The Cardio-VASCULAR System

- ○ Anatomy
- ○ Histology
- ○ Pathology
- ○ Pharmacology
- ● Physiology
- ○ Microbiology

Lec #: **17**

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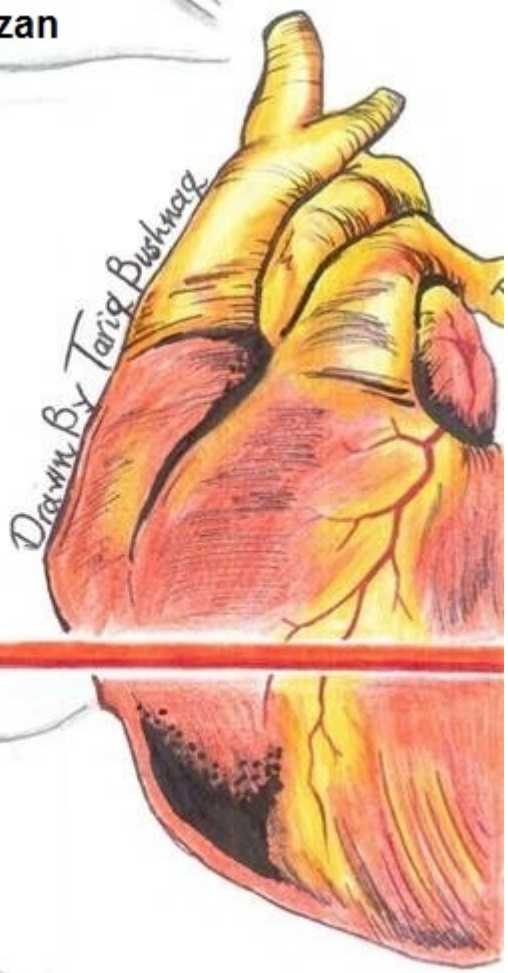
- ○ Handout
- ● Sheet
- ○ Slide



Intermediate and long term regulators

Last time we talked about short-term regulation of blood pressure and we've ended talking about the **chemoreceptors**.

These receptors are located in the same areas of arterial baroreceptors in the carotid sinus and the aortic arch.

The carotid body and the aortic body are highly vascularized to the extent that their arterial blood O2, CO2, and Hydrogen concentrations **is the same** as their interstitial fluid O2, CO2, and Hydrogen concentrations.

Any change in the concentration of O2, CO2, or Hydrogen will affect the chemoreceptors.

The chemoreceptors are not stimulated until the pressure falls below 80.

How can we change the chemical concentration?

By increasing or decreasing the bloods flow.

$$\text{Blood Flow} = \frac{\Delta P}{TPR}$$

If there is a **DECREASE in the pressure** this will lead to the decrease in the blood flow, which will affect the chemical concentration by ↑CO2 ↑H+ ↓O2 and these will stimulate the chemoreceptors. Impulses will be sent to the cardiovascular centers and vasomotor area this will stimulate the vasoconstrictor area and the cardio-acceleratory center.

∴ More sympathetic to the heart and vessels

∴ More sympathetic to the vessels → vasoconstriction ↑TPR

∴ Less parasympathetic to the heart

∴ ↑Heart Rate ↑SV ↑Cardiac output

So both CO and TPR have increased in this case in order to maintain the MAP to its normal value.

If there is **INCREASE in the pressure** this will lead to the increase in the blood flow, which will affect the chemical concentration by ↓CO_2 ↓H^+ ↑O_2 and these will inhibit the chemoreceptors leading to inhibition in the vasoconstrictor area and the cardio-acceleratory center.

∴Less sympathetic to the heart and vessels

∴Less sympathetic to the vessels → vasodilation ↓TPR

∴More parasympathetic to the heart

∴↓Heart Rate ↓SV ↓Cardiac output ↓contractility

* The peripheral chemoreceptors are very important in the respiratory system.

In patients with **chronic respiratory diseases** (low O_2 and high CO_2), the central chemoreceptors that are located the medulla oblongata are adapted to the high level of CO_2, so this high level of CO_2 will not stimulate them anymore. These patients are living under the stimulation of ↑CO_2 to *the peripheral chemoreceptors* instead of the central.

