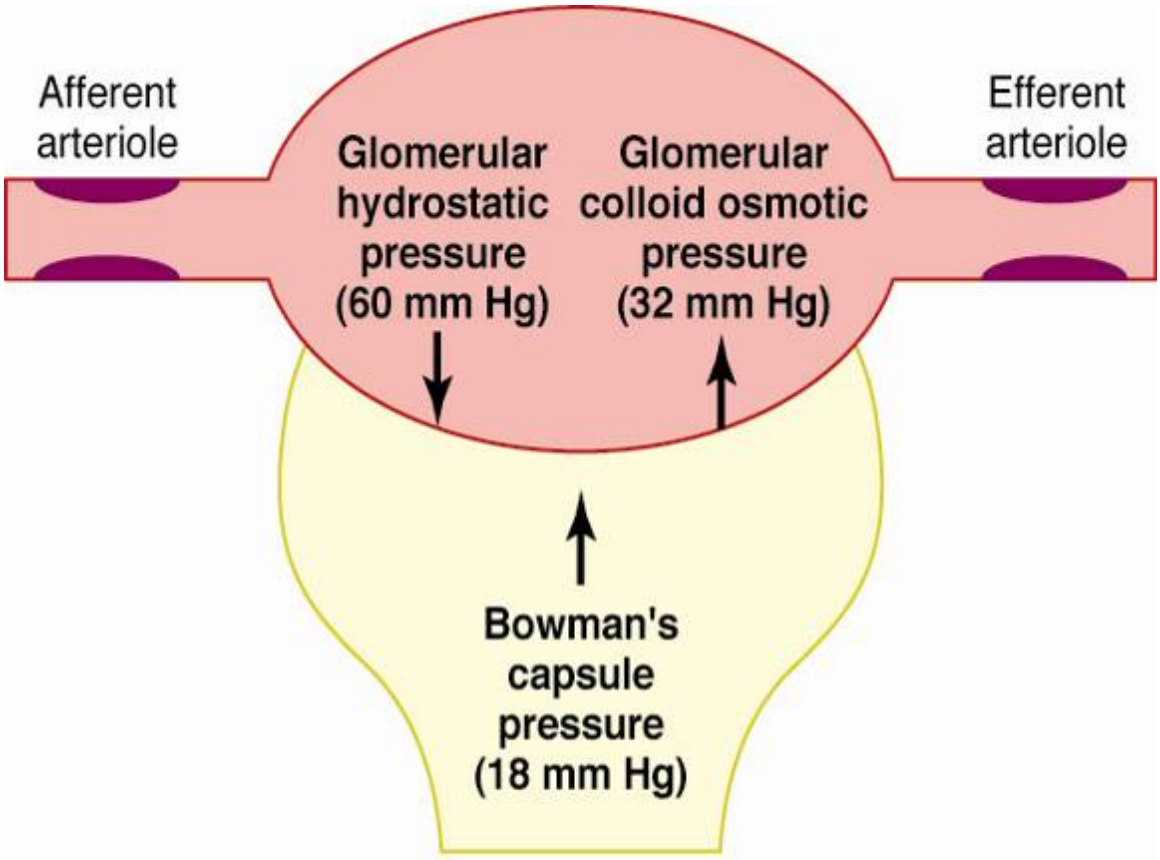

**Refer to page 34 and read the paragraph highlighted in green then return to this page**

3. **$P_i$:** the hydrostatic pressure generated by the interstitial fluid. It is the pressure in the Bowmans space. It averages 18 mm Hg. Normally changes as a function of GFR, not a physiological regulator of GFR

4. **$\pi_i$:** the colloid osmotic pressure of the interstitial fluid. Since filtered plasma is free of proteins, it equals zero.

✦**Note**: in other organs, $\pi_i$ plays an important role in determining filtration rate. This depends on the permeability of the capillaries to proteins. In the liver interstitium, for instance, $\pi_i$ is very high due to the very high permeability of the liver capillaries to plasma proteins.

- $P_c$ favors filtration while $P_i$ and $\pi_c$ favor reabsorption. Therefore, net filtration pressure equals **60 – 18 – 32, or 10 mm Hg**.




Net filtration pressure (10 mm Hg) = Glomerular hydrostatic pressure (60 mm Hg) – Bowman's capsule pressure (18 mm Hg) – Glomerular oncotic pressure (32 mm Hg)

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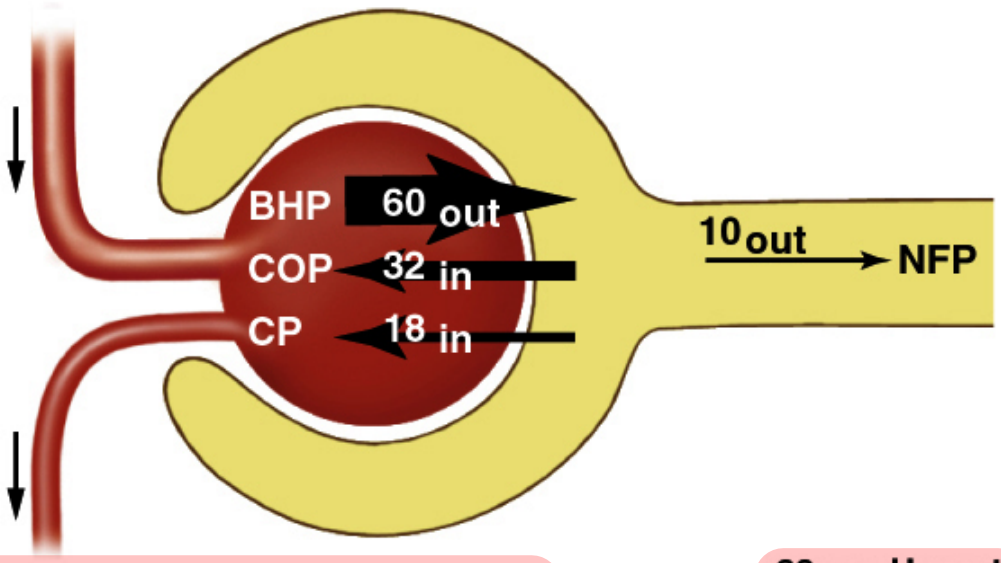
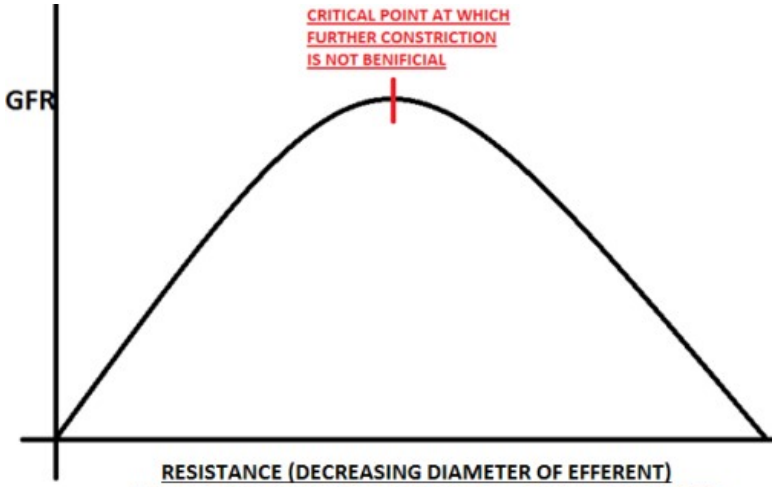
- Hypoalbuminemia →↑GFR.




