PHYSIOLOGY

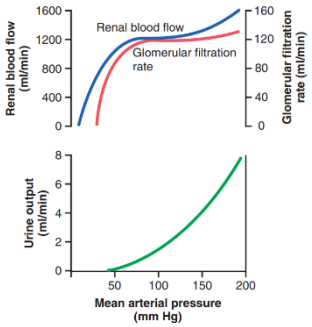
- SHEET NO. 4
- WRITER : Hamza Abu-Farsakh
- CORRECTOR :
- DOCTOR : Ebaa

In this lecture we will discuss mainly the GFR regulation methods

General notes:

- The glomerular capillary hydrostatic pressure has been estimated to be about 60 mm Hg under normal conditions.
- Changes in glomerular hydrostatic pressure serve as the primary means for physiological regulation of GFR.
- Increases in glomerular hydrostatic pressure raise the GFR, whereas decreases in glomerular hydrostatic pressure reduce the GFR.

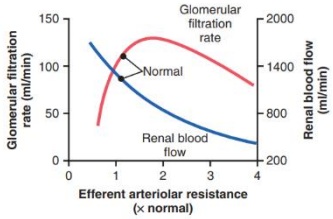
HYDROSTATIC AND ONCOTIC EFFECTS ON GFR



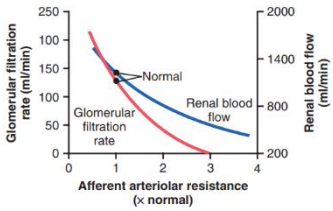
Glomerular hydrostatic pressure is determined by three variables, each of which is under physiological control:
(1) arterial pressure
(2) afferent arteriolar resistance
(3) efferent arteriolar resistance.

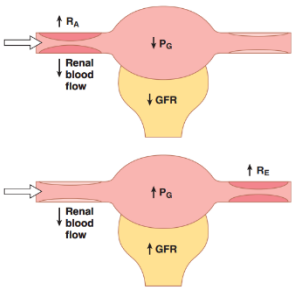
Increased arterial pressure tends to raise glomerular hydrostatic pressure and, therefore, to increase the GFR. (However, as discussed later, this effect is buffered by autoregulatory mechanisms that maintain a relatively **constant glomerular pressure** as blood pressure fluctuates.)

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



- Constriction of the efferent arterioles increases the resistance to outflow from the glomerular capillaries. This mechanism raises glomerular hydrostatic pressure, and as long as the increase in efferent resistance does not reduce renal blood flow too much, GFR increases slightly (see Figure 27-6). However, because efferent arteriolar constriction also reduces renal blood flow, **filtration fraction and glomerular colloid osmotic pressure increase as efferent arteriolar resistance increases**. Therefore, if constriction of efferent arterioles is severe (more than about a *threefold increase* in efferent arteriolar resistance), the rise in colloid osmotic pressure exceeds the increase in glomerular capillary hydrostatic pressure caused by efferent arteriolar constriction. When this situation occurs, the net force for filtration actually decreases, causing a reduction in GFR.





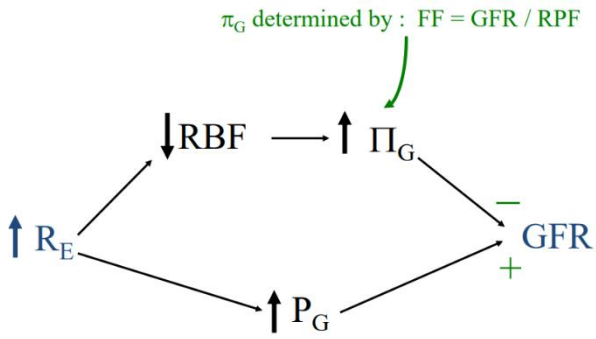
Thus, efferent arteriolar constriction has a **biphasic** effect on GFR :

A) At moderate levels of constriction, there is a slight increase in GFR.
B) But with severe constriction, there is a decrease in GFR.

To summarize, constriction of afferent arterioles reduces GFR. However, the effect of efferent arteriolar constriction depends on the severity of the constriction; modest efferent constriction raises GFR, but severe efferent constriction (more than a threefold increase in resistance) tends to reduce GFR.