The main stimulus for these patients for the peripheral chemoreceptor is the low O_2.

Giving these patients for example 100% OXYGEN might kill them because the peripheral chemoreceptors (which they're living on) will be inhibited, and less stimulation to the respiratory center → Respiratory Failure.

Treatment: increasing their oxygen gradually.

Blood Pressure Regulation – PART 2

The intermediate term and long term regulators.

Factors affecting the total peripheral resistance:

1. Blood viscosity
2. Arteriolar radius: affected by local vasodilators (high CO2,highH+,low O2, K+, Bradykinin, adenosine) and local vasoconstrictors.

There are two types of vasodilators and vasoconstrictor:

1-Local: works locally

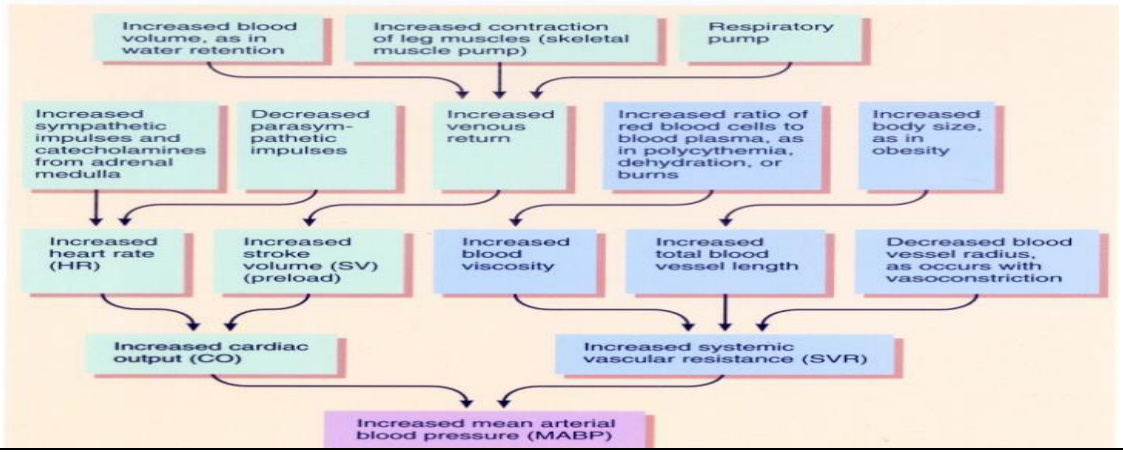
2-Systemic: works systematically (Epinephrine, Norepinephrine, Angiotensin 2, vasopressin)

Mean Arterial Pressure = TPR * CO

∴MAP is affected by many factors and we can conclude these factors from the equation above.

= TPR: Vasodilators and vasoconstrictors by affecting the radius (main factor), length of the vessel (the least to affect), viscosity.

= CO: Stroke volume, venous return, heart rate (sympathetic, parasympathetic). CO= SV * HR



Intermediate term regulators

If a patient had a car accident and start bleeding, unfortunately the ambulance couldn't reach him immediately and he continued bleeding. What will happen?

Blood volume ↓ MAP ↓ (Venous return curve will shift to the left)

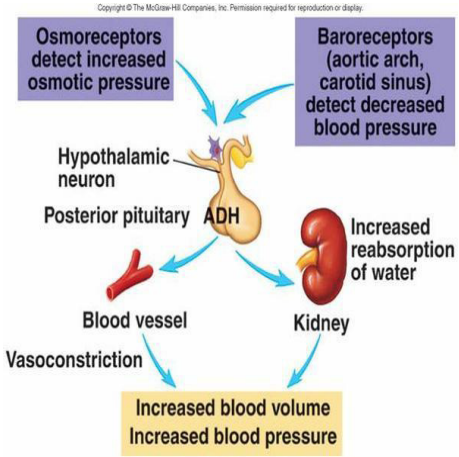
∴Activation of baroreceptor within minutes trying to ↑MAP

If he is still bleeding <u>after 10 minutes</u> other systems must be activated**, *Epinephrine and norepinephrine system*** from the adrenal medulla. The delay in the activation of this system, is due to the time needed for the kidney to synthesize new EPINEPHRINE and norepinephrine as the already formed ones are not enough.