| | |
|---|---|
| Blood hydrostatic pressure (BHP) | 60 mmHg out |
| Colloid osmotic pressure (COP) | –32 mmHg in |
| Capsular pressure (CP) | –18 mmHg in |
| Net filtration pressure (NFP) | 10 mmHg ou |

- Any obstruction to urine flow (e.g., in prostate hypertrophy and stone formation) increases the hydrostatic pressure inside the Bowman's capsule, decreasing the GFR.
- **Note:** From the glomerular capillaries, 180 L/day are filtered. In contrast, only 20 L/day are filtered throughout the rest of the body. This is attributable to the relatively low $P_c$ in other body capillaries, plus high **($K_f$)** in the kidney.
- **Always remember Ohm's law:** Flow is directly proportional to driving force and inversely proportional to R. We replace R by **($K_f$)**: GFR=$P_f$***($K_f$) so more filtration is either due to increase in filtration pressure or ($K_f$)or both.**
- $K_f$ = 12.5 ml/min per mmHg, or 4.2 ml/min per mmHg/ 100gm (400 x greater than in many other tissues)
- $K_f$ = hydraulic conductivity * surface area. (Cannot b measured directly but indirectly, exactly like resistance, do you remember from the respiratory physiology when I told you that resistance and permeability are both vague concepts and cannot be measured directly in our body)
- Disease that can reduce $K_f$ and GFR: hronic hypertension, obesity / diabetes mellitus increases the thickness of the basement membrane, glomerulonephritis

- Normal GFR must be maintained. Increased GFR as a result of an increase in $P_c$ or an increase in the permeability of the capillaries, for example, results in generalized edema; decreased GFR causes waste products to accumulate in the plasma.



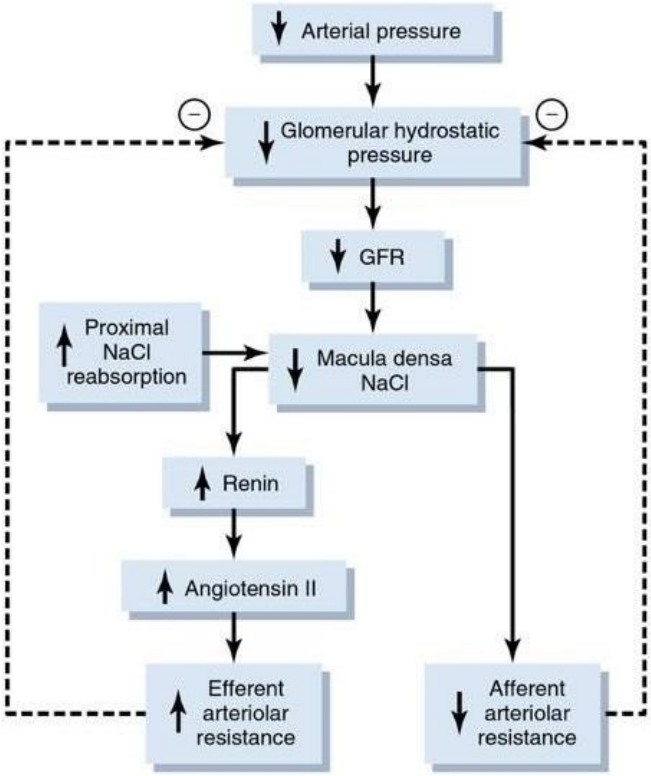
*INCREASING RESISTANCE OF EFFERENT AND ITS EFFECT ON GFR*

- $P_c$ can be physiologically increased or decreased markedly by changing efferent and afferent arterioles diameters. Constricting the afferent arteriole causes decreased blood reaching the capillaries, hence decreased $P_c$ and filtration rate. Also, constricting the efferent arterioles causes blood to accumulate in the capillaries. This results, at the beginning, in increase in $P_c$ and filtration rate. However, after a while, fluid leaving the capillaries will leave behind very concentrated proteins (i.e., high $\pi_c$) which would oppose further filtration.

