Vascular - physio

Hemodynamics

Objectives

- ✓ Point out the physical characteristics of the circulation :
  - distribution of blood volume
  - total cross sectional area
  - velocity
  - blood pressure
- ✓ List the determinants of blood flow (pressure gradient ΔP and resistance)
- ✓ Define and calculate blood flow, resistance, and pressure
- ✓ Define and calculate conductance (conductance is the inverse of resistance)
- ✓ Apply Poiseulle's law (which is a law of flow)

Function of the Circulation

What's the function of blood flow to the tissue?

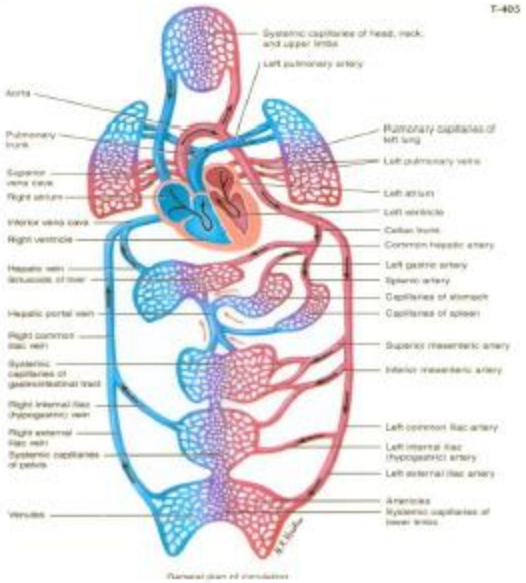
- Delivery of O_2 and removal of CO_2 from tissue cells.
- Gas exchange in lungs.
- Absorption of nutrients from GIT.
- Urine formation in kidneys.

The Circulatory System

There are 2 types of circulations:

- Pulmonary (lesser) circulation
- Systemic (greater) circulation

The exchange occurs ONLY at the level of capillaries.

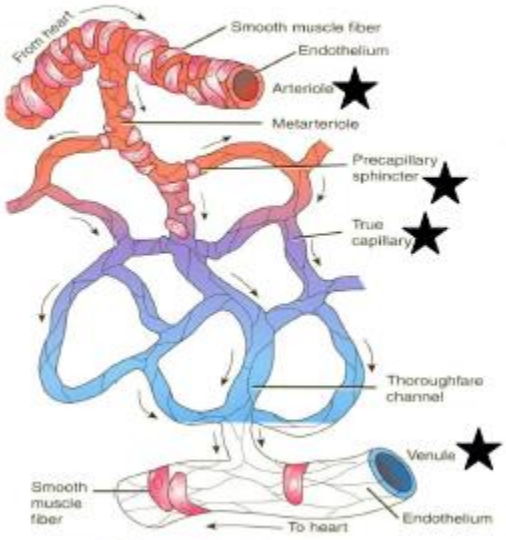


The Capillaries

*The professor said that he will not talk about capillaries BUT he will ask us about them.

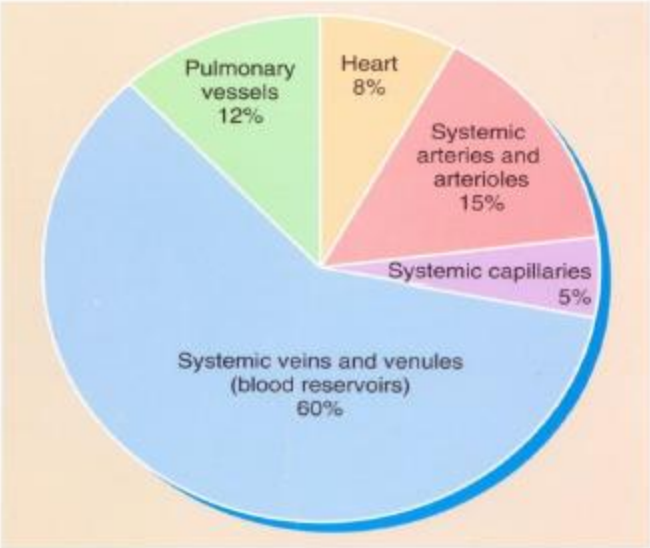
The capillaries do not have smooth muscles so there is neither vasoconstriction nor vasodilation in the capillaries.

Vasoconstriction & vasodilation are present in arterioles & venules.



(a) Details of a capillary network

Blood Volume Distribution



- Blood = 5 litres
- 2/3 of our blood is found in the veins.
  That's why venoconstriction & venodilation affect the MSFP much more than vasoconstriction & vasodilation of the arteries.
- < 15 % of our blood volume is found in the arteries at any instance.
- Flow in every part of the circulation is the same.
- The flow in the aorta per minute = the flow in all big arteries per minute = the flow in the whole medium size arteries per minute = the flow in all capillaries per minute = CO

- There are around 12 billion capillaries in our body.
- Every small capillary has blood flow & it's so small, BUT when you multiply by 12 billion, the end result = CO

Systemic & pulmonary circulation

- ✓ **Systemic Circulation**
  - Serves all tissues except the lungs
  - Contains 84% of blood volume
  - Also called the *peripheral circulation*
- ✓ **Pulmonary Circulation**
  - Serves the lungs
  - Lungs contain 9% of the blood volume
  - Heart contains 7% of the blood volume

Blood Reservoir Function of Veins

- ✓ 60% of the blood is in the veins.
- ✓ Under various physiological conditions, blood is transferred into arterial system to maintain arterial pressure.
- ✓ The spleen, liver, large abdominal veins, and the venous plexus also serve as reservoirs.
- ✓ Spleen also serves as a special reservoir for red blood cells.

Basic Theory of Circulatory Function

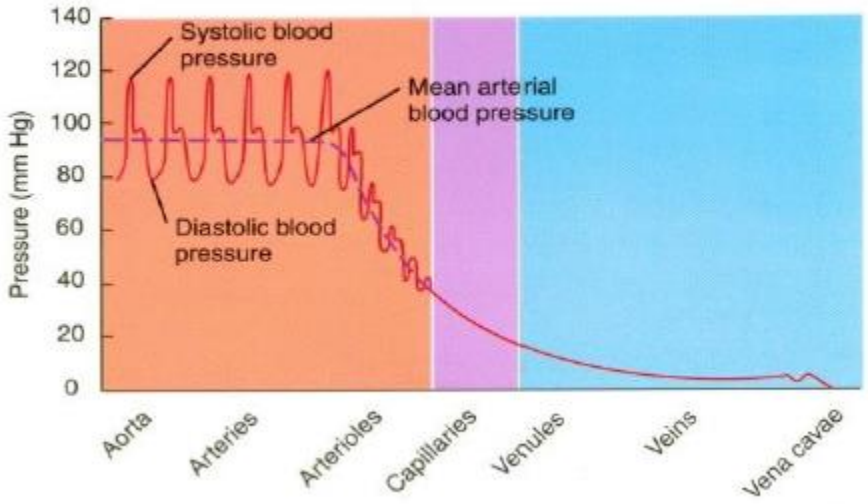
- *Blood flow* to tissues is controlled according to tissue needs (the need for O_2).
- *Cardiac output* is mainly controlled by local tissue flow.
- CO = Sum of blood flow to the tissues so if the CO increases the flow will increase & vice versa
- *Arterial pressure* is controlled **independently** of local blood flow control and cardiac output control.

Our mean systemic arterial pressure stays almost constant because there are too many factors that play a role in maintaining it.

When the MSFP is almost constant, how can the tissue blood flow be increased?

By vasodilation & decreased by vasoconstriction.

Pressure Changes in the Circulation



Arterial Pressure Change

In aorta, pressure ranges between 80 to 120.

The most important pressure is the MAP (NOT the systolic & diastolic pressures).

MAP = 1\3 systolic pressure + 2\3 diastolic pressure

This is due to the fact that the duration of ventricular systole = 0.3 seconds, while the duration of ventricular diastole = 0.5 seconds.

MAP in the aorta is around 93 mmHg.

One of the characteristics of pressure in the aorta is its **pulsatility**.

Flow = ΔP / R

Let's assume that the MAP in the aorta is 100 and the MAP in the arteries is 95 >> then ΔP = 100 – 95 = 5 mmHg.

In order for the flow to remain the same, resistance should equal 5, so 5/5 = 1.

When you come to the beginning of the arterioles, the pressure = 85.

ΔP = 100 – 85 = 15 mmHg >> so the resistance = 15

The pressure at the beginning of arteriole = 85 & at the end of the arteriole = 35

P = 85 – 35 = 50 so resistance = 50

* The greater drop in the pressure is when there is high resistance (R)

The arterioles are the major resistance vessels.

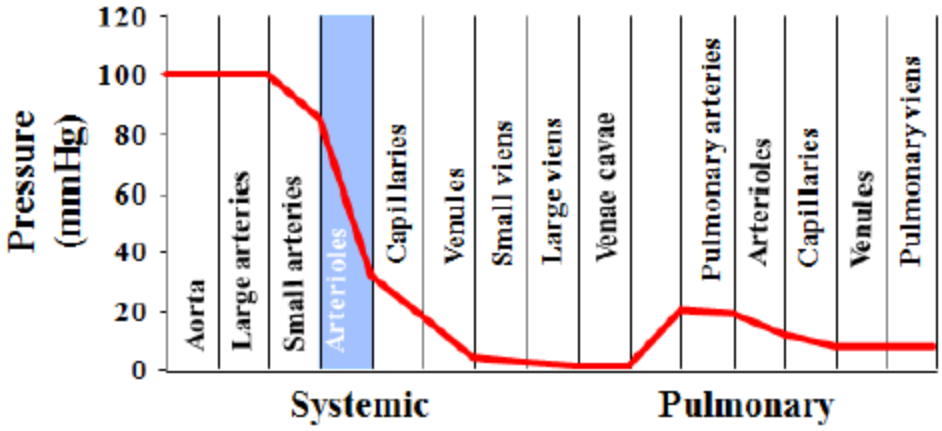
We call the veins capacitance vessels because they have a large capacity.

* There is no pulse in the capillaries or in the veins so if you feel the pulse in a vein or capillary >> then this is an abnormality.

*Beyond the arterioles, pulsatility of the arterial system lost (there is damming for the pulsation because of the very high resistance).

The pressure is dropping from the aorta to the Rt atrium (pressure = 0).

This happens in order to have a pressure gradient which allows blood to flow.



- There are high pressures in the arterial part of the circulation.
- There are low pressures in the venous part of the circulation.
- There is a large pressure drop across the arteriolar-capillary junction.

Changes in the velocity and the cross sectional area

- The flow of blood in a vessel equals the cross sectional area multiplied by the velocity.

$$F = A \times V$$

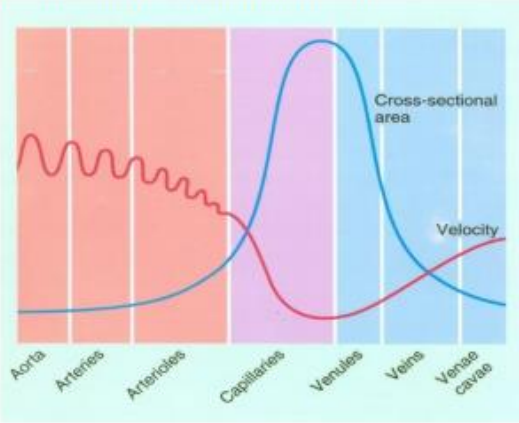
- The flow of blood in each part of the circulation is the same, and it equals the cardiac output (**F = CO**). But the total cross sectional area and the velocity are different.
- The velocity is inversely proportional to the cross sectional area.

$$V = \frac{F}{A}$$

- Now the largest cross sectional area we have is in the capillaries, why? Because we're combining the cross section of all capillaries, not just one. So, we have a very low velocity.
- The velocity is fastest in the aorta, because we only have one aorta and it has a small cross section (2.5cm).
- In the venules, the velocity increases again because the cross sectional area decreases.

Vessel	Cross-Sectional Area (cm^2)
Aorta	2.5
Small arteries	20
Arterioles	40
Capillaries	2500
Venules	250
Small veins	80
Venae cavae	8

- As you can see, the velocity in the venae cavae is much lower than the aorta, because we have two venae cavae (higher cross sectional area).
- Having a low velocity in the capillaries is very beneficial, because the capillaries are the site of exchange of material. So we're giving the capillaries enough time to exchange nutrients. In addition to that, the high cross sectional area facilitates the movement of material.

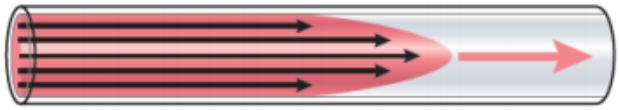


Blood flow is the quantity of blood that passes a given point in the circulation in a given period of time (mL/sec). And it equals the change in pressure over the resistance. We will talk about this later.

Laminar vs. turbulent flow

- Blood does not flow as a plug in large vessels, because our vessels are not rigid.
- We have two types of blood flow in our vessels:

1. Laminar or stream line flow:
    - It is more effective than turbulent flow.
    - It is usually silent (we can't hear it).
    - Laws are applied mainly to it.