Physical Determinants*	Physiological/Pathophysiological Causes
$\downarrow K_f \rightarrow \downarrow GFR$	Renal disease, diabetes mellitus, hypertension
$\uparrow P_B \rightarrow \downarrow GFR$	Urinary tract obstruction (e.g., kidney stones)
$\uparrow \pi_G \rightarrow \downarrow GFR$	↓ Renal blood flow, increased plasma proteins
$\downarrow P_G \rightarrow \downarrow GFR$ $\downarrow A_P \rightarrow \downarrow P_G$	↓ Arterial pressure (has only a small effect because of autoregulation)
$\downarrow R_E \rightarrow \downarrow P_G$	↓ Angiotensin II (drugs that block angiotensin II formation)
$\uparrow R_A \rightarrow \downarrow P_G$	↑ Sympathetic activity, vasoconstrictor hormones (e.g., norepinephrine, endothelin)

*Opposite changes in the determinants usually increase GFR.
A_P, systemic arterial pressure; GFR, glomerular filtration rate; K_f, glomerular filtration coefficient; P_B, Bowman's capsule hydrostatic pressure; π_G, glomerular capillary colloid osmotic pressure; P_G, glomerular capillary hydrostatic pressure; R_A, afferent arteriolar resistance; R_E, efferent arteriolar resistance.

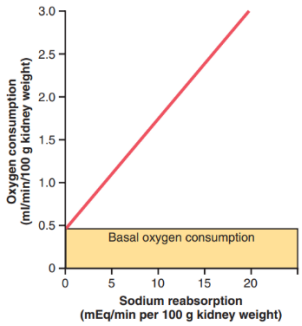


Renal Blood Flow

Kidneys receive an extremely high blood flow compared with other organs (22% of cardiac output). As with other tissues, blood flow supplies the kidneys with **nutrients and removes waste products**. But The purpose of this additional flow is to supply enough plasma for the **high rates of glomerular filtration** that are necessary for precise regulation of body fluid volumes and solute concentrations. As might be expected, the mechanisms that regulate renal blood flow are closely linked to the control of GFR and the excretory functions of the kidneys.

On a per-gram-weight basis, the kidneys normally consume oxygen at **twice the rate of the brain** but have almost **seven times the blood flow of the brain**. A large fraction of the oxygen consumed by the kidneys is related to the high rate of **active sodium reabsorption by the renal tubules**. If renal blood flow and GFR are reduced and less sodium is filtered, less sodium is reabsorbed and less oxygen is consumed.

Therefore, renal oxygen consumption varies in proportion to renal tubular sodium reabsorption, which in turn is closely related to GFR and the rate of sodium filtered. If glomerular filtration completely ceases, renal sodium reabsorption also ceases and oxygen consumption decreases to about one-fourth normal. **This residual oxygen consumption reflects the basic metabolic needs of the renal cells**.



CONTROL OF GFR AND RENAL BLOOD FLOW

Renal blood flow is determined by the pressure gradient across the renal vasculature (the difference between renal artery and renal vein hydrostatic pressures), divided by the total renal vascular resistance:

$$\frac{\text{(Renal artery pressure} - \text{Renal vein pressure)}}{\text{Total renal vascular resistance}}$$

As in other vascular beds, the total vascular resistance through the kidneys is determined by the **sum of the resistances in the individual vasculature segments,** including the arteries, arterioles, capillaries, and veins.

Most of the renal vascular resistance resides in three major segments:

1- interlobular arteries
2- afferent arterioles
3- efferent arterioles

Resistance of these vessels is controlled by the **sympathetic nervous system**, various **hormones**, and local **internal renal control** mechanisms. An increase in the resistance of any of the vascular segments of the kidneys tends to reduce the renal blood flow, whereas a decrease in vascular resistance increases renal blood flow, those factors change the GFR by altering both the **glomerular hydrostatic pressure** and the **glomerular capillary colloid osmotic pressure**.