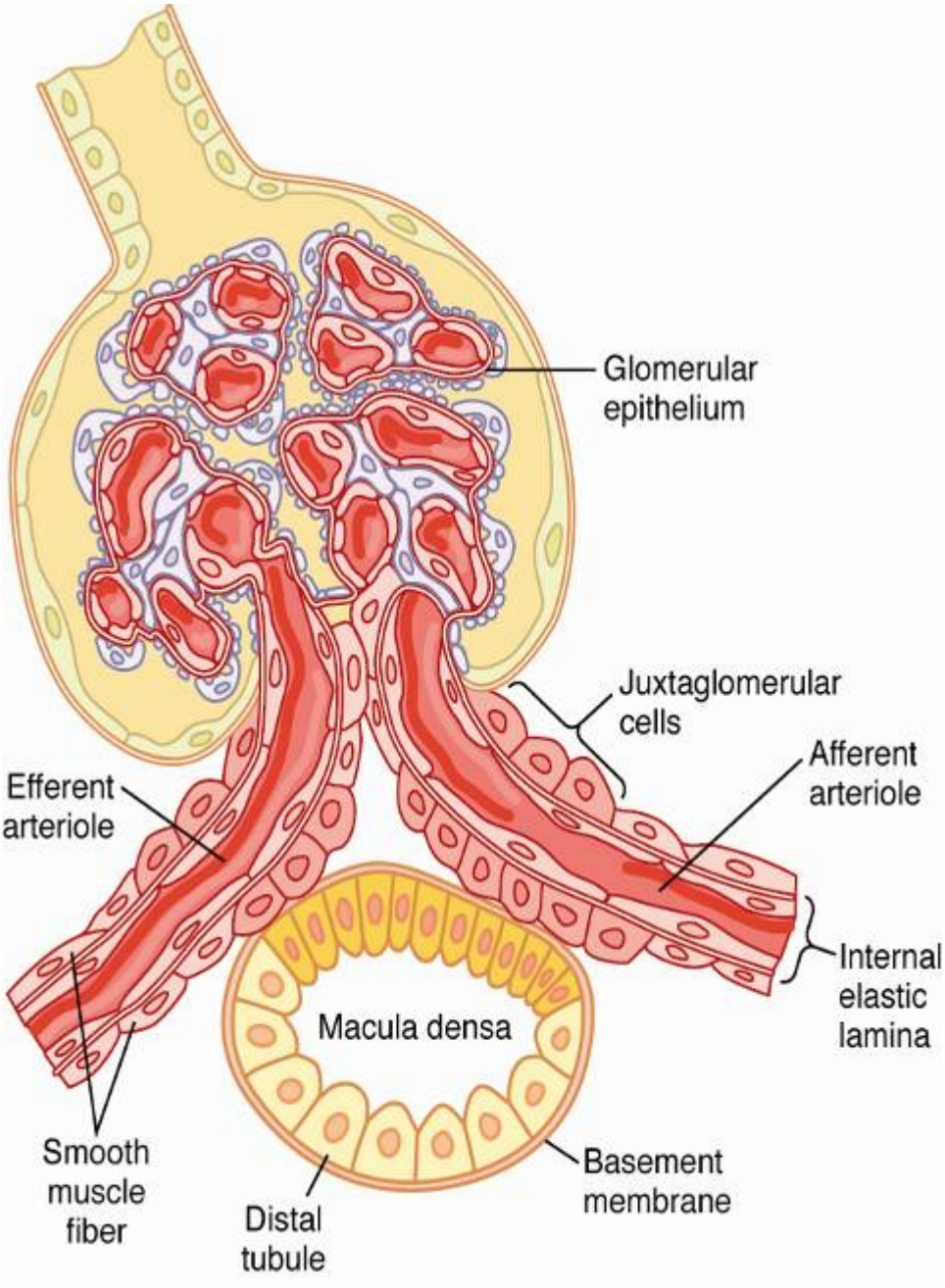
  Thus, any drug that, directly or indirectly, constricts the afferent arterioles can decrease the GFR. NSAIDs for example inhibit the formation of prostaglandins, which normally dilate the afferent arterioles. Therefore, kidney functions must be monitored regularly whith NSAIDs administration, especially for chronic diseases; Even a slight incrase in creatinine level after the administration of such drugs may require stopping the drug, especially in old-aged patients, whose GFR is already declining.

- The GFR is not affected by a small increase or decrease in mean arterial pressure (MAP). Otherwise, even an MAP of 90 mm Hg, which is not far from normal value (93 mmHg), would decrease $P_c$ to 50 mmHg. This would, in turn, stop filtration.

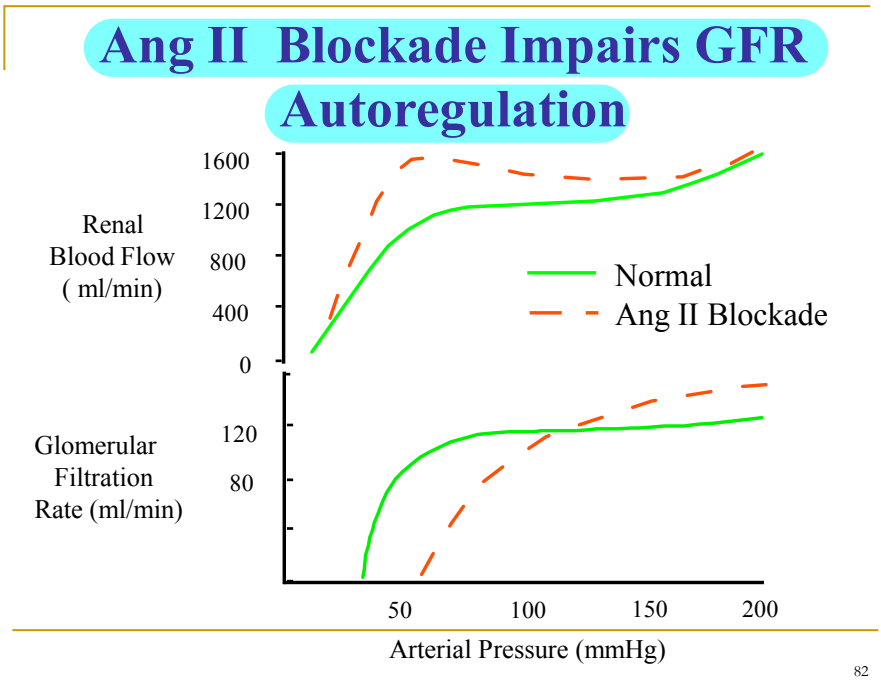
- How does the body maintain constant GFR despite the huge daily fluctuations in MAP? There are two physiological mechanisms that function to ***autoregulate* GFR** and RPF. To answer the question, the juxtaglomerular complex must be discussed first.

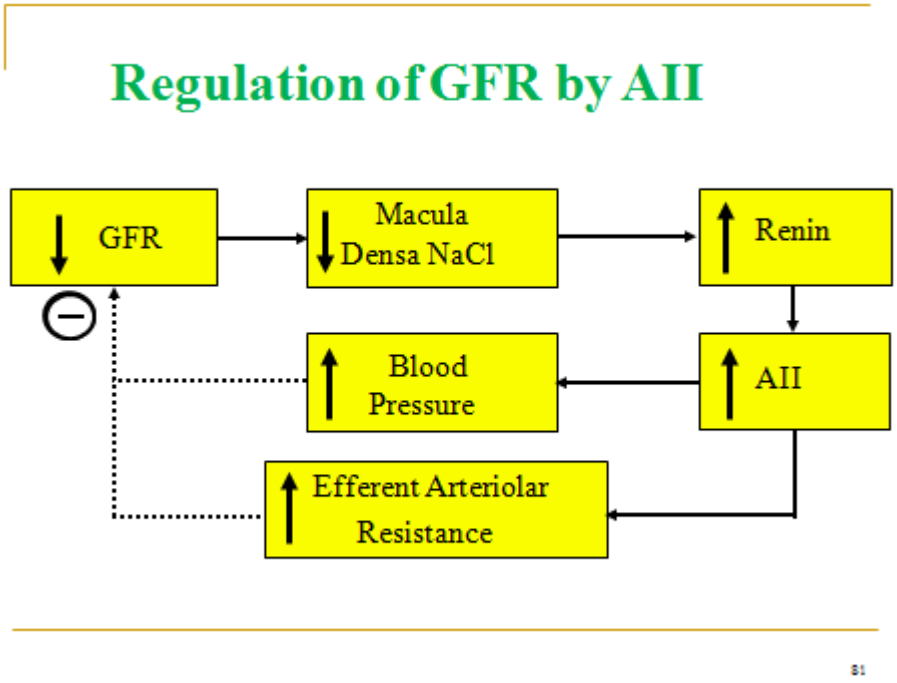


- This complex consists of 2 types of cells:
  - Macula densa which is a group of specialized epithelial cells located in the initial portion of the distal tubule.
  - Juxtaglomerular cells which are located in the walls of the efferent and afferent arterioles. They are the major storage sites for the enzyme, renin.