    - When the blood is flowing inside the vessel, there's a very high resistance on the wall, and the resistance decreases when you go to the center. So because of the high resistance on the wall the velocity is low there and larger in the center. And this results of what we call: **parabolic structure**.
    - This produces layers of blood with uniform speeds at certain distances from the wall.
    - If the flow rate is increased, the trend for turbulence will increase.

2. Turbulent flow:
    - Blood goes in all directions, described as "eddy currents" (not effective).
    - It is not silent, turbulence of blood produces sounds.
    - Heart sounds are due to turbulence of blood around the closed valves.

    - When we measure the blood pressure using the sphygmomanometer, we increase the pressure above the systolic level to close the brachial artery (no flow). Then we slowly release the pressure in the cuff. As the pressure in the cuff falls, a whooshing sound is heard when blood flow starts again in the artery. This sound is due to turbulent flow of blood, because the vessel was constricted. The pressure at which this sound began is recorded as the systolic blood pressure. The cuff pressure is further released, the flow gradually turns into laminar flow until the sound can no longer be heard. This is recorded as the diastolic blood pressure.

- Causes of turbulent flow:
  - High velocities.
  - Sharp turns in the circulation (curvatures).
  - Rough surfaces.
  - Rapid constrictions.

- Pathological causes:
  - Atheromas.
  - Severe anemias.
  - Stenotic or incompetent cardiac valves.

- Turbulent flow could be dangerous in cases of atherosclerosis because it predisposes to the formation of a thrombus, which can lead to embolism and infarction.
- Normally, turbulent flow is present at the branching of blood vessels and in the roots of the aorta and pulmonary arteries.

Reynold's number

❖ It is a quantity that is used to help predict the flow pattern in different situations. It's defined as:

$$Re = \frac{\rho v d}{\eta}$$

Where:

- ρ (Rho) is the density of blood.
- v is the velocity.
- d is the diameter of the vessel.
- η (Eta) is the viscosity of the blood.

❖ If Reynold's number (Re) was lower than 400 the flow is laminar. If it was above 1000 the flow is turbulent.

- If the number is between 400 and 1000 then it depends on the condition; if there's atheroma or curvature it's more turbulent than laminar. If there's nothing and the vessels are normal then it's more laminar than turbulent.

The Peripheral Resistance

- It is the resistance to blood flow through a vessel caused by friction between the moving fluid and the vascular wall, most of it occurs in arterioles (50%) and capillaries (25%) so it is called peripheral resistance.

Ohm's Law

- In relating Ohm's law to blood flow, the current is the blood flow. The voltage difference is the pressure difference. And the resistance is the resistance to flow of blood offered by the vessels.

$$F = \frac{\Delta P}{R}$$

- For the flow in a blood vessel, ΔP is the pressure difference between any two points along a given length of the vessel.
- When describing the flow for a certain organ, pressure difference is generally expressed as the difference between the arterial and the venous pressure.
- In the systemic circulation, the flow of blood equals the cardiac output.
- Therefore, if we re-write Ohm's law for the hemodynamics of cardiac output we get:

$$CO = \frac{mean\ arterial\ pressure - right\ atrial\ pressure}{total\ peipheral\ resistance}$$

- And since the right atrial pressure equals zero, then:

$$CO = \frac{mean\ arterial\ pressure}{total\ peipheral\ resistance}$$

- The cardiac output is directly proportional to mean arterial pressure, and inversely proportional to the vascular resistance.
- If you need to change the mean arterial pressure, you change the cardiac output or the total peripheral resistance or both.
- You change the cardiac output by changing the stroke volume or heart rate or both.

Poiseuille's law

- Developed by the French physicist Jean Marie Poiseuille.
- It describes blood flow in relation to the pressure gradient, the radius, the viscosity and the length of the blood vessel.

$$\boldsymbol{F = \frac{\Delta P \pi r^4}{8 \eta L}}$$

- In order to know the effect of a certain factor we must fix all the other factors and change only one factor.
- By fixing all factors and changing ΔP, Poiseuille found that the flow is increasing linearly by increasing ΔP. And decreasing linearly by decreasing ΔP. Which means that the flow is directly proportional to the pressure gradient.
- By changing the length, he started by measuring the flow in a vessel with a length of 10cm. He cut the tube in half (5cm) and measured the flow again and found that it was doubled. Which means that the flow is inversely proportional to the length.
- The length of the vessels does not change that much in our bodies (it changes a bit in children because they are growing), so it is the least changing factor.
- By changing the viscosity, he brought a fluid with a viscosity of 1 the flow was 1L/min. He changed the viscosity to 2, the flow is now 0.5L/min. So, he concluded that the flow is inversely proportional to the viscosity.
- The last one is the diameter, he brought a vessel with 1mm radius the flow was 1L/min. He changed the radius into 2mm, the flow was 16L/min. 3mm radius, flow was 81 L/min. That means that the flow is directly proportional to the radius to the power of four (r^4).
- The flow of blood is exquisitely sensitive to change in radius.

$$\boldsymbol{F = \frac{\Delta P \pi r^4}{8 \eta L}} \qquad \boldsymbol{F = \frac{\Delta P}{R}}$$

And by combining the two equations to get ***R***:

$$\boldsymbol{R = \frac{8 \eta L}{\pi r^4}}$$

- Therefore, a vessel having twice the length of another vessel (each having the same radius) will have twice the resistance to flow. Similarly, if the viscosity of the blood increases two folds, the resistance will increase by two folds.

- In contrast, an increase in radius will reduce resistance to the power of four of the change in radius.
- For example: a two-fold increase in radius decreases the resistance by 16 folds!
- So, the main factor that changes the resistance is the radius.
- Note: the conductance is the same as the resistance.

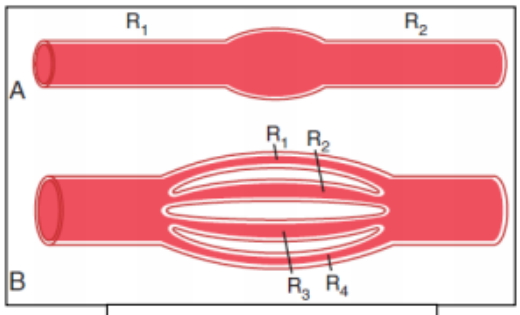
The resistance of the vessels

- If the resistors are in series, total resistance would be higher than the highest resistance.

$$R_{total} = R_1 + R_2 + R_3$$

- If the resistors are parallel, total resistance would be lower than the lowest resistance. (Like in arterioles and capillaries).

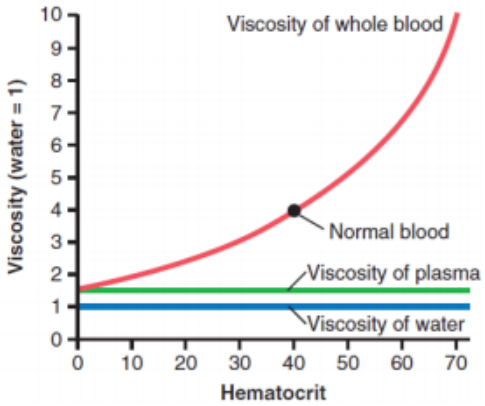
$$\frac{1}{R_{total}} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3}$$



A, in series and **B,** in parallel

Factors affecting the viscosity

- Number of RBCs (Hematocrit).
  - Normally it's 45%.
  - When the hematocrit increases the viscosity increases **curvilinearly** (not linear).
  - For example: when hematocrit increases from 45% to 60%, the viscosity increases more than eight times.
  - This is very hazardous because when the viscosity increases too much, the flow will decrease (according to the previously mentioned equation).
  - And the decrease in flow (stasis) will predispose to thrombosis and ischemia in some cases.
  - <u>We can increase the flow by decreasing the resistance</u> (vasodilation).



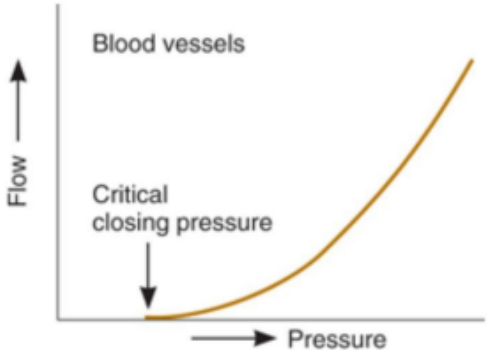
- Concentration of plasma proteins.
- Temperature (the higher the temperature the less the viscosity).
- The diameter of the vessel.

Relation between the pressure and the flow

- Sometimes, you might have pressure in the vessel without any flow. This is called critical closing pressure. Meaning that there is pressure but the radius is zero.
- Critical closing pressure depends on the law of Laplace "the tension on the wall equals the distending pressure multiplied by the radius".

$$T = P\,x\,r \rightarrow P = \frac{T}{r}$$

- We will talk about this concept in more details in the respiratory system.



Distensibility and compliance

- Distensibility is the proportional change in volume per unit change in pressure.

$$D = \frac{\Delta V}{\Delta P\,x\,V} = \frac{increase\ in\ vloume}{increase\ in\ pressure\ x\ the\ original\ volume}$$

- If I have 100ml volume (the original volume), how much volume (increase in volume) do I need to increase the pressure 1mmHg?
- If I need 10ml, the distensibility would be:

$$D = \frac{10ml}{1mmHg\ x\ 100ml} = \frac{10}{100}\ \textbf{and it's a proportion, so:}\ \frac{10}{100}x100\% = 10\%$$

- Compliance is the total distensibility. It is how much a vessel can accommodate volume per unit change in pressure.

$$C = D\,x\,V = \frac{\Delta V}{\Delta P}$$

- Let's apply to the same example above:

$$C = 10\%\ x\ 100ml = \frac{10ml}{1mmHg} = 10$$

- Veins are 6 to 8 times more *distensible* than arteries. That means than they are 24 to 32 times more *compliant* than arteries. Because the veins hold about 60% of our blood volume, and arteries about 15% so $60\%/15\% = 4$. Therefore, the veins are more compliant than arteries by $D\,x\,V = (6\ to\ 8)\ x\ 4 = 24\ to\ 32$ times.

Pulse pressure

- The difference between the systolic and the diastolic pressure readings is called the pulse pressure.
- It represents the force that the heart generates each time it contracts.
- If the resting blood pressure is 120/80 mmHg, pulse pressure is 40 mmHg.
- Pulse Pressure gives us the pulsations in the circulation. If there was no difference between the systolic and the diastolic pressure, there won't be any wave of pulsation.

Factors affecting the pulse pressure

- Increase in the systolic pressure will increase the pulse pressure and vice versa.
- Increase in the diastolic pressure will decrease the pulse pressure and vice versa.
- When blood is pumped through the aorta, the aorta will distend. But it's compliance is limited, so, the pressure must increase.
- The aortic pressure increases when the aorta recieves blood volume (storke volume). If the storke volume is higher, you expect that the systolic pressure is higher, thus a higher pulse pressure.

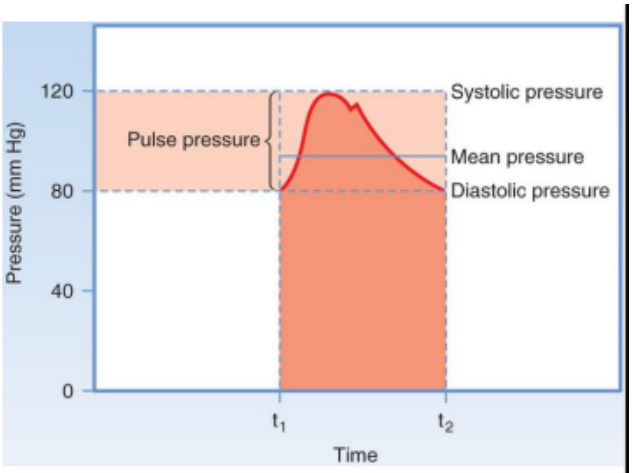
The pulse pressure directly related to the stoke volume.

- If the vessel is compliant, it can enlarge without increase in pressure.
- If the vessel is rigid, in case of atherosclerosis, its compliance is low, and that means high pulse pressure.
- If the compliance is high, that means there is no change in pressure (low pulse pressure).

The pulse pressure is inversley related to the compliance.

- So, the pulse pressure is a ratio that depends on both the stroke volume and the compliance. You might increase or decrease both of them without any increase in pulse pressure.
- Pulse wave travels through the arterial wall. <u>And the velocity of travel is inversely proportional to compliance</u>.

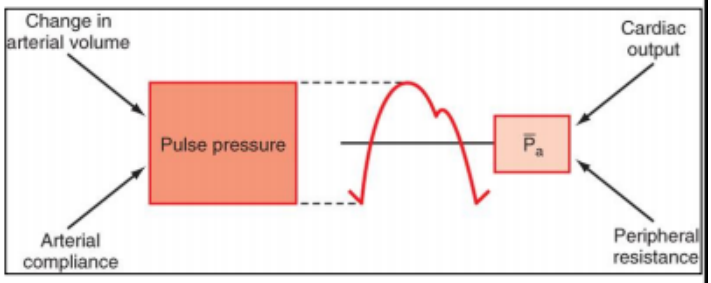
- The speed of transmission in the aorta (high compliance) is around 5m/s. The speed in a medium sized artery 10m/s. while the speed in small arteries is around 40m/s. That's why when you feel the radial pulse, it comes almost with the first heart sound.