This system is activated by sympathetic stimulation; as blood pressure falls baroreceptors are activated sending messages to cardiovascular centers which send too much sympathetic, part of this sympathetic will go to the adrenal medulla stimulates epinephrine and norepinephrine synthesis.

So the epinephrine and norepinephrine are increased and the advantage is that they will cause systemic vasoconstriction, trying to ↑MAP.

If he is still bleeding <u>after 30 minutes</u> other system will start to work, which is the ***ADH system "vasopressin"*** *by the stimulation of hypothalamus to secret ADH, this will*



try to increase the TPR byvasoconstriction and by increase water reabsorption from the distal part of the kidneys' tubules trying to ↑extracellular fluid volume ↑Blood volume ↑MSFP ↑VR ↑CO ↑EDV ↑SV , to ↑MAP.

After one hour, still there is no medical help. A third system will be activated ***Renin-Angiotensin-Aldosterone system.***

In case of hypotension low blood pressure; the pressure of the afferent arterioles of the kidney goes down, then Renin is secreted from afferent arteriolar cells (in a system called Juxtaglomerular Apparatus), Renin works on Angiotensinogen (14 amino Acids peptide) by breaking it into Angiotensin I (10 amino acids peptide) will circulate in the body, and in the lungs it is broken down into Angiotensin II (8 amino acids peptide).

Note: Angiotensin II is the most potent vasoconstrictor in the body. It also works as a positive inotropic agent ↑contractility trying to increase the pressure up.

Angiotensin II goes to the adrenal cortex, in the cortex there are 3 zones from the outside to the inside: (GFR)

1- Zona glomerulosa (G)

2- Zona fasiculata (F)

3- Zona reticularis (R)

Angiotensin II primarily goes to zona glumerulosa and stimulates the release of aldosterone, which is a steroid, that goes to the distal tubule of the kidney and stimulates Sodium and water reabsorption thus increasing the extracellular fluid volume:

↑blood volume

↑MSFP

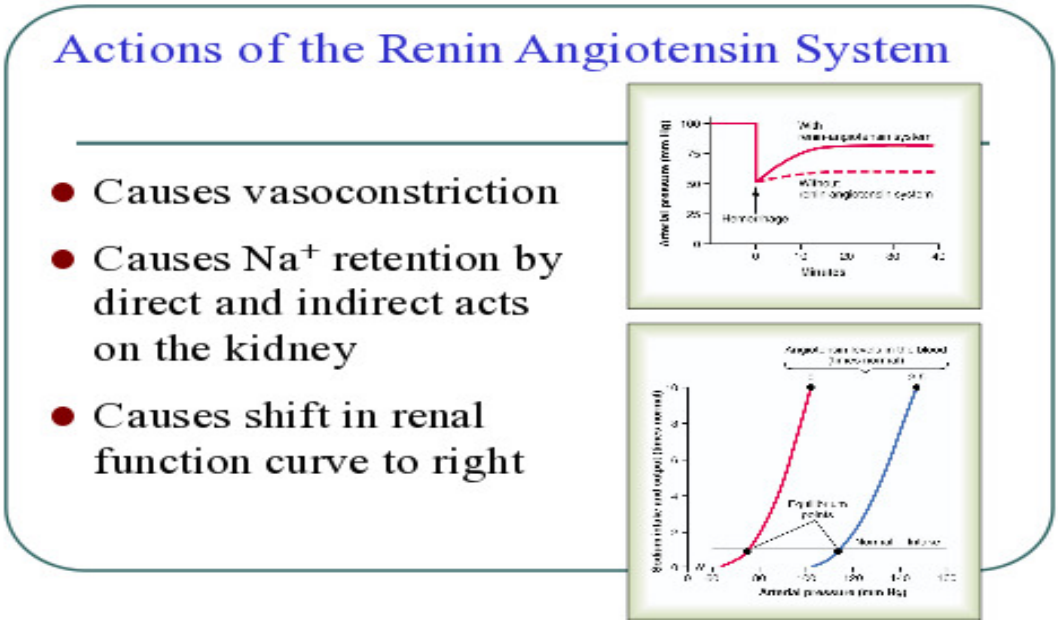
↑Venous Return

↑EDV

↑SV

↑Cardiac output

↑Blood pressure



If these systems have failed to increase his blood pressure, the patient will go to **irreversible shock** (his organs start to fail).