Glomerular epithelium
Juxtaglomerular cells
Afferent arteriole
Efferent arteriole
Internal elastic lamina
Macula densa
Smooth muscle fiber
Basement membrane
Distal tubule

✦




- Decreased GFR slows the flow rate in the loop of Henle causing increased reabsorption of $Na^+$ and $Cl^-$ in the ascending loop of Henle, thereby decreasing their concentrations at the macula densa cells. This initiates a signal from the macula densa, which:
  - Decreases resistance to blood flow in the afferent arterioles raising $P_c$ and helping returning GFR toward normal.
  - Increases renin release from the juxtaglomerular cells.

- Renin enzymatically cleaves angiotensinogen forming angiotensin I, which is further cleaved by a converting enzyme in the lungs to form angiotensin II.

- Angiotensin II helps to correct the GFR by
  - Potently constricting the arterioles of the body increasing MAP.
  - Constricting the efferent arterioles increasing $P_c$ in the glomerular capillaries and helping returning GFR toward normal.
  - Directly increasing the reabsorption of $Na^+$ from the nephron, especially the proximal tubules.
  - Increasing aldosterone secretion from the adrenal glands. This increases Na+ and water reabsorption, as discussed later.

- Constricting the efferent arterioles is not only important to increase $P_c$ in the capillaries but also to decrease $P_c$ ahead of the efferent arterioles (i.e., peritubular capillaries). This causes the hydrostatic pressure in these vessels to decrease allowing the opposing forces to increase reabsorption, thereby conserving body fluids, at the same time get rid of waste products (urea/Cr)

- With these mechanisms, the GFR changes only a few percentage points, even with large fluctuations in MAP between the two limits (75 and 160 mm Hg).

- **Remember**: Since only 0.5% of fluids passing through most other systemic capillaries are filtered, $\pi_c$ does not change significantly throughout the capillaries (i.e., remains 28 mm Hg) **Remember**: albumin, *and not globulins*, is the main protein which determines $\boldsymbol{\pi_c}$ although plasma concentration of albumin is only slightly higher than that of globulins. The reason for this is that the molecular weight of albumin is much less than that of globulins, 70,000 and 200.000, respectively. This means that 1mg/ml of albumin would contain more molecules than similar concentration of globulins. Since *osmolality is determined by the number of particles*, albumin exerts more oncotic pressure than globulins at same concentrations.

# Importance of Autoregulation

| Arterial Pressure | GFR | Reabsorption | Urine Volume |
|---|---|---|---|
| 1- Poor Autoregulation + no change in tubular reabsorption | | | |
| 100 | 125 | 124 | 1.0 |
| 120 | 150 | 124 | 26.0 = 37.4 L/day! |
| 2- Good Autoregulation + no change in tubular reabsorption | | | |
| 120 | 130 | 124 | 6.0 |
| 3 Good Autoregulation+adaptive increase in tubular reabsorption | | | |
| 120 | 130 | 128.8 | 1.2 |

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## Control of GFR and renal blood flow

1. Sympathetic Nervous System /catecholamines

$\uparrow\uparrow R_A + \uparrow R_E \longrightarrow \downarrow GFR + \downarrow\downarrow RBF$

e.g. severe hemorrhage.

Under normal conditions Sympathetic tone have little influence on RBF.

Sympathetic system may not influence RBF under normal circumstances, but in severe sympathetic stimulation it may decrease RBF significantly

2. Angiotensin II

$\uparrow R_E \longrightarrow \longleftrightarrow GFR + \downarrow RBF$

(prevents a decrease in GFR)

e.g. low sodium diet, volume depletion

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3. Prostaglandins

$\downarrow\downarrow R_A + \downarrow R_E \longrightarrow \uparrow GFR + \uparrow\uparrow RBF$

Blockade of prostaglandin synthesis → ↓ GFR

This is usually important only when there are other disturbances that are already tending to lower GFR. If Aspirin is administered which suppresses PGs then a severe decrease in GFR might occur.

e.g. nonsteroidal antiinflammatory drugs NDAID in a volume depleted patient, or a patient with heart failure, cirrhosis, etc

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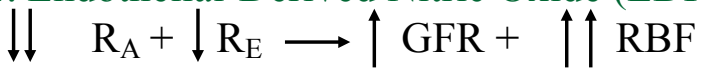
## Control of GFR and renal blood flow

4. Endothelial-Derived Nitric Oxide (EDRF)




- Protects against excessive vasoconstriction
- Patients with endothelial dysfunction (e.g. atherosclerosis) may have greater risk for excessive decrease in GFR in response to stimuli such as volume depletion

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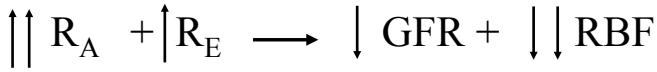
## Control of GFR and renal blood flow

5. Endothelin




- Hepatorenal syndrome – decreased renal function in cirrhosis or liver disease?
- Acute renal failure (e.g. contrast media nephropathy)?
- Hypertensive patients with chronic renal failure?

Endothelin antagonists may be useful in these conditions

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## Other Factors That Influence GFR

- Fever, pyrogens: increase GFR
- Glucorticoids: increase GFR
- Aging: decreases GFR 10% / decade after 40 yrs
- Hyperglycemia: increases GFR (diabetes mellitus)
- Dietary protein: high protein increases GFR
  low protein decreases GFR