- Now how to calculate the Mean Arterial Pressure?
  We calculate the area under the curve then we divide it by the time using this integration:

$$\overline{P_a} = \frac{\int_{t_1}^{t_2} P_a \, dt}{t_2 - t_1}$$

- And as we talked before, the factors that affect the mean arterial pressure are the CO and peripheral resistance. And the factors that affect the pulse pressure are the stroke volume and and the compliance.



Abnormal pulse pressure contours

- Atherosclerosis: there is a very high pulse pressure because of decreased compliance.
- Patent ductus arteriosus: blood escapes to the pulmonary arteries and flows back to the left ventricle. This will increase the stroke volume, and a higher stroke volume means a higher systolic pressure and thus a higher pulse pressure. The diastolic pressure will drop, because there's no volume in the aorta, elastic recoil is pushing the blood through ductus arteriosus. This low diastolic pressure will increase the pulse pressure even more.
- Aortic regurgitation: blood is pumped to the aorta, but during diastole, part of it will go back to the left ventricle. So, the diastolic pressure will drop. The systolic pressure will increase (left ventricle is pumping more blood). Pulse pressure will increase due to lower diastolic and higher systolic.
- 120/0 pressure indicates a severe case of aortic regurgitation (severe aortic incompetance) what happens to the aortic pressure curve in this case?
  The dicrotic notch (incisora) will be absent, due to incompetant aortic valve.

Notes:

- Any given change in volume within the arteries results in larger increases in pressure than in veins, because their compliance is low.
- When veins are constricted, large quantities of blood are transferred to the heart (higher venous return) because the mean systemic filling pressure depends on volume. And thereby higher cardiac output.

Blood pressure regulation

Regulators of blood pressure:

1. **Short term regulators** are fast regulators. For example, if you were lying down and you suddenly stood up, the pressure will drop really fast, but there are very fast regulators that regulate this pressure to prevent the pressure from falling, otherwise the blood flow in the brain will be compromised and you will fall down. These short term regulators work through the nervous system (because neurons work the fastest).

2. **Long term regulators** include: epinephrine, antidiuretic hormone (ADH), Renin–Angiotensin–Aldosterone system, atrial natriuretic peptide (ANP), and kidney-body fluids.

3. **Intermediate term regulators** (will be discussed in the next lectures).

Mercury sphygmomanometer

This type of sphygmomanometers is no longer used because it might break, and the mercury is very toxic. Nowadays we use other types like aneroid or digital sphygmomanometers.

Whatever the type, the principle is the same.

- How to measure the blood pressure using a sphygmomanometer:

1. You put a cuff around the arm.
2. You raise the pressure above the systolic pressure (120); at this point you won't hear any pulsation because there's no blood flow (no sound).
3. Then you decrease the pressure in the sphygmomanometer to a value that is equal to the systolic pressure, at this point there is blood flow during the systole. However, because there is a constriction, the type of blood flow is **turbulent** flow, so you would hear tapping sound called **(Korotkoff sound)**.

> **Note**:
> In general, the blood flow is **laminar**, which means it flows linearly and smoothly in adjacent layers, but under pressure or high flow, like in the ascending aorta the laminar flow becomes chaotic, disrupted and **turbulent**.

4. Upon decreasing the pressure in the sphygmomanometer you keep hearing these Korotkoff sounds, until there's no more compression in the artery, that's when you reach the diastolic pressure.
   At this point the flow changes from turbulent to laminar again, and the laminar flow has no sound, so the Korotkoff sounds disappear.
5. The first encounter with Korotkoff sounds marks the systolic pressure, and then the absence of the sound marks the diastolic pressure.

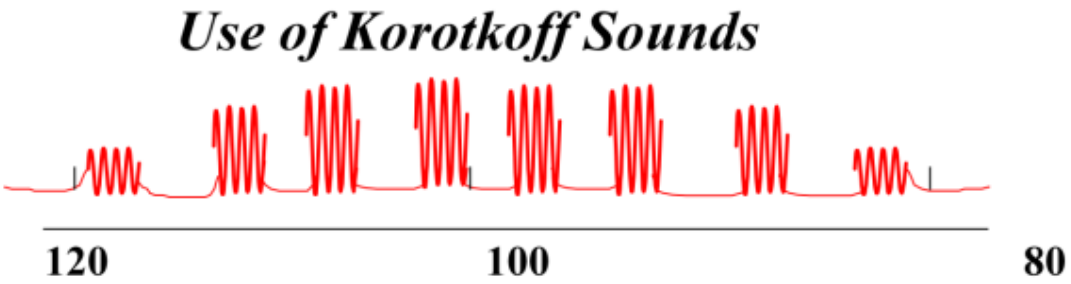
Notes:

- This method that requires sphygmomanometer with stethoscope to measure the blood pressure is called **(Auscultatory method**).
- Sometimes, if you don't have a stethoscope, you can use your hands to feel the pulse. this is called the (**Pulpatory method**) , you put your hands at the site of the brachial artery lower than the cuff , and you sense the pulse , upon rising the pressure in the sphygmomanometer above the systolic , you won't feel any pulsation as there's no blood flow in the artery , and that would mark the systolic pressure **. BUT, in** this method you can't measure the diastolic pressure, as the pulse won't disappear upon reaching the diastolic pressure. So this is only used to measure the systolic pressure.

- the effect of cuff pressure on brachial blood flow

Cuff pressure > 120	**NO FLOW**
Cuff pressure < 80	**FREE FLOW**

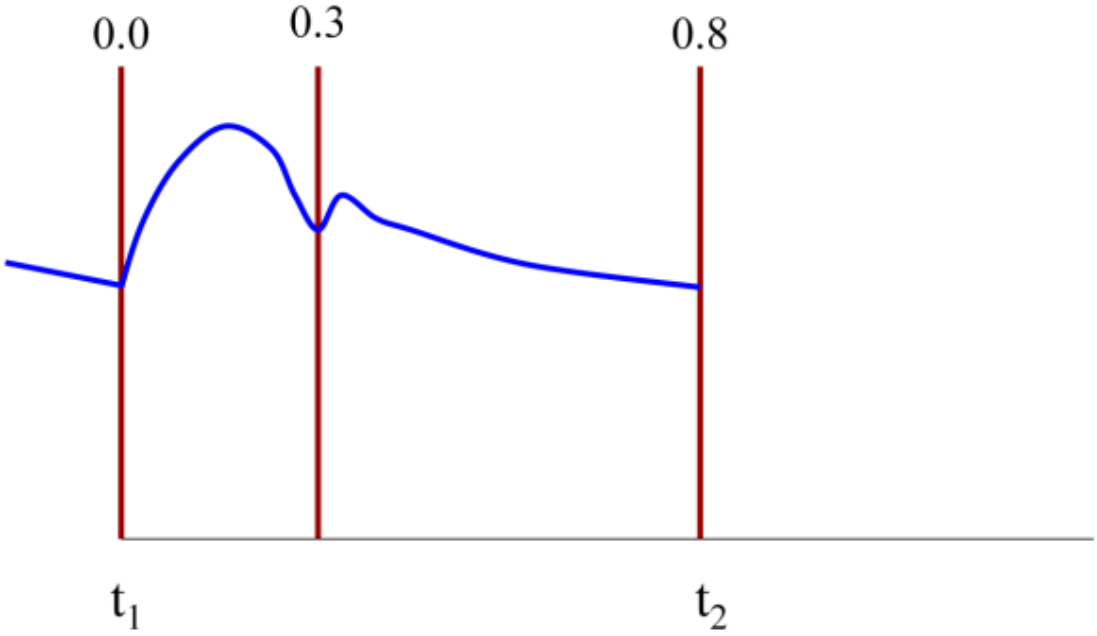
Korotkoff Pressure



In the diagram above, notice that Korotkoff sounds begin at 120 mm Hg, and disappear at 80 mm Hg because there's no compression anymore and the blood flow becomes laminar again.

Mean Arterial Pressure (MAP)

- It is the pressure that pushes the blood in the circulation.
- MAP is closer to the diastolic pressure than the systolic pressure, that's because the diastolic time is longer than the systolic time.
- It equals two thirds of the diastole, plus one third of the systole.



The figure shown above graphically represents the changes in the aortic pressure

How is the area under the scale calculated?

By an integration from t2 to t1

$$MAP = \int_{t2}^{t1} dp.dt$$

How to calculate the MAP from the scale?

We divide the area by the time interval (t2 – t1)

$$MAP = \int_{t2}^{t1} dp.dt/(t_2 - t_1)$$

This method of calculation is usually automated; you just connect the machine to a transducer that measures the pressure, and it will automatically calculate the MAP.

How can the MAP be calculated manually?

We use the following equations:

MAP = 1/3 systolic pressure + 2/3 diastolic pressure

Or

MAP = diastolic pressure + 1/3 pulse pressure

Remember that: (Pulse pressure = systolic – diastolic)

Both equations are the same and give the same answer.

Factors Affecting MAP

CO = MAP / TPR
MAP = CO * TPR

To alter the MAP, we either change the cardiac output or the total peripheral resistance.

Remember:

- **The vessels are only supplied by the sympathetic** nervous system, and they are **NOT** supplied by the **parasympathetic** nervous system.
- **There is a basal amount of supply from the sympathetic to these vessels,** so the vessels normally are a little bit constricted, this is called **(the basal tone**), and it's similar to the skeletal muscle tone that we previously studied, which makes the muscle a little bit constricted (muscle tone). You can find the muscle tone in normal living individuals. However, you don't find this basal tone in dead bodies.
- The smooth muscles in the myocardium around the vessels are constricted a little bit. This is called the basal tone, and it's supplied by the sympathetic nervous system.
- **This basal tone provides a positive and a negative control,** which means it give the vessels the ability to constrict or dilate, but if this basal tone didn't exist, then the vessel can only constrict but not dilate.

- **The parasympathetic only supplies the atrial part of the heart.** Therefore, this means that the parasympathetic innervation has some control over the heart rate.

Parasympathetic >> controls heart rate (controls heart function only)
Sympathetic >> controls heart rate and contractility and the resistance in the vessels (controls both heart function and the circulation)

- **All vessels are supplied by sympathetic innervations except the capillaries (including precapillary sphincters and metarterioles)** because they don't have smooth muscles.
- Innervation of small arteries and arterioles allows the **sympathetic nerves to increase vascular resistance** when they are stimulated.
- **Parasympathetic nervous system is mainly important for controlling the heart rate via the vagus nerve.**

Short term regulators:

1. Baroreceptors

2. Low pressure baroreceptors

3. Chemoreceptors: chemoreceptors are of 2 types according to their location:

1. Baroreceptors

Let's assume that the blood pressure is always changing. If the blood pressure goes down it should be elevated to normal pressure, and if it goes up it should be dropped to normal pressure.

How does the system know that blood pressure is rising or dropping?

Baroreceptors or **pressoreceptors** sense any **change in the blood pressure** whether it was up or down, and accordingly they serve their purpose.

They are also called **high pressure regulators** because they work in areas of high pressure such as the aortic arch.

Where are they located?

If they were located in the leg, the person would die before they sense any change in the blood pressure. So logically:

1. <u>They should be very close to the heart</u>, so that they would sense any change in the pressure.
   They are called **aortic Baroreceptors** and they are found in the **aortic arch.**
2. <u>They should be found close to the brain</u>, because the brain is a vital organ and any compromised blood flow to the brain would affect the brain.
   These receptors are called **carotid baroreceptors** and they are found in the **carotid sinus** – because that's where the blood flows to in the brain.

Mechanism of action:

- The **aortic receptors** are innervated by a branch from the **vagus** nerve (cranial nerve number 10), and they send impulses that are transmitted to the cardiovascular center in the medulla oblongata in the brain stem.
- The **carotid receptors** are innervated by **a branch of the glossopharyngeal nerve** (cranial nerve number 9), AKA **Hering's nerve**. This nerve sends the impulses from these carotid baroreceptors to the cardiovascular center in the medulla oblongata in the brain. The carotid sinus is found just after the bifurcation of the common carotid artery in the internal carotid artery.
- These baroreceptors are stretch receptors which are found in the wall of the artery, so if the wall stretches they are stimulated.
- **When do we see more stretch?**
  When the pressure increases, the vessels are stretched. Therefore, when there's too much pressure, the impulses from these receptors increases and goes to the cardiovascular center.

- **The cardiovascular center is made up of two parts**, the cardiac and the vascular parts.

1. **The cardiac part contains two parts**, cardio-acceleratory and cardio-inhibitory.
   - **The cardio-acceleratory** part sends its impulses down to the heart via sympathetic fibers to increase the heart rate and contractility which increases the stroke volume (positive chronotropic and positive inotropic).
   - **The cardio-inhibitory** part sends its impulses through the vagus nerve (parasympathetic) which decreases the heart rate and decreases contractility.