The Atrial Natriuretic Peptide (ANP)

This hormone of 28 Amino Acid is secreted from the atria primarily from the right atrium and causes sodium execration followed by water. ∴↓Blood volume.

It is secreted in case of *hypertension* and inhibited in case of *hypotension.*

The stimulus in the ANP system is the atrial stretch.

More volume in the right atrium →More stretch → More stimulus

In case of hypertension there is less sympathetic outflow, less epinephrine and NE secretion, less ADH secretion, Low Angiotensin II, but ANP is increased.

A patient who was bleeding because of a car accident two hours ago came to the emergency room, and when you measured his blood pressure it was in the normal range, you as a doctor should not be misled by this blood pressure and let this patient go. This almost normal blood pressure is due to the high level of angiotensin II and high levels of Epi and NE and overstimulation of the baroreceptors.

Treatment: IV FLUID to reverse the effect of the hormone.

If the bleeding patient (that we talked about before) is still bleeding and his blood pressure went below 60 mmHg (Remember we said that baroreceptors work within BP from 60 -180 mmHg.)

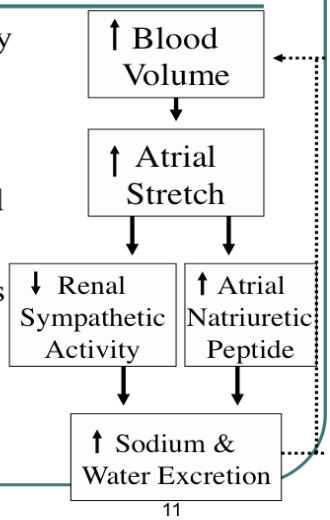
So in this case the patient will suffer from ischemia in the brain, CNS ischemia.

The last chance for this patient to survive is by the ***CNS Ischemic response***, which sends extensive sympathetic stimulation to the whole body trying to increase the MAP , so if it works he is safe, if not he unfortunately will go into organ failure

The doctor then read these two slides:

Atrial and Pulmonary Artery Reflexes

- Low pressure receptors in atria and pulmonary arteries minimize arterial pressure changes in response to changes in blood volume.
- Increases in blood volume activates low pressure receptors which in turn lower arterial pressure.
- Activation of low pressure receptors enhances Na^+ and water by:
  - Decreasing rate of antidiuretic hormone
  - Increasing glomerular filtration rate
  - Decreasing Na^+ reabsorption



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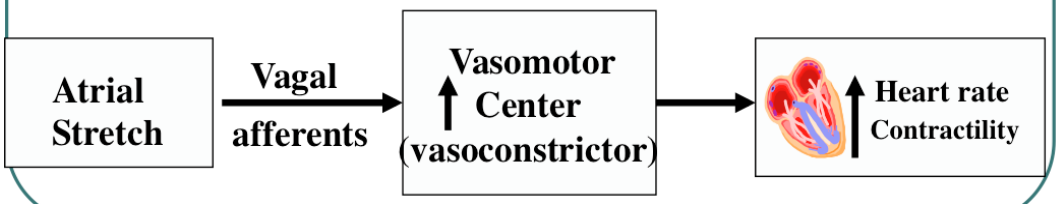
Bainbridge Reflex

- Prevents damming of blood in veins atria and pulmonary circulation.
- Increase in atrial pressure increases heart rate.
- Stretch of atria sends signals to VMC via vagal afferents to increase heart rate and contractility.



Why do we need the long-term regulators when we already have the short ones?

Because the short regulators that are usually nervous system *adapt the change* and in two to three days they no longer work. In addition, short regulators are reseting systems, have low gain system, and the error is high.

Long-term pressure regulators:

Renal body fluid system plays a dominant role in long-term pressure control.