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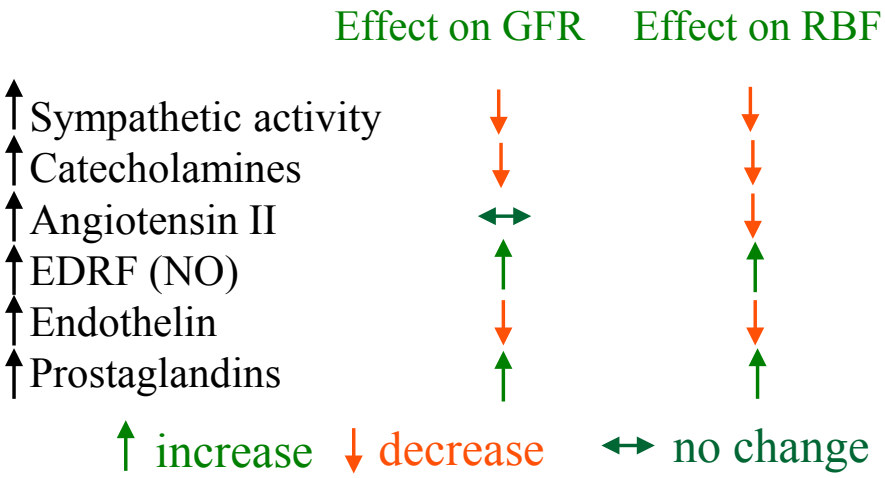
## Summary of neurohumoral control of GFR and renal blood flow

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## Other Factors That Influence GFR

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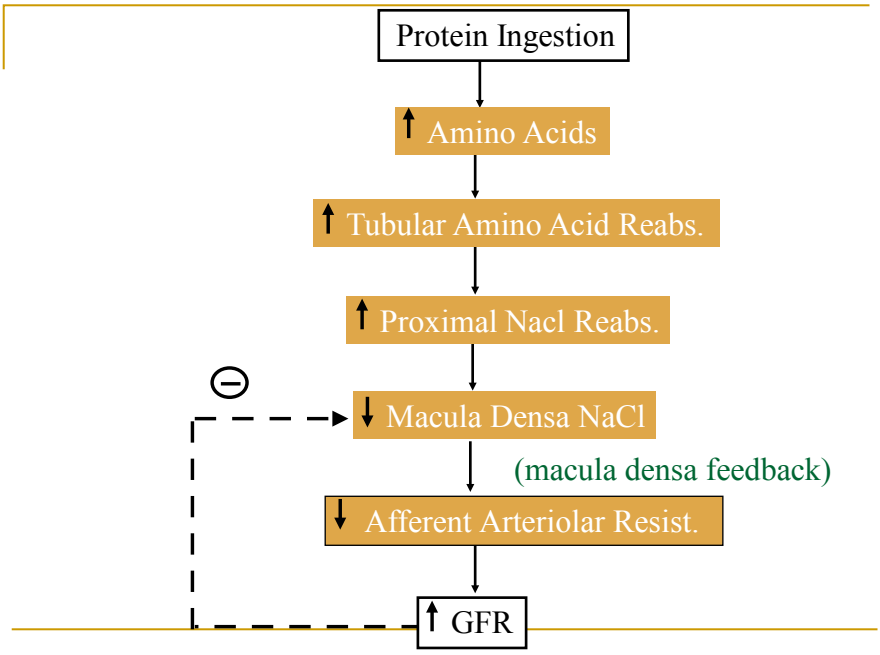


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**••Measuring GFR (Both tGFR and eGFR)**

**Filtered Load**

- If a substance is freely filtered in the kidneys (i.e., its filterability is 1), then the filtration rate of that substance is referred to as the filtered load and is calculated as follow:

**Filtered load** (amount per unit time (mg/min)) = **GFR x plasma concentration**

To measure GFR, you use glomerular marker (Freely filtered, *neither absorbed nor secreted*).

What is going to be filtered /min = what is going to be excreted / min

Do we have such a substance? Actually we do. But we really don't use, since it is an exogenous substance and maintaining its plasma level constant is headache and actually not practical. Anyway this substance is "inulin"

- Inulin is a starch-like polymer of fructose (MW 5000) that is freely filtered (i.e., its filterability is 1). What special about this substance, making it suitable for measuring GFR, is that it is *neither absorbed nor secreted.* In other words, *Inulin that is filtered is that excreted*. Thus, the clearance of inulin is, in fact, the GFR. It doesn't under-or-over-estimate GFR. Mathematically:

- $C_{inulin}$=**GFR x $P_s$ = V x $U_s$.**

- Regardless of its plasma concentration, $C_{in}$ remains constant

- Let us practice calculating plasma clearance using the clearance equation. Assume that the urine production rate (V) is 2 ml/min. Let's start with the substance inulin (not insulin!). If after equilibrium (takes several hour) of inulin, your urine has 30 mg/ml and your plasma has 0.5 mg/ml of this substance, what is the inulin clearance rate? If you got 120ml/min, you are correct. If you did not get 120ml/min, look at the following calculation and recheck your work

  - 120 ml/min = 2 ml/min x 30 mg/ml/ 0.5 mg/ml

  - Test your ability to conduct further calculations by calculating the clearance rate for the following substances:

  - Substance Urine concentration Plasma concentration

  - **Urea** 7.0 mg/ml 0.2 mg/ml

  - **Glucose** 0.0 mg/ml 1.0 mg/ml

  - **Penicillin** 298 mg/ml 0.7 mg/ml

  - Remember that the urine production rate (2ml/min) will be the same for all of the above calculations. The clearance rate for each of the above substances will be: **Urea** = 70 ml/min; **Glucose** = 0 ml/min; **Penicillin** = 851 ml/min!!!too much. Were you able to get the right answers? If not, go back and restudy the clearance process.

- Inulin, like PAH, is an exogenous substance. This makes it only suitable to measure GFR for researchpurposes, and not routine clinical, purposes.

**Creatinine: comes from creas in Latin means flesh اللحم**

Another substance that is endogenous (it is advantage to have endogenous leased at constants rate and does not fluctuate significantly by food intake, physical activity, fasting, . Because It is endogenous source, …we don't need to infuse it to the person. It is frequently used in clinical practice o measure the GFR. Unlike urea, it is not affected by food intake, or dehydration, GIT bleeding etc.Cr concentration does not fluctuate from day to day in plasma

- Small molecule (MW is 114), so it is freely filtered. To convert mg/dl of creatinine to µmol/l, multiply by 88.4. Can you do it to urea (MW 60 concentration 15mg/dl???)

  Freely filtered, not reabsorbed but SLIGHTLY SECRETED (we will deal with this small secretion later on).