2. **The vascular part is called the vasomotor center (VMC)** which is located bilaterally in the reticular **substance of the medulla oblongata** and is made up of **3 areas**: the vasoconstrictor area, the vasodilator area, and the sensory area.
   - The area that receives the impulses from the baroreceptors is the **sensory area**, and the sensory area distributes these impulses to the rest of the areas in the vasomotor center and also to the cardiac part of the cardiovascular center.
   - **The only area that transmits it's impulses down to the vessels is the vasoconstrictor area**. It sends its impulses through the sympathetic nervous system (the impulses go down to the spinal cord, then through a sympathetic ganglion and finally exit the ganglion through a sympathetic fiber) and to the vessels. Thus, if this area is stimulated, it results in vasoconstriction and if it is inhibited then vasodilation will occur.
   - **The vasodilator area and the sensory area work upward,** meaning that they send their impulses to the CNS. The vasodilator area sends its impulses through the vagus nerve (cranial nerve X).

CASE A

- Suppose there was an **increase in the blood pressure.**
- An increase in pressure causes **more stretch** of the wall of the carotid and the aortic arch.
- Stretching the arterial wall causes **more streams of impulses** to the cardiovascular center.
- This increase in the stream of impulses to the cardiovascular center **inhibits the vasoconstrictor area** (fewer impulses to the vessels which causes vasodilation, less resistance, decrease in the MAP) and **stimulates the vasodilator area**.
- The impulses also reach the **cardio-acceleratory** area through the sensory area and **inhibit it**. This means that the cardio-acceleratory area will send less sympathetic stimulation to the heart (less HR→less contractility→less SV→less CO and when the CO goes down, the MAP goes down), and it **stimulates the cardio-inhibitory** area, which sends more parasympathetic stimulation to the heart (less HR→less CO→decrease in MAP).

CASE B

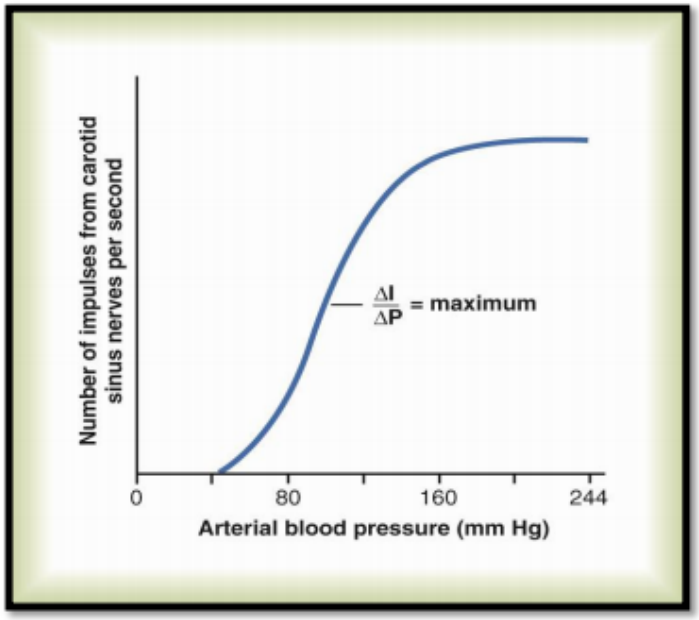
- Suppose there was a **decrease in the blood pressure.**
- The **number of impulses sent from the baroreceptors decreases**.
- When the number of impulses decreases, the **cardio-acceleratory area** is not inhibited anymore, so it is **stimulated** (more sympathetic stimulation to the heart→more HR→more contractility→more SV→more CO→increase in the MAP), and the **cardio-inhibitory area in inhibited**.
- The inhibition on the vasoconstrictor area is also removed because there are fewer impulses, so the **vasoconstrictor area is stimulated** (causes vasoconstriction in the vessels, increases the total peripheral resistance, and hence increases MAP).

Arterial Baroreceptor Reflex

- This reflex is initiated by stretching in the walls of the large systemic arteries which stimulates the **stretch receptors** (AKA baroreceptors, or pressoreceptors) that exist in the walls of these arteries.
- **These receptors will send impulses to the VMC**, which works to decrease the arterial pressure back to **normal** (by the mechanisms mentioned previously).
    - **Note**: these baroreceptors are considered **buffers** for the blood pressure, as buffers always maintain things in their normal range and just like the buffer system, which depends on pKa in its function, the **arterial baroreceptor reflex works best around 100 mmHg.**
- Baroreceptor reflex is **most sensitive at 100 mmHg**, which means that the reflex changes easily with any small increase or decrease in the arterial blood pressure around 100 mm Hg, but if the change in pressure is much higher or much lower than 100, then the reflex doesn't change drastically.
- Carotid sinus baroreceptors respond to pressure **between 60 and 80 mmHg.**
- Baroreceptor reflex is most sensitive around 100 mm Hg which is the MAP.

Observe the following sigmoid curve:

ΔI = change in impulses
ΔP = change in pressure

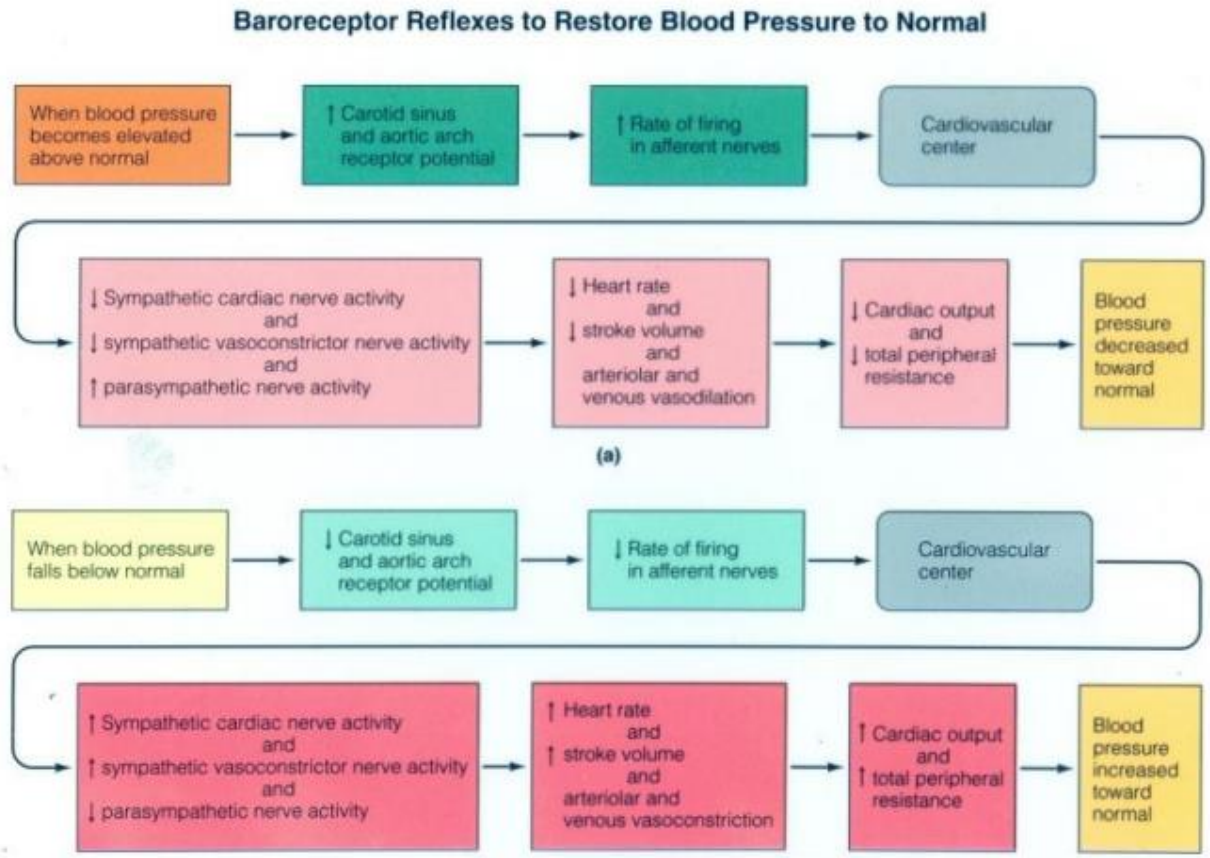


- ✓ **ΔI / ΔP** indicates the point where <u>any small change in pressure up or down causes a huge change in the number of impulses per second</u>. **This point is 100 mmHg**, which means baroreceptors are most sensitive around 100 mmHg.

- ✓ Notice that if the pressure increases or decreases too much away from 100, then **the sensitivity decreases drastically**, and no matter what the change in the pressure was, the **number of impulses won't change.**

Notes:

- Rate of firing = impulses sent from the baroreceptors
- The reflex works to maintain the normal blood pressure
- If BP increases, the reflex decreases→the BP returns **back to normal.**
- If BP decreases, the reflex increases→the BP returns **back to normal.**



What happens when we stand?

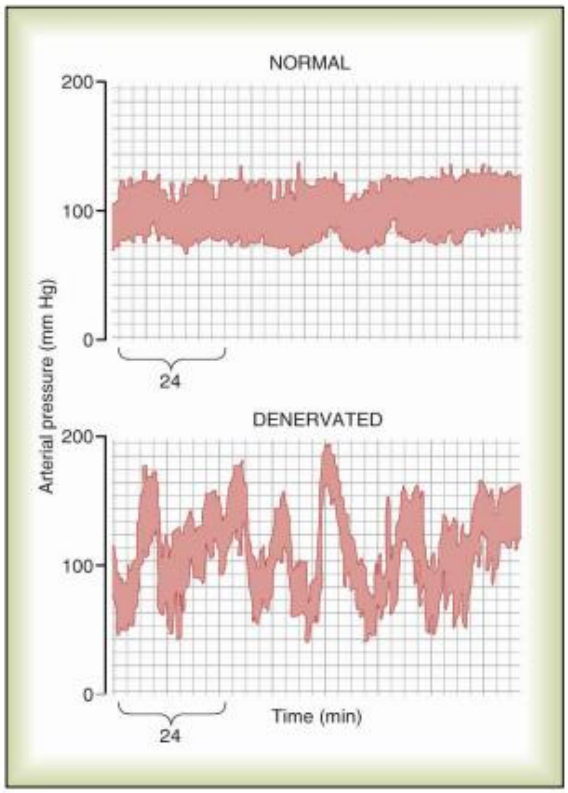
- When we stand, the <u>venous return to the heart is decreased</u> → CO and the arterial pressure decrease.
- The baroreceptors sense this change in the arterial pressure, and send impulses to increase the sympathetic stimulation to the heart to increase the CO and the arterial pressure.
- <u>This process happens really fast in young individuals.</u>
- <u>In older people</u>, the baroreceptors **are less sensitive** because of the atherosclerosis. This makes them feel dizzy once they stand up after they've been lying down, so older people are advised to stand slowly to avoid feeling lightheaded.

Functions of Baroreceptors

1. **Maintain relatively constant pressure despite changes in body posture**
    - If we wanted to measure the change in the blood pressure after denervating the baroreceptors (cutting their innervations), what would it be?
    - Provide the patient with a pressure transducer for 24 hours which will measure the blood pressure many times a day.
    - When the **baroreceptors are innervated** (normal), the readings would be around 100 mm Hg most of the time.
    - However, **if the baroreceptors were denervated**, we would find 25 readings that give 100, and the remaining 75 readings would be split in half: one part with readings higher than 100, and the other part with readings lower than 100. In this case, the range and the variations are much higher (not part of homeostasis), while in the innervated baroreceptors the range will be very close to 100, which means that these receptors are part of the homeostasis and they maintain the BP around 100.

2. **Oppose either increases or decreases in the arterial pressure thereby reducing the daily variations arterial pressure.**
3. **They are insignificant in long term control of arterial pressure because the baroreceptors adapt.**

The figure on the right shows variation in the arterial pressure in normal and denervated baroreceptors.



Remember:

- CO = SV × HR
- SV increases by increasing the end diastolic volume, or by increasing the sympathetic stimulation.
- The end diastolic volume increases by increasing the venous return.
- The heart rate increases by the sympathetic stimulation and decreases by the parasympathetic stimulation.

How do the sympathetic and parasympathetic nerves affect the cardiovascular system?

1. **Parasympathetic**: only works on the heart→it decreases HR→less CO→decrease in BP.
2. **Sympathetic**: works on three parts:
   i. Heart: it increases contractility which increases the SV + HR. They both increase the CO, which causes an increase in the BP.
   ii. Arterioles: it causes vasoconstriction, which increases the total peripheral resistance, thus increasing the BP.
   iii. Veins: causes venoconstriction → increase in the **mean systemic filling pressure MSFP** (that's because veins contain 2/3 of the blood volume) → increases the venous return→higher SV→more CO→increase the BP.

2. Low Pressure Regulators

- These are located in low pressure areas, in the **right atrium** and **the right ventricle** (and sometimes in the pulmonary arteries).
- These are sensitive to **changes in volume.**
- If there is **an increase in blood volume** → increase in venous return → increase CO → increase in MAP → which causes a **decrease in the pressure in the right atrium**
- In order to fix this decrease in pressure, we should bring the other factors (CO, MAP, venous return) down, or increase the venous return to the right atrium, this is done by low pressure baroreceptors that are found in the right and left atria.