Regulating the MAP, mainly by increasing or decreasing the extracellular fluid in a long term manner, as extracellular fluid volume *increases* arterial pressure *increaes.*

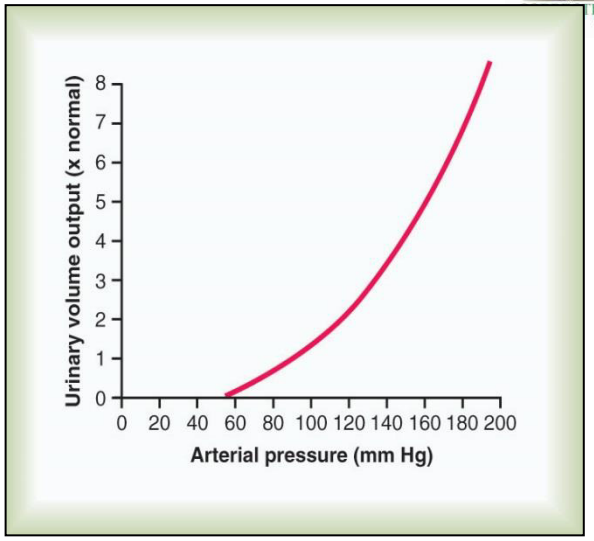
> If we give a patient IV fluid, blood pressure will increase by the increase of blood volume that will increase MSFP, ↑Venous Return,↑EDV,↑SV,↑Cardiac output,↑Blood pressure.
>
> Increasing the CO will stimulate the kidney to produce more urine.

The increase in arterial pressure will cause the loss of Na and water from the kidney, which returns extracellular fluid volume to normal, this effect is called ***pressure diuresis and natriuresis***, more formation of urine.

#The effect of pressure to increase water excretion is called **pressure diuresis**.

#The effect of pressure to increase Na excretion is called **pressure natriuresis**.

This curve represents the renal function curve



*This curve is Normal

MAP: normal level of angiotensin II - #high levels of angiotensin II (due to a kidney disease) , the curve will be shifted to the right 》 MAP is high

Treatment:

1) Angiotensin converting enzyme inhibitor and angiotensin II receptor blockers

2) Diuretics and decrease Na intake

#low levels of angiotensin II ,The curve will be shifted to the left MAP is low So, the curve can be shifted to the left or right by increasing or decreasing angiotensin II even though the intake is constant.

Renal body fluid feedback system has an infinite gain.

The gain of uncontrolled system= correction/error

If the MAP was 100 mmHg and it goes higher for example 120 mmHg the baroreceptor try to bring it back to normal but what happens here is that it will not reach 100 mmHg it instead might reach 105 mmHg so there is an error of 5 mmHg and the correction is (120-105) = 15 mmHg.

The gain of uncontrolled system = 15/5 = 3

In contrast, the long term regulators take longer time and when the MAP increase above its normal value they will bring it back to 100.0001, the correction is 19.999 and the error is 0.0001 almost ZERO.

The gain of uncontrolled system= 19.999/ZERO = $\propto$ (infinite)

If the gain is *High* the system is good, if the gain is *Low* the system is bad, taking in consideration how fast the systems are