  Plasma creatinine by itself (without creatinine clearance) is a good indicator of renal function because it does not relate to food intake or level of exercise

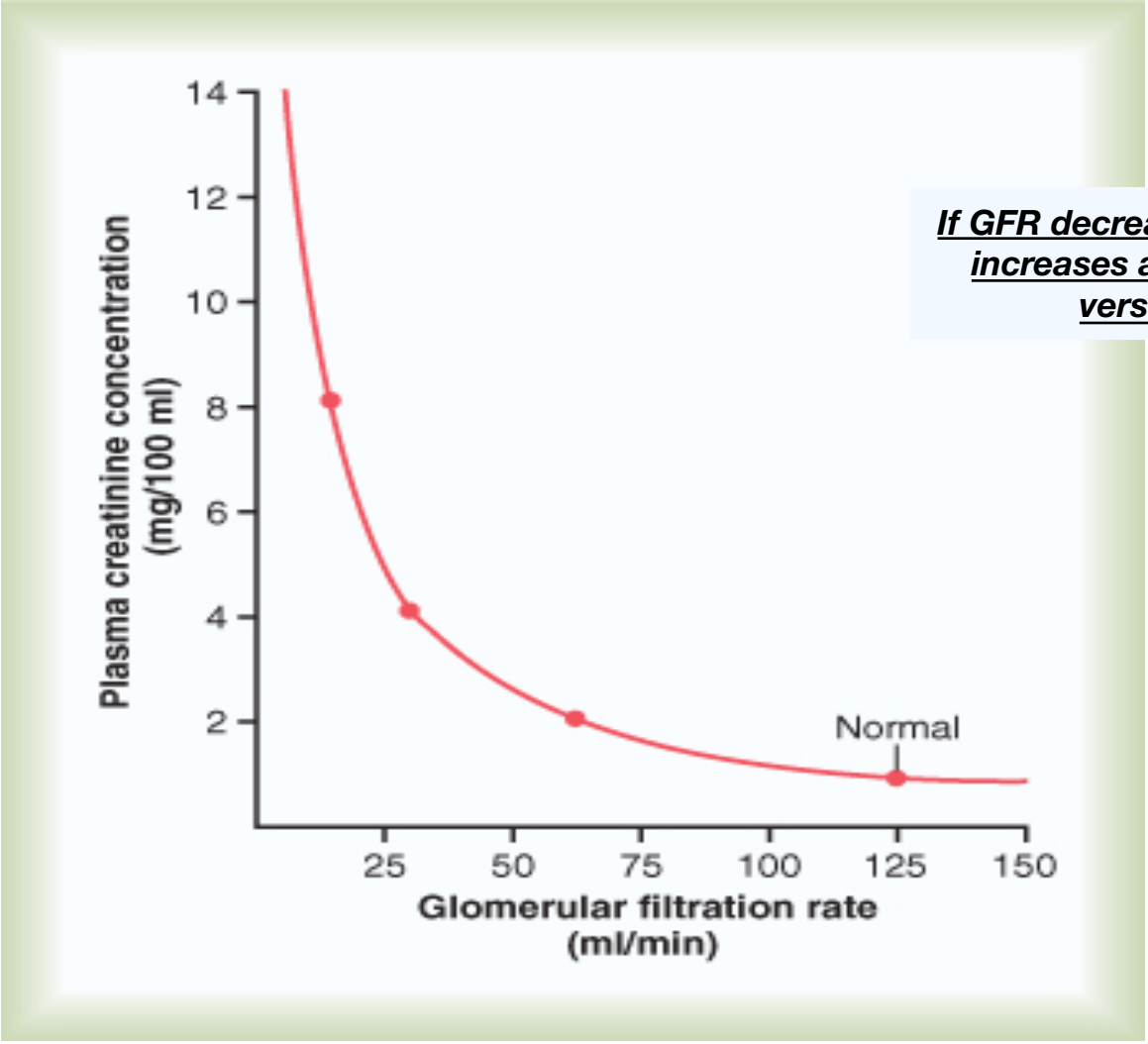
- Creatinine in the urine comes from: 90% filtered and 10% through secretion. This has the potential to overestimates GFR by 10%. But in actuality it does not…why? In fact, it does overestimate GFR in end-stage renal failure…again WHY? Look for the answer in both cases

- Creatinine is freely filtered but around 10% of the excreted comes from secretion (overestimation of GFR at this point..wait). This overestimate the GFR. However, in plasma, 10% of creatinine is bound to proteins, and thus not filtered. This underestimates GFR. Since GFR will be 10% overestimated and 10% underestimated, measured GFR is almost the actual GFR. (they cancel each others)

- **Creatinine**
  As mentioned before, the typical reference ranges are: Men 0.7 to 1.2 mg/dL (60-110 µmol/l), for women: 0.5 to 1.0 mg/dL (about 45-90 µmol/l) . While a baseline serum creatinine of 2.0 mg/dL (150 µmol/l) may indicate normal kidney function in a male body builder (too much muscle), a serum creatinine of 0.7 mg/dL (60 µmol/l) can indicate significant renal disease in a frail old woman.

In the United States, creatinine is typically reported in mg/dL, while in Canada and Europe µmol/litre may be used. 1 mg/dL of creatinine is 88.4 µmol/l.

- **Note:** when measuring plasma creatinine concentration, you should ask the lab which one is measured (is it the free cr or the total cr?)
- Plasma concentration of creatinine is 1 mg/dl (there is wide range0.7-1.2 mg/dl). Therefore, filtered load of creatinine can be calculated by multiplying 1 mg/dl by GFR which is 125 ml/min. This yields 1.25 mg/min or 1.8 g/day. From this you can understand that we excrete 1.8 g of cr/d.




***If GFR decreases, P Cr increases and vice versa***

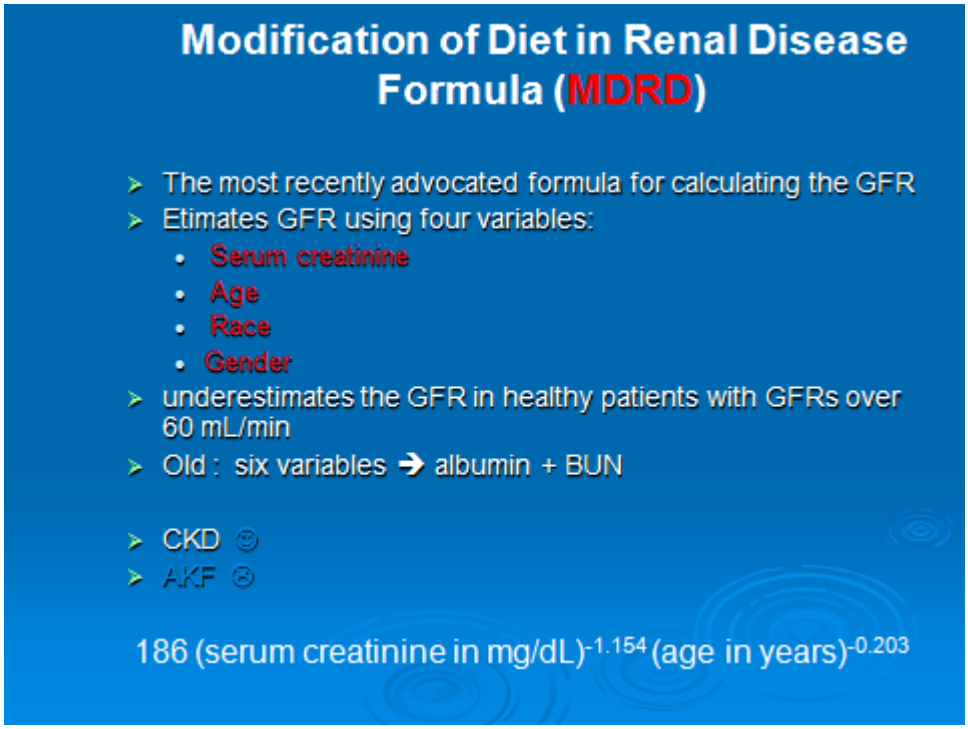
- Creatinine excretion (and formation) rate is also 1.8 g/day. It is not much affected by muscular activity and a range between 1.5 and 2 g/day is considered normal. Females and children have less muscle mass and thus less creatinine levels in plasma and urine.