Atrial Hypothalamic Reflex

- In this reflex, the right atrium and the hypothalamus communicate.
- When there's an increase in right atrial pressure, the receptors send impulses to the hypothalamus, and **the hypothalamus reduces the secretion of ADH.**

- **ADH has two important jobs:**
  1. Water reabsorption from the collecting ducts in kidneys. This retained water will contribute to the extracellular volume (ECV). If ECV increases then blood volume increases, and the mean systolic filling pressure will be increased→more venous return→more end-diastolic volume→higher SV→higher CO.
  2. Vasoconstriction
     If ADH is decreased → less vasoconstriction and more vasodilation.

- **That's why ADH has two names**; one for every function. The first name is antidiuretic hormone, and the second is vasopressin.

In summary, if the BP is low in the right atrium, more venous return is needed so ADH is stimulated. If the BP in the atrium is high, less venous return is needed so ADH is inhibited.

Atrial Renal Reflex

- In this reflex, the right atrium and the kidney communicate.
- An increase in the volume of the right atrium means high BP in the right atrium.
- Right atrium sends impulses to the kidney to dilate the afferent arterioles that supply the nephron; this increases the blood flow to the nephron→increases the glomerular filtration rate (GFR).
- When GFR increases this means that more water is lost through the kidney→ECV decreases→the venous return decreases→lower SV→lower CO→lower MAP.
- On the other hand, if there was a decrease in the blood volume in the right atrium that would cause vasoconstriction in the afferent arterioles and less water is lost through the kidneys.
- Affecting the GFR means affecting the urine volume.

3. Chemoreceptors

- These receptors are **located at the same areas as the baroreceptors** (in the aortic arch and the carotid sinus).
- They are called the **aortic bodies** and the **carotid bodies**.
- The blood flow around these receptors is very high to an extent where the O_2 and the CO_2 concentrations around these areas are the same as the O_2 and CO_2 concentrations in the arteries.
- These receptors are sensitive to pO_2 (partial pressure of O_2), pCO_2, and the hydrogen ion concentration (pH).
- These receptors are called **peripheral chemoreceptors**
- The peripheral chemoreceptors are highly sensitive to:
    1. **Low** O_2 concentration
    2. **High** CO_2 concentration
    3. **High** H concentration

❖ **Very important note** : chemoreceptors are less sensitive than the baroreceptors , they are not activated until the MAP reaches around **80 mmHg** , while baroreceptors work around **100 mmHg**

❖ So , when MAP reaches 80 mm Hg , chemoreceptors start to work and respond to the decrease in the BP , while baroreceptors will be already working.

Peripheral Chemoreceptors in Chronic Smokers

- The peripheral chemoreceptors are very important to chronic smokers who have **respiratory failure**.
- In respiratory failure, the central chemoreceptors have **adapted** to high CO_2 concentrations (adaptive receptors), so they **are not sensitive** to changes in CO_2 concentration anymore. In this case, the main effectors on the respiratory control are the peripheral chemoreceptors, because they are highly sensitive to any reduction in O_2 concentration. The concentration of O_2 in chronic smokers is very low while the CO_2 concentration is very high.
- Chronic smokers who have respiratory failure **depend on the stimulation** of the respiratory center through the impulses that come **from the peripheral chemoreceptors only.** *Therefore, these patients cannot be given high oxygen concentrations through a mask because this would over-stimulate the peripheral chemoreceptors (which are highly sensitive to pO_2) to give rapid impulses to the respiratory center. Such patients should be provided with oxygen gradually through nasal tubes.*

Second: long term regulators

In this section we will discuss:

- ✓ The importance of long term regulators
- ✓ Targets of long term regulators
- ✓ Long term regulators mechanism of action
- ✓ CNS ischemic response

1) First: importance of long term regulators

Why aren't short term regulators enough??

1. Adaptation: short term regulators adapt, this means that after few days, baroreceptors become insensitive to the increase in the BP. (adaptation), and the impulses that's coming from these receptors demolish.
2. Low Gain : any control system has a gain , (gain = correction / error) , for better understanding :
    - Let's assume that the MAP was 100 mm Hg, and it increased to 120 mm Hg, what kind of regulators work first? Baroreceptors. Baroreceptors worked and it decreased the BP to 105 mmHg.

Correction = 15

Error = 5

Gain = 15/5 = 3

- But in the case of long term regulators, they will bring the BP from 120 to (100.0001) mm Hg.

  Correction = almost 20

  Error = almost 0

  Gain = 20/0 (dividing any number by zero gives infinity)

- So long term regulators have infinite gain

- And whenever we compare control systems wither they are bad or good, we compare their gain.

  To sum up :The higher the gain the better the control system.

2) Targets of long term regulators:

Cardiac output= MAP/ TPR

So MAP= C.O * TPR

When TPR increases → MAP increases

When C.O increases → MAP increases

So In order to regulate blood pressure (MAP) we either control TPR , C.O , or BOTH.

1. TPR regulation

What affects the TPR?

1. Arteriolar radius : the major factor that affects the TPR , because according to Poiseuille's law , the resistance is inversely proportional with the radius to the power 4 (r^4)

   What affects the radius?

   I. **Vasoconstrictors**: like vasopressin (ADH), Angiotensin II, Epinephrine and Norepinephrine, and also the sympathetic activity. here TPR increases

   II. **Vasodilators**: mainly local vasodilators (discussed later), like changes in the O2, CO2, H concentrations. Other vasodilators are histamine release, heat or cold, myogenic responses to stretch. Here the TPR decreases.

2. To some extent, blood viscosity: the viscosity increases when the ratio of RBCs to plasma proteins increases, this happens in Polycythemia, dehydration, and burns.

When viscosity increases →TPR increase → blood pressure increase.

3. Total blood vessels length: this could increase by obesity or increased body size.

   When vessel length increases →TPR increase → blood pressure increase.

2. C.O regulation

C.O= HR * SV

CO is mainly affected by HR and SV

1. HR: The parasympathetic and sympathetic activity are the main affecters on the HR

2. The SV is controlled by preload which is regulated by venous return (very important regulator) and filling time.

   Note that filling time is regulated by the heart rate.

   Please revise pages 2 , 3 ,and 4 in sheet 12

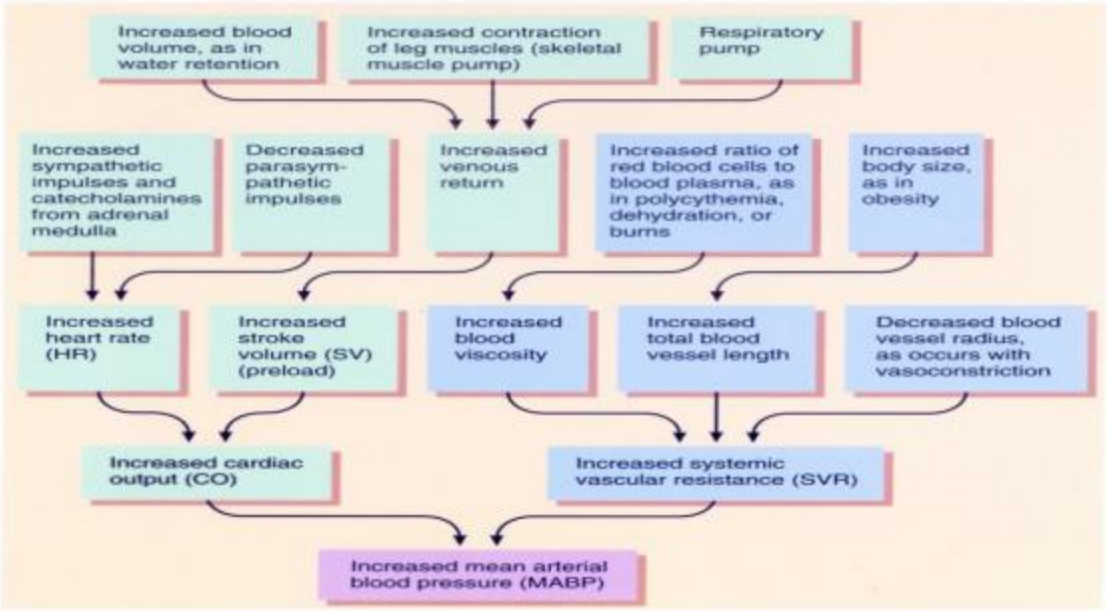
   Now, What increases the venous return? Many factors increase venous return but the following ones are the most important:

   1. Skeletal muscle pump
   2. Respiratory pump
   3. Increase in blood volume: this is the main affecter on the mean systemic filling pressure. (MSFP)

Note: remember we talked about the mean systemic filling pressure. If the right atrial pressure equals the MSFP, then the **venous return= zero** when the right atrial pressure decreases to be less than the MSFP, then **the venous return increases.**

❖ This figure is very important; the doctor mentioned it more than one time, so please memorize it.

To sum up :MABP (mean arterial blood pressure = MAP) is mainly affected by CO and the systemic vascular resistance.



3) *Intermediate / long term regulators mechanism of action:*

They include:

a. Epinephrine – adrenal medulla center

b. ADH (vasopressin) system

c. Renin –Angiotensin- Aldosterone system

d. Atrial Natriuretic Peptide

We're going to start with a practical example for a better understanding: (clinical example will be highlighted)

A person was going to the airport , in his way , he got into an accident , he was bleeding a lot , his blood volume decreased and

the MSFP decreases , the venous return decreases , the end diastolic volume decreases , BP goes down .

When BP decreases this will first stimulate the baroreceptors , baroreceptors are stimulated to raise the MAP back to 100 , baroreceptors fail to raise the BP , because he's still bleeding and his BP is still going down , now there is a very strong sympathetic outflow , the sympathetic outflow goes to the adrenal medulla and stimulates it to release epinephrine.because the adrenal gland will need time to synthesize Epinephrine /Norepinephrine those catecholamines are considered long term regulators.

a. Epinephrine –adrenal medulla system : intermediate /start working after 10 min

Epinephrine causes vasoconstriction. the importance of this step is that the sympathetic stimulation (caused by decreased blood pressure) may not reaches all vessels in our body , but epinephrine and norepinephrine reach all vessels everywhere in our body and cause vasoconstriction , to increase the TPR . And increase contractility in the heart to increase the CO.

Notes regarding epinephrine:

- ✓ as we took in the endocrine system, 80 % of adrenal medulla secretions are epinephrine, so it mainly secretes epinephrine and only a small amount of Norepinephrine is secreted
- ✓ when adrenal glands are stimulated ,they will secrete epinephrine but epinephrine concentration won't increase rapidly and it will take at least 10 min for it to rise to a concentration that permits its action. Why does it take epinephrine 10 minutes to work?

  Because when the adrenal glands are stimulated they will immediately release their stored catecholamines but the amount released is very low and the adrenals will start synthesizing new catecholamines which will take time.

But unfortunately, the paramedics didn't reach the guy; he's still bleeding and his BP in still going down.

After half an hour of bleeding and depression in BP, another system in stimulated which is the ADH (vasopressin) system.

b. ADH- Vasopressin system : start working after 30 min
Considered intermediate and long term regulator.

ADH secretion from the hypothalamus increases , ADH has two functions :

1. **Water reabsorbtion** from the distal tubule and the collecting duct. , this increases the ECF volume , then the venous return increases
2. **Vasoconstriction** , which increases the TPR and thus blood pressure.

If the paramedics still didn't come, and the patient is still bleeding and his BP in still dropping, after one hour another system starts to work, which is the Renin – Angiotensin- Aldosterone system.

c. Renin- Angiotensin- Aldosterone system : start working after 30 min
Considered intermediate and long term regulator.

If the blood pressure is still down, and the other systems couldn't raise the BP, this system is stimulated, how?

I. The pressure decreases in the afferent arteriole of the kidney; this causes the afferent arteriole to secrete Renin.

II. Renin is an enzyme that works on the alpha 2 globulin Angiotensinogen (14 a.a peptide) which is a precursor , and is converted to Angiotensin I by Renin

III. Angiotensin I (deka peptide / 10 a.a) circulates mainly in the lung endothelium , where we have (Angiotensin converting enzyme) that converts it to Angiotensin II

IV. Angiotensin II (octa peptide / 8 a.a) functions as:

- **very potent vasoconstrictor** (increases the TPR),

- **Positive inotropic agent** (increases the contractility and SV) , in the heart , Angiotensin II has receptors , which affects the contractility .

- **It stimulate the secretion of Aldosterone from the adrenal cortex** (zona glomerulosa) : aldosterone receptor is found in the distal tubule of the nephrone , and it increases the reabsorbtion of Na^+ , Na+ is going to be absorbed along with water (absorbed water increases the ECF volume , increase the venous return and the CO) .

Meanwhile, another system will be suppressed which is Atrial Natriuretic Peptide (ANP)

D. Atrial Natriuretic Peptide (ANP):

Atrial natriuretic peptide (ANP) : this 28 a.a peptide in secreted mainly from the right atrium due to increase in volume or stretch (increased blood pressure). How??

An increase in volume in the RA means an increase in the BP .

Thus , this peptide is secreted when there is an increase in the BP , not when BP decreases .

What's the effects of ANP ?

It increases the secretion of natrium / sodium (Na) outside the body. How??

Increase the GFR (glomerular filtration rate) →increased loss of Na+ and water → urine formation. (By loosing water from the body the blood volume decreases and the BP decreases).