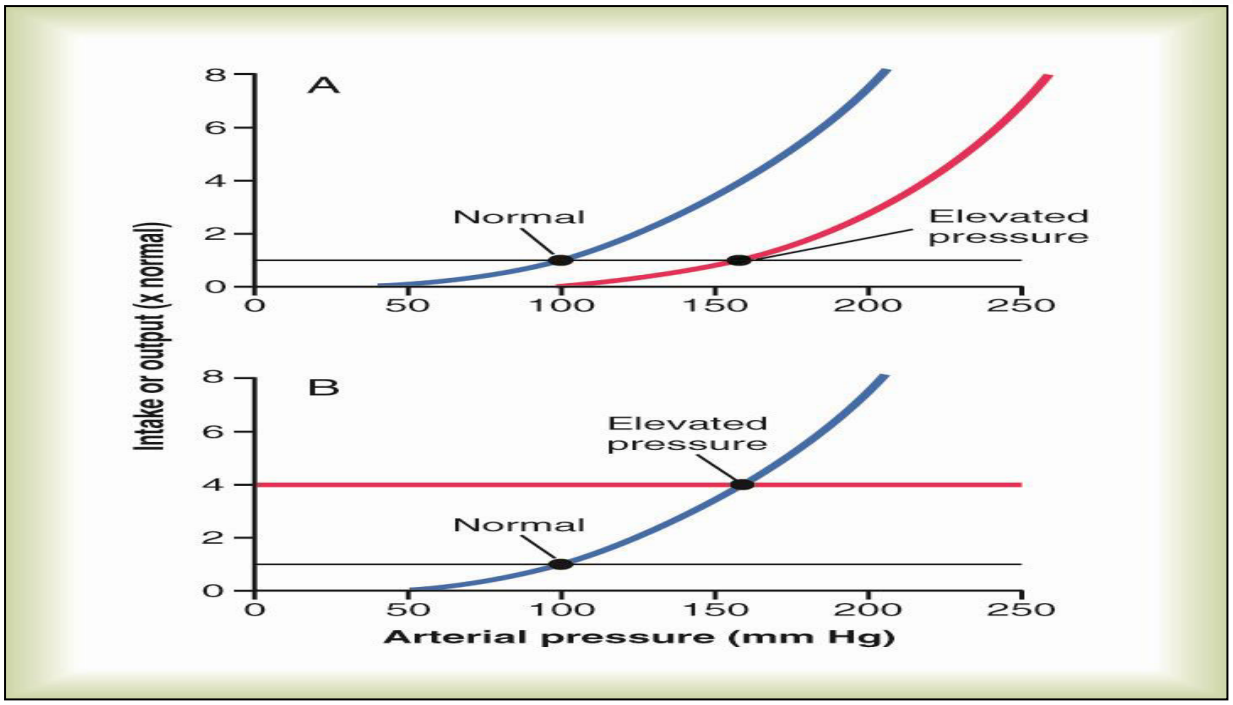


Figure B:

Red line: very high intake of fluids in a long-term manner

Blue line: normal kidney function curve

Elevated MAP.

Figure A:

With normal fluid intake and a renal disease.

The curve will shift to the *Right*.

Elevated MAP.

#Equilibrium point is where intake and output curves intersect.

Factors that affect MAP on the long term:

1- Renal function
2- Salt and fluid intake

How can I shift the red curve in figure A to the left?

By giving ACEI that inhibits the synthesis of Angiotensin II.

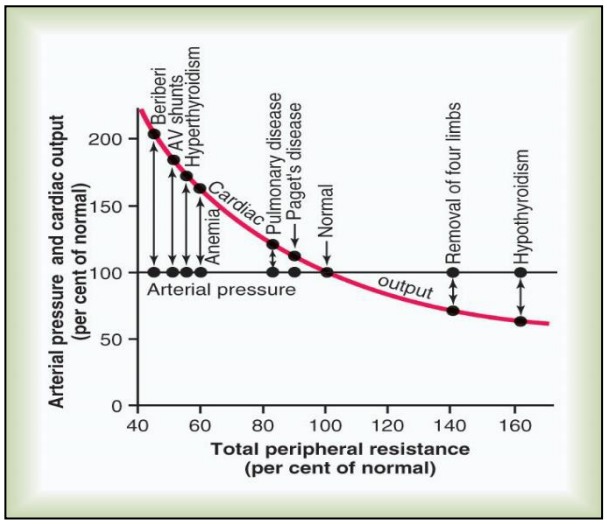
Or by giving ARB that blocks Angiotensin II rec

Vasodilators are given to patient with an acute hypertension (SHORT TERM)

Remember: The main reason for secondary hypertension is Renal Disease.

Changing the **TPR** is not important in long term regulation of blood pressure, because when TPR is changed CO will change to the extent that MAP will not change.

That's why vasodilators are not diven as along term treatment of HTN.



But in cases of emergency HTN vasodilators are given to decrease his pressure rapidly, but we will not discharge the patient on vasodilators.

But changing renal vascular resistance does lead to long-term changes in arterial pressure.

Sodium is a Major Determinant of ECFV:

Sodium causes hyperosmolarity, stimulates the thirst center, and ADH secretion. As Na^+ intake is increased; Na^+ stimulates drinking ↑Blood Volume.