- Note that the plasma creatinine concentration reflects the GFR. If, for instance, measured to be 3 mg/dl, then one can tell that this 3-fold increase is a result of a decrease in GFR to 1/3: two thirds of nephrons are gone.
- Using the equation of clearance, the clearance of creatinine or **GFR = ($U_{cr}$ x V) / $P_{cr}$.**
- Plasma and urine concentrations of creatinine are easily measured. In contrast, urine volume over the day is not always compatible due to the patients' incompliance, especially elderly and children. Therefore, two equations are used to estimate GFR (ml/min/1.73$m^2$) without the need to collect urine. The first is used to estimate GFR for adults and the second for children:
- **GFR = (140 – age) x ideal body weight x 1 (for males) or 0.85 (for females) / (72 x $P_{cr}$).**
- **GFR = K x height (cm) / $P_{cr}$, where K depends on muscle mass which varies with child age.**
- $C_{creatinine}$
- Cockcroft and Gault formula (in Adults)
- $eC_{cr}$ Estimated creatinine clearance =
- (140–age in yr) x weight (kg) x 0.85 (if female)] divided by serum creatinine concentration (mg/dl)X 72.
- 
- **According to Schwartz Formula in Children** (الارقام والمعادلة للإستئناس وليس للحفظ)
- GFR (mL/min/1.73 $m^2$) = k * Height (cm) / Serum Creatinine (mg/dl)
- k = 0.33 in premature Infants
- k = 0.45 in Term infants to 1 year old
- k = 0.55 in Children to 13 years
- k = 0.65 in Adolescent male

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

- 
- Cockcroft and Gault published an equation to predict creatinine clearance based on age, weight, height and plasma creatinine, together with correction factors. Although helpful, it has many inherent limitations, having been derived mostly from hospitalized men (with only nine females in the cohort), all of whom had CKD. The requirement for weight and height to be provided also restricted its ability to be reported by the laboratory. Despite these shortcomings, it has achieved a considerable prominence, more through cumulated experience than a solid evidence base
- ANY Equation which does not incorporate lean body mass will mislead us.

- **Formulas Used To Estimate GFR (You don't have to memorize** any of them). Ask Google to make the calculation for you. But it is good to understand the origin of these equations.
- Modification of Diet in Renal Disease (MDRD) formula
- Cockcroft-Gault formula
- CKD-EPI formula
- Chronic Kidney Disease Epidemiology Collaboration
- Mayo Quadratic formula
- Schwartz formula

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- The advantage of this equation over Cockcroft and Gault's was the lack of requirement for either body weight or height to be supplied and it became the preferred equation. The MDRD study equation was subsequently validated in patients with diabetic kidney disease, renal transplant recipients, and African-Americans with non-diabetic kidney disease. Given that the MDRD equation was originally derived from a group of CKD patients, its utility for healthy individuals remains unclear, and strictly it has not been validated in children under 18 years of age, in pregnant women, in patients above 70 years of age, and in ethnic groups other than African-American. More importantly, given the rise in the epidemic proportions of global obesity, the MDRD equation has not yet been validated at extremes of body weight, further limiting its usefulness in targeting individuals at higher risks of developing CKD

- Serum creatinine can be affected by age, gender, ethnicity, dietary protein intake, and lean mass and may remain within the reference range despite marked renal impairment in patients with low muscle mass. Consequently, the sensitivity of serum creatinine for the early detection of kidney disease is poor and not a good predictor when analyzing the elderly
- Conversely, theoretically, serum creatinine may be falsely increased in individuals with higher muscle mass and normal tGFR.
- **Cystatin C**, a low molecular weight basic protein (13 kD) that is freely filtered. is an endogenous filtration marker that is being considered as a potential

replacement for serum creatinine. Unlike serum creatinine, the serum concentration of cystatin remains constant up to 50 yr of age. It is commonly accepted that cystatin is produced at a constant rate in virtually all nucleated cells and that it is unaltered by inflammatory conditions. The advantages of using cystatin C as a filtration marker are less influence by age, gender, weight, and muscle mass than serum creatinine. An overall meta-analysis based on 46 studies performed on adults and children demonstrated, by means of receiver operating characteristic analysis, that cystatin C is superior to serum creatinine as a marker of kidney function.

- Blood urea varies with daily protein intake, G.I bleeding, exercise, hypercatabolic states (fever, thyrotoxicosis, trauma etc) and dehydration.
- The ratio of urea to creatinine can be used to determine the etiology of acute renal failure. Normally, the ratio is 10 to 1. The ratio usually exceeds 20 in prerenal failure due to decreased renal perfusion, such as occurs with hypertension, hemorrhage, or dehydration. Postrenal diseases, such as urinary tract obstruction, also increase the ratio between 10 and 20. In intrinsic renal disease because urea and creatinine rise proportionately. The clinical usefulness of this ratio is limited by nonrenal factors that increase urea such as; GI bleeding, parenteral nutrition, and glucocorticoid therapy. GI bleeding increases urea more than creatinine because of increased amino acid absorption from digested blood and hypovolemia.

## BUN:Cr

| BUN:Cr | Urea:Cr | Location | Mechanism |
|---|---|---|---|
| >20:1 | >100:1 | Prerenal (before the kidney) | BUN reabsorption is increased. BUN is disproportionately elevated relative to creatinine in serum. Dehydration is suspected. |
| 10-20:1 | 40-100:1 | Normal or Postrenal (after the kidney) | Normal range. Can also be postrenal disease. BUN reabsorption is within normal limits. |
| <10:1 | <40:1 | Intrarenal (within kidney) | Renal damage causes reduced reabsorption of BUN, therefore lowering the BUN:Cr ratio. |

- Note that the accuracy of GFR measurement using these equations is around 95%. However, in end-stage renal failure, these equations cannot be used since, in this case, GFR approaches zero and thus, excreted amount is the secreted, not filtered; thus, creatinine clearance overestimates GFR.

