The Cardio-VASCULAR System

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

Lec #: 18

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Done By: Ali Khrisat

- ○ Handout
- ● Sheet
- ○ Slide

Regulation of blood flow to tissues

And special circulations

Note : this sheet is written according to section 2 recording . I've added all the extra informations in the slides

Objectives

1- List factors that affect tissue blood flow.

2- Describe the vasodilator and oxygen demand theories.

3- Point out the mechanisms of autoregulation.

4- Describe how angiogenesis occurs.

5- Inter-relat how various humoral factors affect blood flow.

Local control of blood flow

- Each tissue controls its own blood flow this is called local control and the tissue blood flow is kept to the **minimum needed amount** .

- When we say local control it means that the control is dependant on the local metabolites secreted by the tissue and it is **not neural** .

- Most of the tissues in the body depend on local factors to regulate its blood flow except the **skin and the GI tract** their blood flow control is mainly neural .

- Blood flow is needed for the tissue in order to : provide Oxygen and nutrients to the tissue and remove CO2 and toxic metabolites from the tissue , transport hormones to their target tissues

- Blood flow to the tissue is closely related to the **metabolic rate of the tissue** this is true because the curve of cardiac output and the curve of Oxygen consumption go parallel to each other and since the CO is the sum of blood flow to all tissues , the blood flow will increase to the tissues with high O2 consumption

Written by Ali Khresat

- There is variation in the distribution of cardiac output to peripheral tissues for example :

  1- Adrenal glands and the thyroid receive high levels of blood flow per 100 gram of tissue and that's because they're relatively small not because they have high metabolic rate .
  2- **The kidneys** receive the **highest** flow per 100 gram of tissues and that's because it filters the blood to form urine not because it needs more oxygen .

- As we said increase in tissue metabolism increases the blood flow and the reason behind that is that when the metabolism of the tissue increases -> O2 consumption increases -> this will decreases O2 concentration within the tissues causing **oxygen lack** -> this Oxygen lack along with accumulation of certain local metabolites causes local vasodilation in the arterioles that supplies the tissue -> which decreases the resistance and increase the local blood flow

- On the other hand , if the tissues metabolic rate is low the oxygen consumption will be low so oxygen concentration will increase and CO2 concentration will decrease as well as the H concentration, this will cause vasoconstriction of the arterioles which increases the resistance and decreases local blood flow .

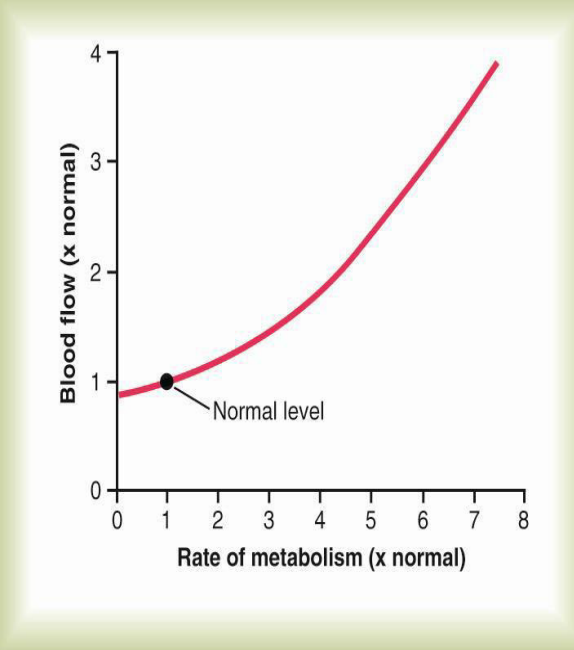
- 2 theories have been conducted to explain local blood flow to tissues which are :

  1- The vasodilator theory
  2- The Oxygen demand theory

The vasodilator theory

- This theory states that increase in tissue metabolism leads to the release of **local vasodilators** which dilate arterioles decreasing resistance -> increasing flow .

- What are those local vasodilators ? initially they thought that CO2 is the main local vasodilator since it accumulates in the tissue metabolic rate increases , but it was found that CO2 accumulation doesn't explain the local vasodilation in all tissues .



- They jumped from CO2 to Hydrogen since hydrogen concentration increase (pH decrease) in tissues with high metabolic rate but H+ alone didn't explain the entire story .

- They jumped to **Adenosine** which is molecule that is produced from breaking down of ATP -> ADP -> AMP -> Adenosine , they found that adenosine is chiefly responsible for vasodilating arterioles in the heart and skeletal muscles but not all tissues .