In the clinical case above the BP is decreasing, so this system is inhibited, and we are no longer loosing water through urine.

Important note: ANP system, the only one that is stimulated by high BP, the rest of the long and intermediate systems are stimulated by low BP.

Now if our guy is still bleeding after all these regulators, he would enter a phase called (circulatory shock) or (hypo volumic shock) , and his BP is going down below 60 mm Hg .

If the BP goes down below 60 mm Hg, this activates a reflex called CNS ischemic response.

Remember that the BP control curve was from 60 to 180 mm Hg , between these two pressures we can have a control , but below 60 mm Hg we don't have a control , and also above 180 mm Hg we don't have a control , and the best control is around 100 mm Hg

Note: if you were in the ER, and a patient comes from a car accident and he was bleeding, and you measures the BP and found 120/80, this doesn't mean that the BP in normal, this means that all these previous systems are working to maintain his BP up, so right away you should put him on IV fluids.

In this kind of cases, if you measure epinephrine, norepinephrine, ADH, Angiotensin II or aldosterone, you find them really high, and if you measures ANP it would be low.

You should also put a catheter in the urinary bladder, because he might have renal failure.

4) **CNS ischemic response**

The CNS would suffer from ischemia if the blood pressure goes below 60 mmHg.

Ischemia in the CNS (increase in CO_2) will extensively stimulate the sympathetic nervous system and the vasomotor center which increases BP.

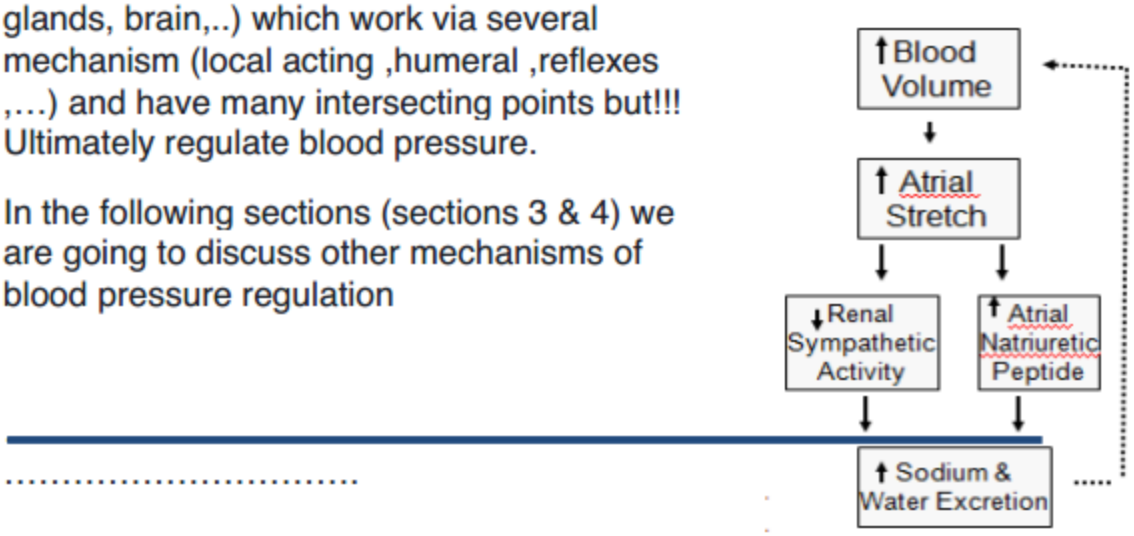
This response is trying to save this person's life , and this is his last chance , if that response succeeded in raising the BP , then this person could be saved and in this phase / case it's called (compensating shock)

But if it fails in correcting the BP ,the patient will develop (irreversible shock) , in this phase no matter what you do for the patient , he would suffer from organ failure .

If the CNS ischemia prolonged, it will cause a depressant effect on the vasomotor center which will further worsen the case.

Dr. Faisal mentioned 3 short term regulators and 4 long term regulators of blood pressure, but physiology of blood pressure control is far more complex and involves several organs (heart and vessels, kidney, glands, brain,..) which work via several mechanism (local acting ,humeral ,reflexes ,…) and have many intersecting points but!!! Ultimately regulate blood pressure.

In the following sections (sections 3 & 4) we are going to discuss other mechanisms of blood pressure regulation



Third: Atrial and pulmonary artery reflexes

A reflex means: "is an involuntary and nearly instantaneous action in response to a stimulus"

Atrial and pulmonary artery reflexes are: instantaneous actions in response to changes in blood volume which aim to minimize changes in blood pressure in response to the change of blood volume.

These reflexes are mediated by low pressure receptors in atria and pulmonary arteries.

Mechanism of action/reflex:

When Blood volume increases→ cause an increase in the atrial pressure (atrial stretch) → activates low pressure receptors → low pressure receptors will lower blood pressure by increasing Na+ and water excretion by:

I. stimulating ANP secretion which decreases Na+ reabsorbtion
II. decreasing secretion rate of ADH (atrio-hypothalamic reflex)
III. Decreasing renal sympathetic activity
IV. Increasing glomerular filtration rate (atrio – renal reflex)

Note: Bainbridge reflex is mentioned in the slides but wasn't discussed in the lecture.

Fourth: role of the kidney in long term control of arterial pressure:

All the regulation mechanisms mentioned above (section 1, 2 ,and 3) are used for short term control of blood pressure (e.g. when the blood pressure suddenly drops due to a massive hemorrhage) but the kidneys are responsible for long term control of blood pressure week after week and month after month.
What makes the kidney suitable for long term control of blood pressure??
Long term control is directly related to the balance between fluid intake and output, which is a job that is handled by the kidney
Note: Dr. Faisal didn't mention that fluid balance is determined by another factor other than the kidney which is the intake of Na+ & water

Clinical correlate:
If you have a patient in the emergency room with a BP 200/130, what would you first give him?
The obvious answer is **Vasodilators**, to decrease his blood pressure. → Short term control

But you don't discharge him with a prescription of a vasodilator like nitroprusside , because vasodilators don't work for the long term , you have to give him instead , diuretics to decrease his ECFV , or Angiotensin converting enzyme inhibitors or Angiotensin II receptor blockers . → Long term control

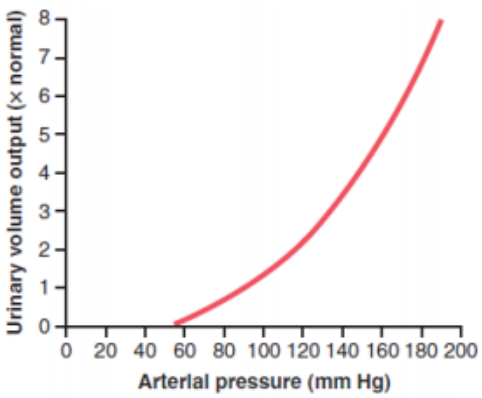
Now let us see how does the fluid balance affect the mean arterial pressure:

If you had a patient and you put him on IV fluids, what happens is that his ECFV (extra cellular fluid volume) increases which increases the cardiac output and the arterial pressure increases, and when the BP increases the urine output increases, look at the figure below

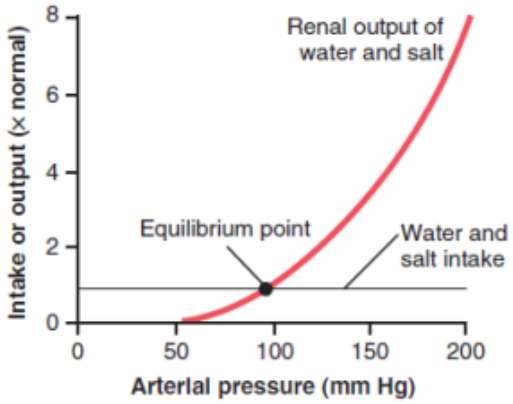
So how does the kidney control blood pressure??

Renal-body fluid system for arterial pressure control

- As we said, if we inject the patient with an IV fluid, this will increase the extracellular fluid volume, which will increase venous return; an increase in venous return will increase the cardiac output, which will increase the arterial pressure resulting in an increased urinary output.
- Therefore, as seen in the figure, an increase in the arterial pressure will increase the urinary output. And this is called the ***renal function curve***.



- To analyze the arterial pressure control by the renal-body fluid system look at the next figure.



- The analysis is based on two separate curves that intersect with each other; where the horizontal curve represents the **water and salt intake**, and the other one represents the **renal output in response in increase in pressure** (the same curve as above). And the intersection of the two curves represents a point where the renal output equals the intake, and this point is called the **equilibrium point**.
- *Over a long period, the water and salt output must equal the intake.*
- But if the pressure increased above normal, as seen in the figure, then the renal output will get higher than the intake. For instance, assume the pressure rises to 150 mmHg. At this level, the renal output of water and salt is about three times as great as intake.

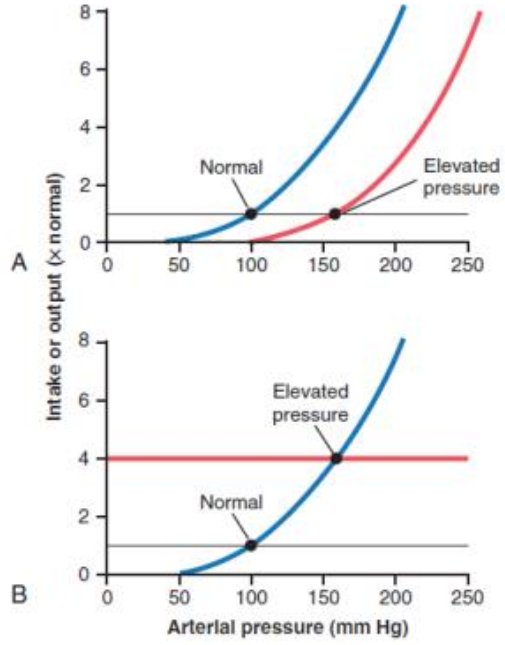
  Therefore, the body loses fluid, the blood volume decreases, and the arterial pressure decreases.

- As long as the two curves representing (1) renal output of salt and water and (2) intake of salt and water remain exactly as they are shown in the last figure, the mean arterial pressure level will eventually readjust to 100 mmHg, which is the pressure level depicted by the equilibrium point of this figure.
- There are only two ways in which the pressure of this equilibrium point can be changed from the 100 mmHg level:
  - One way is by shifting the pressure level of the renal output curve for salt and water.
  - And the other is by changing the level of the water and salt intake line.

❖ A demonstration of these two ways are discussed in our figure on the right, **A** and **B**.

A) Some abnormality of the kidneys has caused the renal output curve to shift 50 mmHg in the high-pressure direction (to the right). Note that the equilibrium point has also shifted to 50 mmHg higher than normal. And here the intake stayed normal and did not increase.

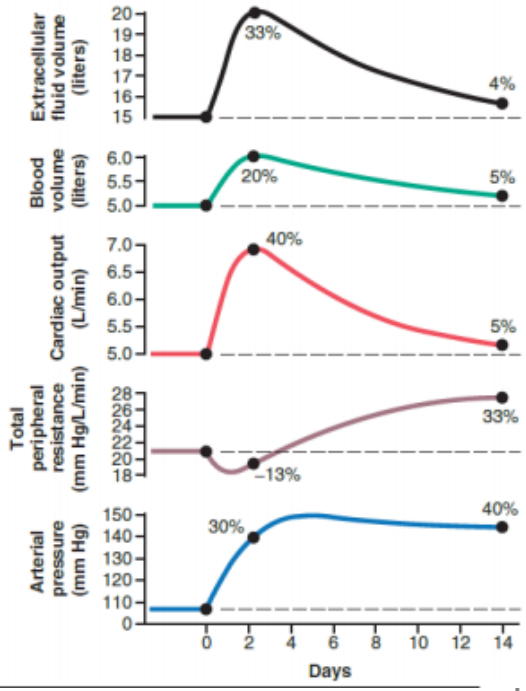
B) Shows how a change in the level of salt and water intake also can change the arterial pressure.



❖ Note: if there's an increase or a decrease in the total peripheral resistance this does not alter the mean arterial pressure, because there's a compensatory increase or decrease in the cardiac output. Meaning that the change in the TPR is not important for long-term regulation.

- The extracellular fluid volume is determined by the amount of sodium in the body, since it's the main cation in the extracellular fluid. That's why they advise people with hypertension to decrease their salt intake.

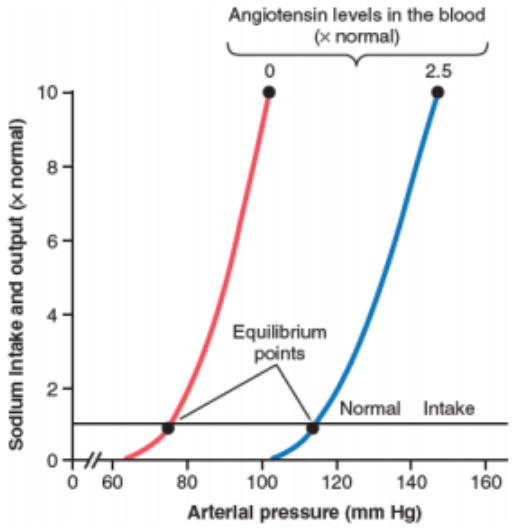
- The volume-leading hypertension:
  - Look at the figure to the right and notice the sequential changes in circulatory function during progressive development of volume-loading hypertension.
  - From the up down; if you increase the extracellular volume, you increase the blood volume, then the cardiac output increases, and the increase in the cardiac output increases the arterial pressure.