P.S : Although changes in arterial pressure have some influence on renal blood flow, the kidneys have effective mechanisms for maintaining renal blood flow and GFR relatively constant over an arterial pressure range between 80 and 170 mm Hg, a process called **autoregulation**. This capacity for autoregulation occurs through mechanisms that are completely intrinsic to the kidneys.

SYMPATHETIC NERVOUS SYSTEM

Both the afferent and the efferent arterioles, are richly innervated by sympathetic nerve fibers.
A) **Strong activation** of the renal sympathetic nerves(ex : hemorrhage) **affects the afferent more** and can constrict the renal arterioles and decrease renal blood flow and GFR, which is very important in such severe conditions.
B) **Moderate or mild** sympathetic stimulation **affects the afferent and efferent equally** so they cancel each other (ex : stress or sports) and has little influence on renal blood flow and GFR.

HORMONAL REGULATION

1- Endothelin :

a **vasoconstrictor** peptide that can be released by **damaged vascular endothelial cells** of the kidneys. Endothelin may contribute to hemostasis (minimizing blood loss) when a blood vessel is severed, which damages the endothelium and releases this powerful vasoconstrictor. Plasma endothelin levels are also increased in many disease states associated with vascular injury, such as, **acute renal failure, and chronic uremi**a, and may contribute to renal vasoconstriction and decreased GFR in some of these pathologies.

- If endothelin is upregulated, it might cause hypertension which can be treated by endothelin antagonist.

2- Angiotensin II

Is released after a series of reactions that starts by the release of renin from juxtaglomerular cell, which is stimulated by:

1- low perfusion
2- low sodium concentration
3- sympathetic stimulation

Angiotensin II Constricts **Efferent** Arterioles in Most Physiological Conditions. A powerful renal vasoconstrictor, angiotensin II, can be considered a circulating hormone and a locally produced autacoid because it is formed in the kidneys and in the systemic circulation.However,

Effect on the afferent arterioles : the afferent arterioles, appear to be **relatively protected** from angiotensin II–mediated constriction in most physiological conditions associated with activation of the renin-angiotensin system, such as during a **low-sodium diet or reduced renal perfusion** pressure due to renal artery stenosis. This protection is due to release of vasodilators, especially **nitric oxide and prostaglandins**, which counteract the vasoconstrictor effects of angiotensin II in these blood vessels.

Effect on The efferent arterioles : they are highly sensitive to angiotensin II. Because angiotensin II preferentially constricts efferent arterioles in most physiological conditions, increased angiotensin II levels raise glomerular hydrostatic pressure while reducing renal blood flow. the increased level of angiotensin II, by constricting efferent arterioles, helps **prevent decreases in glomerular hydrostatic pressure and GFR.**

At the same time, the reduction in renal blood flow caused by efferent arteriolar constriction contributes to decreased flow through the peritubular capillaries, which in turn **increases reabsorption of sodium and water**. Thus, increased angiotensin II levels that occur with a low-sodium diet or volume depletion help **maintain GFR** and normal excretion of metabolic waste products such as urea and creatinine that depend on glomerular filtration for their excretion; at the same time, the angiotensin II–induced constriction of efferent arterioles **increases tubular reabsorption of sodium and water,** which helps restore blood volume and blood pressure.

3- **E**ndothelial-**D**erived **N**itric **O**xide

EDNO decreases renal Vascular resistance and Increases GFR by dilating mainly the **afferent** arterioles . A basal level of nitric oxide production appears to be important for maintaining vasodilation of the kidneys because it allows the kidneys to excrete normal amounts of sodium and water.

In some **hypertensive** patients or in patients with **atherosclerosis**, damage of the vascular endothelium and impaired nitric oxide production may contribute to increased renal vasoconstriction and **elevated blood pressure.**

4- Prostaglandins and Bradykinin

Decrease Renal Vascular Resistance Tend to Increase GFR. Hormones and autacoids that cause vasodilation and increased renal blood flow and GFR include the **prostaglandins (PGE2 mainly)** which are synthesized in the kidneys and bradykinin. Although these vasodilators do not appear to be of major importance in regulating renal blood flow or GFR in normal conditions.
By opposing vasoconstriction of **mainly afferent** arterioles, the prostaglandins may help **prevent excessive reductions in GFR and renal blood flow**. Under stressful conditions, such as volume depletion, Sodium depletion or after surgery, **the administration of nonsteroidal anti-inflammatory agents, such as aspirin, that inhibit prostaglandin synthesis may cause significant reductions in GFR, so NSAIDs are contraindicated.**