Changes in Na^+ intake leads to changes in extracellular fluid volume (ECFV).

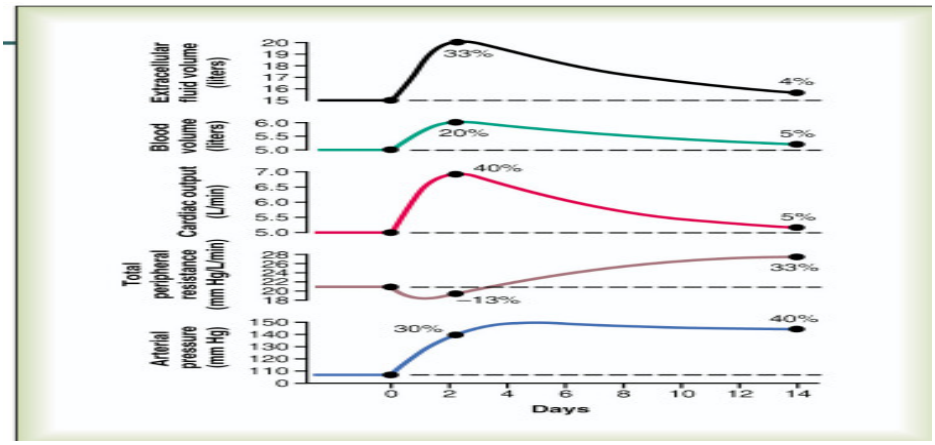
The balance of Na+ intake and output determines ECFV.

Volume loading HTN

Too much ECFV ↑Blood volume ↑CO ↑RAP

The TPR might decrease a little bit because very high pressure exerted on the wall of the vessel might relax them.

Then it gets back to normal because of the increase in urine formation



Renin-Angiotensin System:

Renin is released in response to a fall in pressure.

Renin is synthesized and stored in modified smooth muscle cells in afferent arterioles of the kidney.

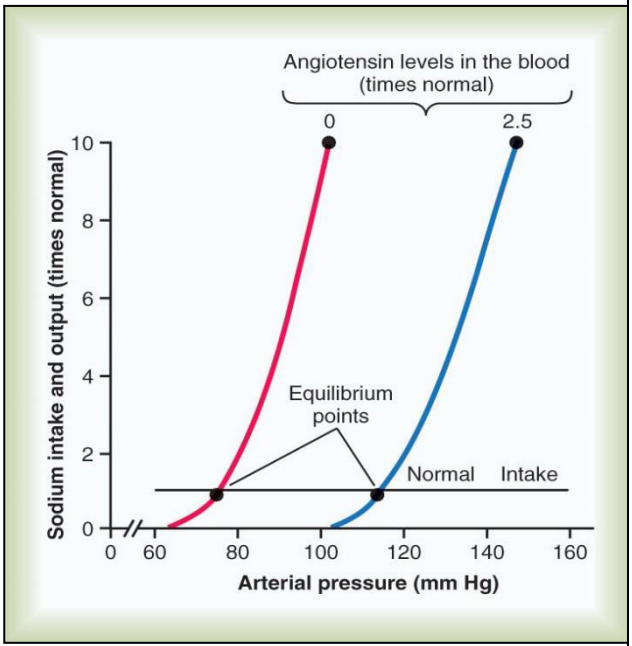
Renin will stimulates the Angiotensin I (mainly in the lungs)

Angiotensin I is converted to Angiotensin II, which works on the heart and vessels causing vasoconstriction.

Actions of the Renin Angiotensin System

This is again the renal function curve.

When we increase the angiotensin level from zero to 2.5, the curve is shifted to the *right*, as the pressure has increased in response to the increased levels of angiotensin.



How to bring the curve back to normal?

To shift the curve to the left, ACEI or ARB is given.

Factors that increase or reduce blood pressure:

Reduce Blood Pressure	Increase Blood Pressure
❖ Atrial natriuretic peptide ❖ Nitric oxide ❖ Dopamine	❖ Angiotensin II ❖ Aldosterone ❖ Sympathetic nervous activity ❖ Endothelin