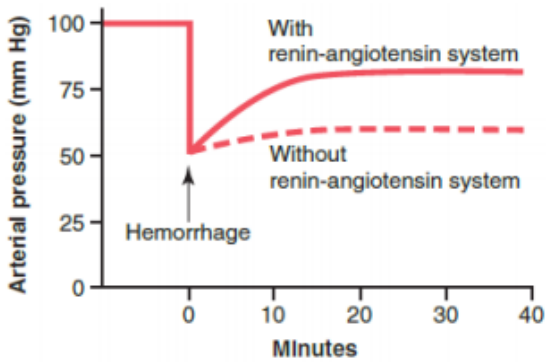
The renin-angiotensin system:

- Renin converts angiotensinogen into angiotensin **I**, angiotensin **I** is converted to angiotensin **II** in the lungs by **angiotensin converting enzyme**.
- The renin-angiotensin system increases pressure by two ways; **first**, by inducing vasoconstriction, and **second**, by decreasing sodium and water excretion.

- In the following figure is an experiment done on dogs; which resembles the principle of giving angiotensin-converting enzyme inhibitors as treatment for hypertension.
  - The left-hand renal function curve (red) is measured in dogs whose renin-angiotensin system had been blocked by an angiotensin-converting enzyme inhibitor drug.
  - The right-hand curve (blue) was measured in dogs infused continuously with angiotensin II at a level about 2.5 times the normal rate of angiotensin formation in the blood.



- And this is another experiment with; a normal renin-angiotensin system, and without a renin-angiotensin system.
- You can see the importance of this system in regulating the arterial pressure.



- Note: aldosterone is secreted from **zona gluomerulosa** from the adrenal gland.
- Note: renin is secreted from the afferent arteriolar cells of the juxtaglomerular apparatus in the kidney when there is hypotension.
- *Factors which decrease renal excretory function and increase blood pressure*
  - Angiotensin II
  - Aldosterone
  - Sympathetic nervous activity
  - Endothelin

  Endothelin is secreted from endothelial cells of the blood vessels and it is a local vasodilator.

  Aldosterone decreases renal excretory function through its absorption of sodium from the kidney.

- *Factors which increase renal excretory function and decrease blood pressure*
  - Atrial natriuretic peptide
  - Nitric oxide
  - Dopamine

  Atrial natriuretic peptide increases glomerular filtration rate and urinary output.

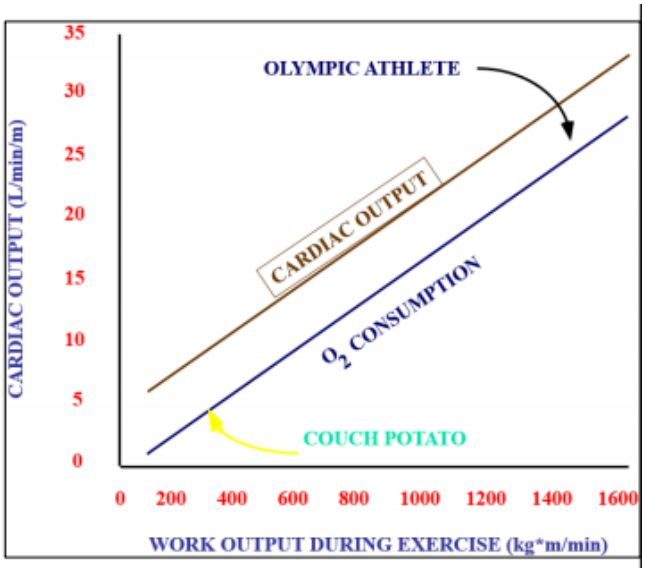
  Nitric oxide is a local vasodilator.

Blood Flow:

- The blood flow to the tissue is regulated by the tissue itself; if the tissue needs more blood, because of increased metabolic rate, then there's a release of certain substances that increase the blood flow. This is called **autoregulation**.
- What does the tissue need the blood for?
  1. Delivery of oxygen to tissues.
  2. Delivery of nutrients such as glucose, amino acids, etc.
  3. Removal of carbon dioxide hydrogen and other metabolites from the tissues.
  4. Transport various hormones and other substances to different tissues.

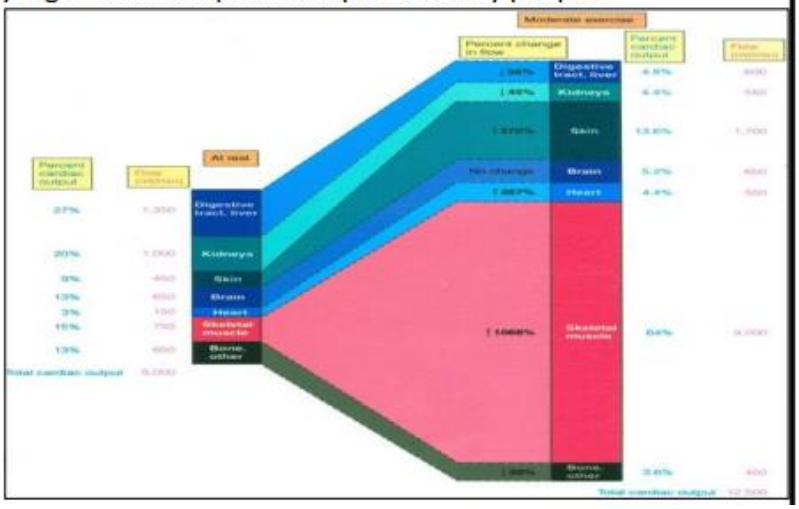
- As we talked in a previous lecture, when relating the change in cardiac output to the change in the work output during exercise, we see there is a positive relationship, but why is that?

  Because during exercise there's an increased metabolism in the tissues, which causes increased O_2 consumption (among other things), so we need more blood flow to the tissues, meaning increase the cardiac output. So it makes sense that the higher the O_2 consumption the higher the cardiac output.



- Note: Olympic athletes have very high O_2 consumption compared to lazy people.

- As the figure to the right suggests (which is more clear in the slides) that at rest state the cardiac output is about 5L/min, and only 15% of these 5L go to the skeletal muscles.
- But during exercise we can see that, first; the cardiac output increases a lot, and

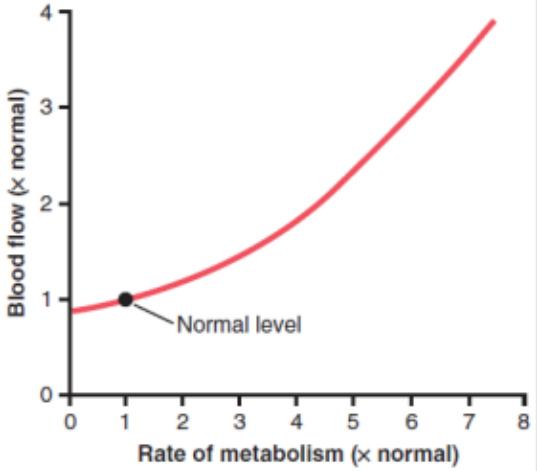


second; the percentage of that blood going to the skeletal muscles increases to about 64%, and also, the blood going to the GI decreases.

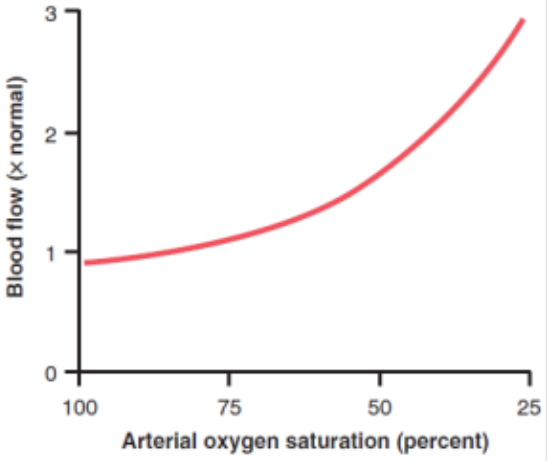
- So the cardiac output redistributes when there's exercise, but why?
  Well, the skeletal muscles are now metabolizing too much, so they need more blood.

Acute Control of Local Blood Flow

- When the rate of metabolism increases the blood flow to the tissue increases.



- And when the rate of metabolism increases this causes decreased PO_2 and increased PCO_2.
- Look at the PO_2 in this curve; when the arterial oxygen saturation is lower, the blood flow is higher.
- Notice that the numbers in this curve are flipped.
- Also, be aware that the doctor said he might bring another figure in the exam that focuses on PCO_2 rather than PO_2, which is basically the opposite.

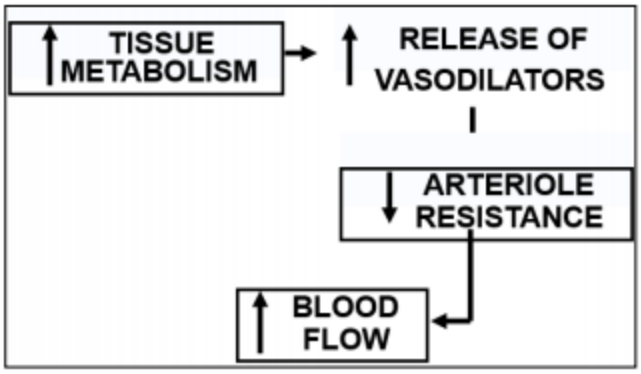


- For the millionth time, and the last time of this system, $\boldsymbol{F = \Delta P / R}$.
- Now the $\boldsymbol{\Delta P}$ is almost kept constant.
- So to play with the flow we cause vasodilation or vasoconstriction, affecting the resistance ($\boldsymbol{R}$).

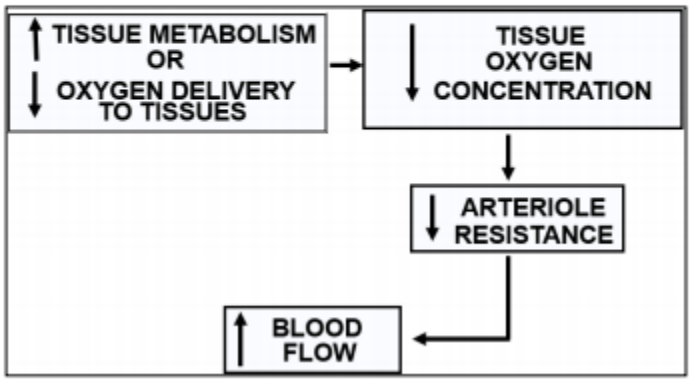
Theories for acute local blood flow regulation:

- Now we said that tissues control their own blood flow (autoregulation). But how do tissues increase their own blood flow when metabolism increases? We have two theories:

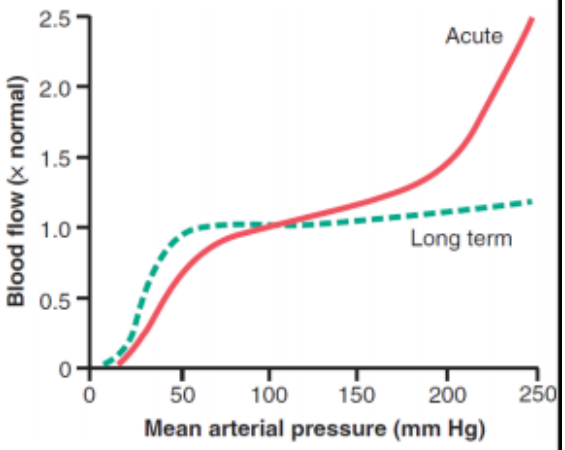
1. <u>The vasodilator theory</u>:
    - When the tissue is metabolizing too much it produces local vasodilators, these local vasodilators cause vasodilation of the arterioles that supply this tissue, which increases blood flow.
    - These **local vasodilators** are: Adenosine, CO_2, Lactic acid, ADP compounds, Histamine, K^+ ions, H^+ ions, Prostacyclin, Bradykinin, and Nitric oxide (NO).
    - Note that there's no one local vasodilator that can explain the story by itself. They work hand in hand.



2. <u>Oxygen demand theory</u>:
    - When there's an increase in tissue metabolism, the oxygen delivery to the tissue is less, and the decrease in the tissue oxygen concentration causes vasodilation, which lastly increases blood flow.