Hormone or Autacoid	Effect on GFR
Norepinephrine	↓
Epinephrine	↓
Endothelin	↓
Angiotensin II	↔ (prevents ↓)
Endothelial-derived nitric oxide	↑
Prostaglandins	↑

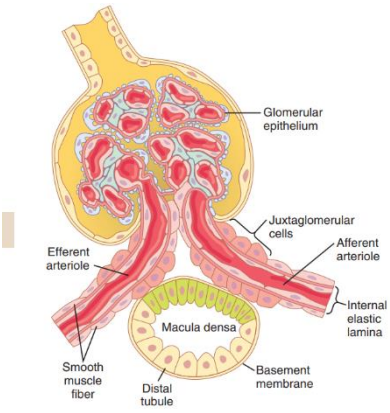
PS: NE & E have the same action as the sympathetic NS.

Autoregulation of GFR and Renal Blood Flow

1- Myogenic Mechanism : which related to the smooth muscle activity of the glomerular arterioles
2- Macula Densa feedback (Tubluloglomerular)
3- Angiotensin II

Tubluloglomerular feedback

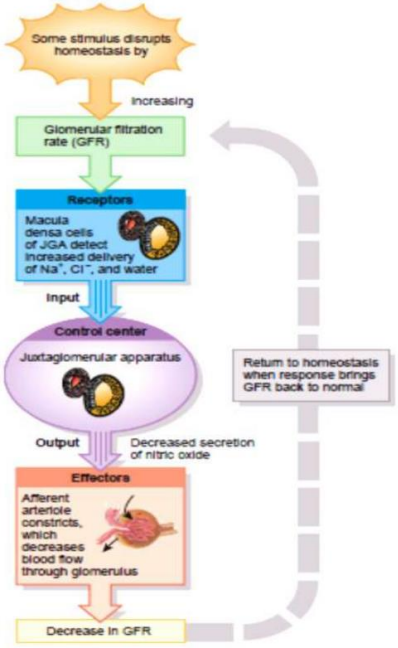
The juxtaglomerular complex consists of macula densa cells in the initial portion of the distal tubule and juxtaglomerular cells in the walls of the afferent and efferent arterioles. The macula densa is a specialized group of epithelial cells in the distal tubules that comes in **close contact** and cross-talks with the **afferent (MAINLY)** and efferent arterioles.

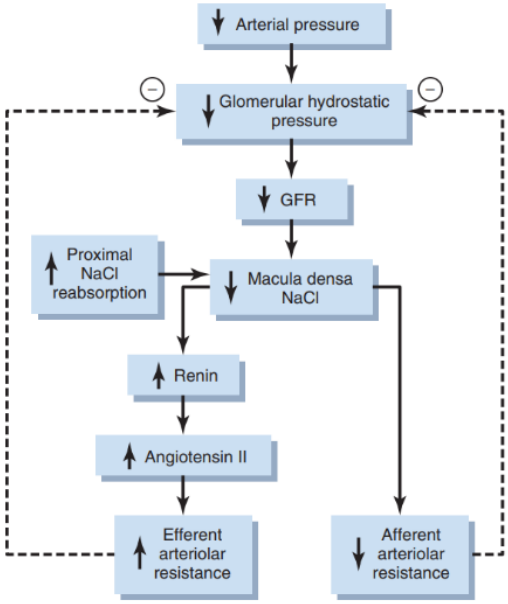


The macula densa cells sense changes in NaCl delivery to the distal tubule and by a way of signaling it changes the resistance in the **afferent arterioles**, so :

A) if NaCl delivery Is high, then GFR is high and we should decrease it → vasoconstriction
B) if NaCl delivery Is low, then GFR is low and we should increase it → vasodilation

The same pathway causes **renin** release from **juxtaglomerular** cells which ends in **Angiotensin II**, so it's also considered a part of the autoregulation mechanisms.





كل التوفيق ♥