- the bottom line is that equations for estimation of GFR are available and accurate. Pcr and anthropometric measures are utilized without the need for 24 hour urine collection.

- Gradual loss of renal function with age is a normal process (1% each year), as in the case of the female patient in the previous example. Although her GFR is markedly reduced, it is probable that she has normal renal function. Even if she has hypertension, it is most likely due to age-related vascular degenerative processes.

- Notice that estimations of GFR are unacceptable in cases of end-stage renal disease.

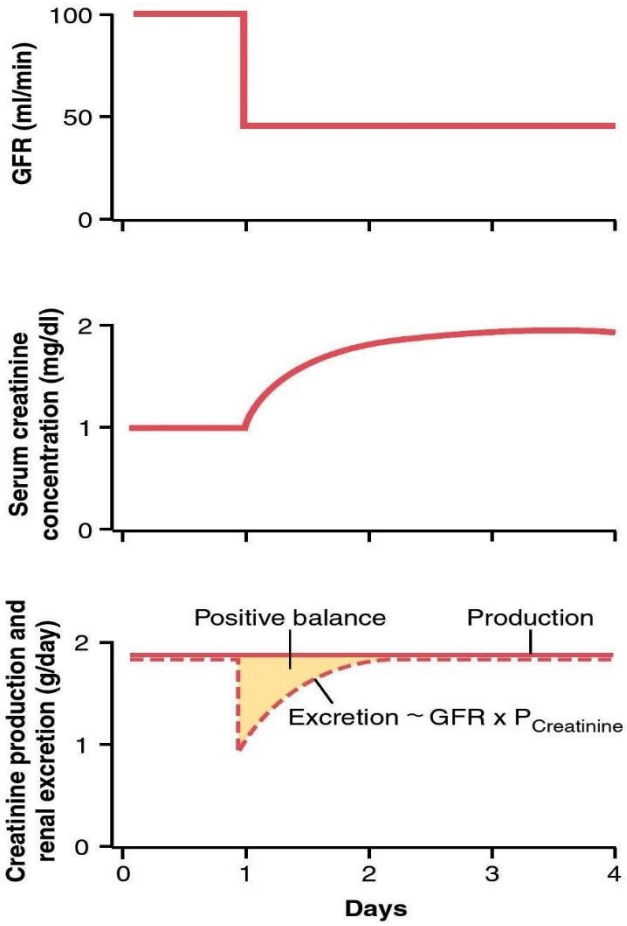
- Renal diseases are classified according to the percentage of GFR to normal:
  - **50-99%:** decreased renal preserve. Usually asymptomatic with normal urea and creatinine levels.
  - **20-49%:** renal insufficiency. Urea and creatinine levels are elevated, and usually, accompanied with anemia and hypertension. However, the patient survives with low salt and protein diet.

  **5-19%:** renal failure. External intervention is needed.

- **<5%:** end-stage renal failure. The patient must undergo hemodialysis and kidney transplant. ○Also, the severity of the renal diseases can be determined by the following classification:
- **60-89%:** mild; **30-59%:**moderate; **15-29%:** severe; **<15%:** end stage renal failure.

- If GFR suddenly decreases by 50%, the kidneys will transiently filter and excrete only half as much creatinine, causing accumulation of creatinine in the body fluids and raising plasma concentration twice normal.

- Plasma concentration of creatinine will continue to rise until the filtered load of creatinine ($P_{Cr}$ × GFR) and creatinine excretion ($U_{Cr}$ × V) return to normal and a balance between creatinine production and creatinine excretion is re-established but at the expense of elevated plasma creatinine concentration.




If P Cr is increased 2 times that means GFR is decreased to 1/2 (loss of 1 million nephrons)
If P Cr increased 4 times that means GFR is decreased to 1/4 (loss of 3/4 of nephrons | only 25% of nephrons are functioning)

| Age | GFR/1.73 m$^2$ | |
|---|---|---|
| | Males | Females |
| 20-29 | 94-140 | 72-110 |
| 30-39 | 79-137 | 71-121 |
| 40-49 | 76-120 | 50-102 |
| 50-59 | 67-109 | 50-102 |
| 60-69 | 54-98 | 45-75 |
| 70-79 | 49-79 | 37-61 |
| 80-89 | 30-60 | 27-55 |
| 90-99 | 26-44 | 26-42 |
| | | |
| | | |

- Use of GFR to classify renal impairment
- 1. Decreased Renal reserve. When 50% of the nephrons are destroyed (One kidney). GFR drops to 50%. Homeostasis is perfectly maintained. Urea and creatinine can be within the normal range.
- 2. Renal Insufficiency: When GFR drops to 20-50%. The earliest sings is isosthenuria or polyuria with isotonic urine. Azotemia, anemia, and hypertension appear too.
- 3. Renal Failure: GFR drops to less than 20% N. All signs and symptoms of uremia (urine in the blood) are present.
- 4. End-stage Renal Disease ESRD: Occurs when GFR drops to less than 5% N. At this stage, dialysis or transplantation are necessary for survival. Is an administrative term rather than medical term. It means that person should be covered by government insurance, because replacement therapy is mandatory

**Note:**
**Some drugs decrease GFR -> tubular fluid in the loop of Henle decreases and because this loop is very thin decrease may lead to crystallization in the loop leading to permanent damage of the kidney**
**And that's why you should follow up with the patient taking these drugs**

- **Staging for Acute Kidney Injury (AKI)** GFR IS USED as a tool
- مرة أخرى ليست الارقام للحفظ ولكن لا مانع من النظر اليها لعلك ترجع لها في سنواتك السريرية )
- The *RIFLE criteria*, proposed by the acute dialysis quality initiative (ADQI) group, aid in the staging of patients with AKI

**Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE) classification**

- Risk: GFR decrease >25%, serum creatinine increased 1.5 times or urine production of < 0.5 ml/kg/h for 6 hours
- Injury: GFR decrease > 50%, doubling of creatinine or urine production < 0.5 ml/kg/h for 12 hours
- Failure: GFR decrease > 75%, tripling of creatinine (> 4 mg/dl) OR urine output below 0.3 ml/kg/h for 24 hours or anuria for 12 hours.
- Loss: persistent AKI or complete loss of kidney function for more than 4 weeks
- End stage renal disease: need for renal replacement therapy (RRT) for more than 3 months