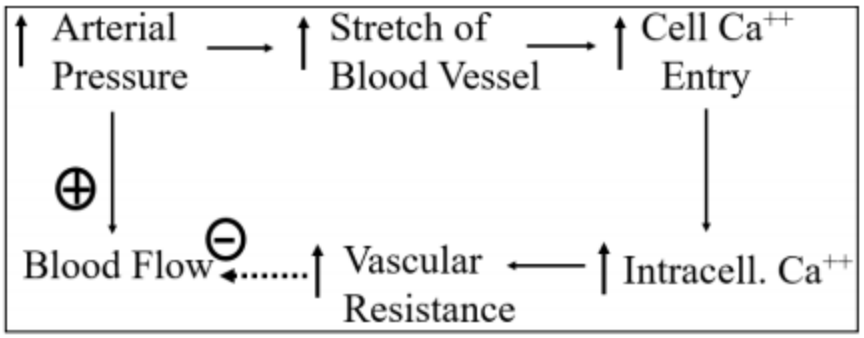


Autoregulation of blood flow during changes in arterial pressure:

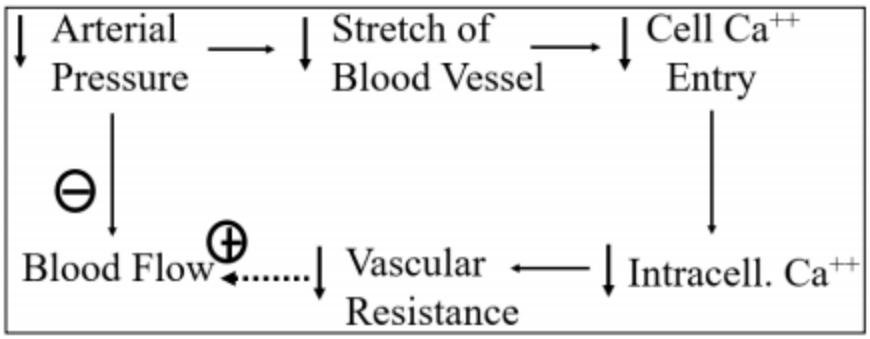


- Look at the continuous (red) curve in the figure, as we will talk about the dashed soon.
- As we can see, the blood pressure can change, and this affects the blood flow to the tissues. But the blood flow to the tissues <u>has to stay constant</u>.
- So the tissue autoregulates its blood flow; if there's an increase in pressure, the tissue decreases its blood flow back to normal, and vice versa.
- Notice in the figure that between arterial pressures of about 70 mmHg and 175 mmHg the blood flow increases only 20 to 30 percent even though the arterial pressure increases 150 percent. So the blood flow almost stayed constant.
- **There are two theories that can explain this autoregulation:**

1. <u>Metabolic theory</u>:
   - When the blood pressure <u>increases</u>:
     When the arterial pressure becomes too great, the excess flow provides too much oxygen and too many other nutrients to the tissues and "washes out" the vasodilators released by the tissues. These nutrients (especially oxygen) and decreased tissue levels of vasodilators then cause the blood vessels to constrict and return flow to nearly normal despite the increased pressure.
   - When the blood pressure <u>decreases</u>:
     it's very similar to the vasodilator theory. When the blood pressure decreases, oxygen or nutrients delivery to the tissues is decreased, resulting in release of vasodilators.
2. <u>Myogenic theory</u>:
   - When the blood pressure <u>increases</u>:
     if there's an increase in the arterial pressure, this increases the stretch of the blood vessel, which in turn increases the permeability of smooth muscles to calcium, so the force of contraction increases (high vascular resistance), and the blood flow decreases back to normal.



- When the blood pressure <u>decreases</u>:
  if there's a decrease in the pressure, this decreases the stretch of the blood vessel, which also decreases the permeability of smooth muscles to calcium. So less force of contraction and vasodilation, and this increases the blood flow back to normal.



❖ We can explain the <u>myogenic theory</u> in terms of maintaining arteriolar **wall tension**.

- Blood vessels, such as arterioles, are built to withstand the wall tensions they normally encounter.
- In the example of a sudden increase in arterial pressure, the increased pressure, if unopposed, will cause an increase in arteriolar wall tension. Such an increase in wall tension is undesirable for the arteriole.
- Thus, in response to the stretch, arteriolar vascular smooth muscle contracts, decreasing the arteriolar radius and returning wall tension back to normal.
- Note that this relationship is explained by Laplace's law we previously talked about:

$$\boldsymbol{Tension = Pressure \times Radius}$$

- So, when the pressure increases, the radius decreases to keep the tension constant. And when the pressure decreases, the radius increases for the same purpose.

The Laplace's law mentioned above is applied to cylinders, not spheres (we will discuss it in RS)

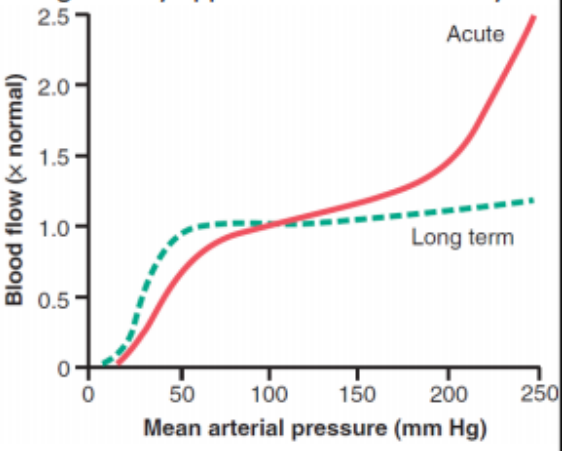
- As you might have noticed, this all seems a bit odd. Like when discussing those two theories we said:
  - When the pressure increases in a vessel, we induce vasoconstriction.
    - But vasoconstriction actually increases the pressure even more, so it's like a positive feedback; we keep increasing the pressure, and this could cause us problems.
  - And when the pressure decreases, we induce vasodilation.
    - Vasodilation induces more decrease in pressure, so it's like a positive feedback as well; we keep decreasing the pressure, and this could produce a shock.

  Well the point here that those two theories don't work in all tissues, they work in some tissues (especially in the kidney) and to a certain an extent.

Long-term Regulation of Blood Flow

- Thus far, most of the mechanisms for local blood flow regulation that we have discussed act within a few seconds to a few minutes after the local tissue conditions have changed.
- Yet, even after full activation of these acute mechanisms, the blood flow doesn't perfectly return back to normal.
- For instance, when the arterial pressure suddenly increases from 100 to 150 mmHg, the blood flow increases almost instantaneously about 100 percent. Then, within 30 seconds to 2 minutes, the flow decreases back to about 10 to 15 percent above the original control value.
- This example illustrates the rapidity of the acute mechanisms for local blood flow regulation, but at the same time, it demonstrates that the regulation is still incomplete because there remains a 10 to 15 percent excess blood flow in some tissues.
- However, over a period of hours, days, and weeks, a long-term type of local blood flow regulation develops in addition to the acute control. This long-term regulation gives far more complete control of blood flow.

- Therefore, in the abovementioned example, if the arterial pressure remains at 150 mmHg, within a few weeks the blood flow through the tissues gradually approaches almost exactly the normal flow level.
- The dashed (green) curve in the figure to the right shows the effectiveness of this long-term regulation of blood flow.
- Note that once the long-term regulation has had time to occur, long-term changes in arterial pressure between 50 and 250 mmHg have little effect on the rate of local blood flow.



- **But what are those long-term regulators?**

1. Change in tissue vascularity:
    - A key mechanism for long-term local blood flow regulation is to change the amount of vascularity of the tissues.
    - For instance, if the metabolism in a tissue is increased for a prolonged period, vascularity increases, a process generally called angiogenesis; if the metabolism is decreased, vascularity decreases.
    - Angiogenesis occurs in response to angiogenic factors released from:
        - Ischemic tissue
        - Rapidly growing tissue (tumors)
        - Tissue with high metabolic rates
    - Most angiogenic factors are *small peptides* such as **vascular endothelial cell growth factors** (VEGF), **fibroblast growth factor** (FGF), and **angiogen**.
2. Development of collateral circulation:
    - The collateral circulation in a person increases as he gets older because of numerous insults throughout life. That's why myocardial infarction is fatal in young people and less fatal in old ones.

Humoral control of the circulation

- **Vasoconstrictor agents:**
  - Norepinephrine and epinephrine
  - Angiotensin
  - Vasopressin
  - Endothelin
- **Vasodilator agents:**
  - Bradykinin
  - Nitric oxide

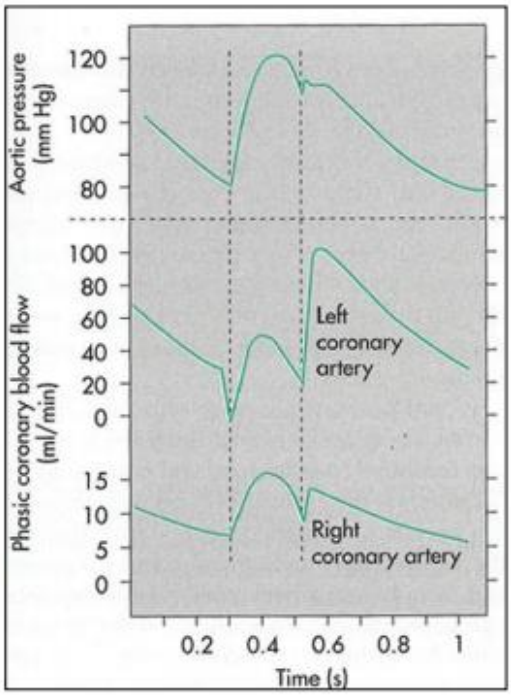
  } They're very important in the heart
  - Serotonin
  - Histamine
  - Prostaglandins
- Note: adenosine is an important vasodilator in skeletal muscles.

Blood Flow: Heart

- Normally, what comes of oxygen to the relaxed skeletal muscle is **20mL** per **100mL** of blood.
- And what goes out through the veins is **15mL** of oxygen per **100mL** of blood.
- So the skeletal muscle takes **5mL** of blood out of **20mL**, 25%. This is called extraction ratio. Meaning that the skeletal muscle usually extracts 25% of oxygen during relaxation.
- One might wonder why does the skeletal muscle only take 25%?
  This is actually better, because if the skeletal muscle needed more oxygen, it will increase its extraction ratio without an increase in the flow of blood. *But this has a limit*, as the extraction ratio of the skeletal muscle does not exceed 75%. And it doesn't go below 25%.
- As for the cardiac muscle, the story is different.
  The extraction ratio of the cardiac muscle **at rest** is **75%**, and it cannot increase above that. So the only solution for the cardiac muscle if it needed more oxygen is to increase its blood flow.

Coronary arteries:

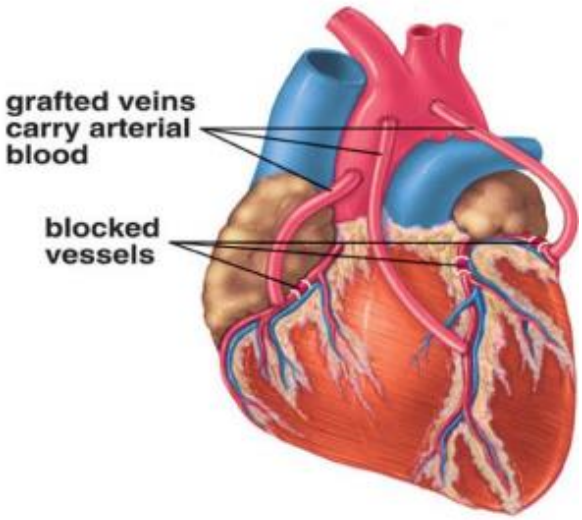
- Now as we took in anatomy, the coronary arteries are superficial, and they're compressed during systole, so the blood flow to the heart is reduced during contraction, *especially the left ventricle*.
- So during systole there's no much blood going through the coronary arteries, and this will result in the accumulation of local vasodilators that will work when the diastole starts to contribute in vasodilation to increase the blood flow.
- You can see in this figure that the blood flow in the coronary arteries, especially the left coronary artery, decreases sharply during systole, and there's very extensive increase during early diastole. So the main blood flow to the heart occurs during diastole.



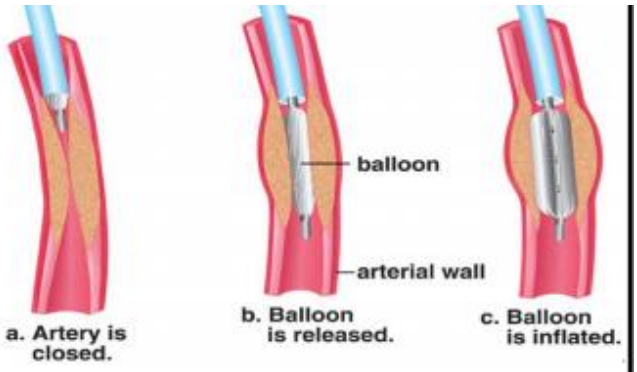
- This is important in certain cases, for instance, if someone has aortic regurgitation, his diastolic pressure is low, and since the coronary arteries originate from the aorta and their blood flow is mainly during diastole, then this patient could suffer from ischemia if he exercised. So you have to be careful with these patients.

Blocked coronary arteries:

- If we have coronary obstruction, and there're at least three vessels that are blocked, then the patient needs a bypass operation; the surgeons take a part of a vein (e.g., saphenous vein), they bypass the block in the coronary artery and they supply the blood from the aorta, as seen in the figure.



- Sometimes you can do other things rather than the bypass. There is a procedure called **angioplasty**; you insert a catheter going to the coronaries, and you inflate a balloon to open the artery where the block is found.



- The last thing that is used normally now is that after the surgeon inflated the balloon and opened the artery, they insert a stent to make sure the problem does not happen again at that site.