  "They didn't find any single substance responsible for local vasodilation in all tissues so then they came up with vasodilator theory which states that increase tissue metabolic rate increase the secretion of different local vasodilators according to the tissue type "

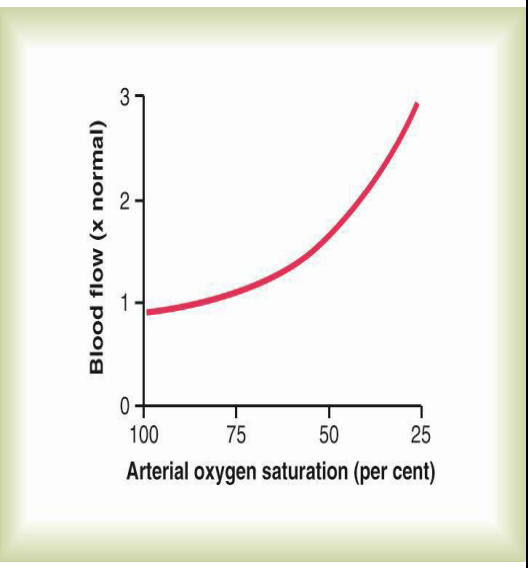
- Examples on local vasodilators include : Adenosine (heart and smooth muscles) , CO2 (brain), Lactic acid(skeletal muscles), ADP compounds, Histamine, K+ ions, H+ ions, Prostacyclin, Bradykinin (heart) , and Nitrous oxide (NO) .

- Bradykinin is released from kinins by the enzyme kallikrein because of wall stretch and it causes local vasodilation (not systemic) . NO was previously known as **endothelium derived relaxing factor** because it was produced from endothelium and they didn't know that it resembles Nitric oxide , this confirms that endothelium is not only a protective layer , it also produces chemicals like NO (vasodilator) and endothelin (vasoconstrictor) .

Oxygen demand theory

- increase in the metabolic rate of the tissue will increase the Oxygen demand which will decrease O2 concentration within the tissue , the theory states that this decrease in O2 concentration leads to arteriolodilation and increase blood flow .

- Notice the figure : as the Oxygen saturation decreases (X-axis) and blood flow to the tissue increase . keep in mind that the doctor can change the X-axis from O2 saturation to CO2 concentration . In this case as the CO2 concentration **increases** Oxygen consumption increases so the blood flow increase (you need to understand the figure and not memorize it blindly)



- To confirm the theory : they monitored the vasomotor activity of arterioles and precapillary sphincters , when the O2 concentration increased the precapillary sphincter remained **closed** , but as they decreased O2 concentration they noticed a change in the vasomotor activity of precapillary sphincter as it kept opening and closing . this experiment indicates the role of Oxygen saturation in the control of local blood flow .

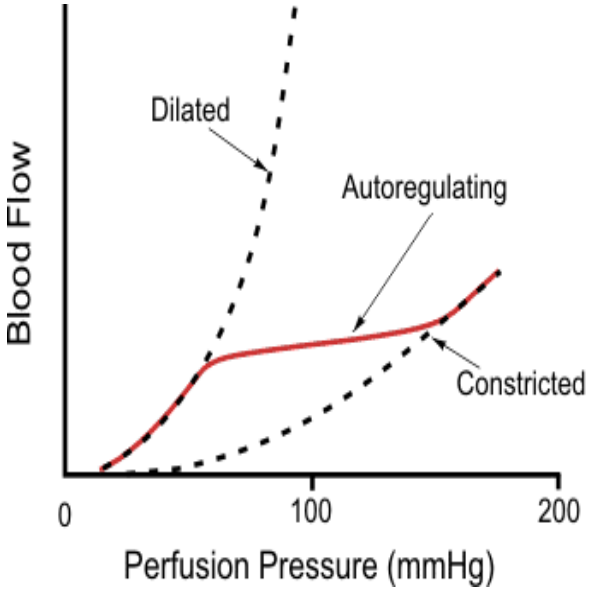
Autoregulation of blood flow

- Autoregulation of blood flow is defined as the intrinsic ability of the organ to maintain a constant blood flow despite changes in arterial blood pressure .

- The blood flow to the tissue is almost constant along with varying blood pressure (between 60-180 mmHg) .

- The Question of the day : why is the blood flow kept constant despite the change in blood pressure?

  Because blood flow to tissue is controlled locally , if the blood pressure increases (hypertension) the arterioles constrict to prevent high amount of blood to enter and if the blood pressure decreases (hypotension) the arterioles dilate to maintain constant organ perfusion .



Theories for autoregulation

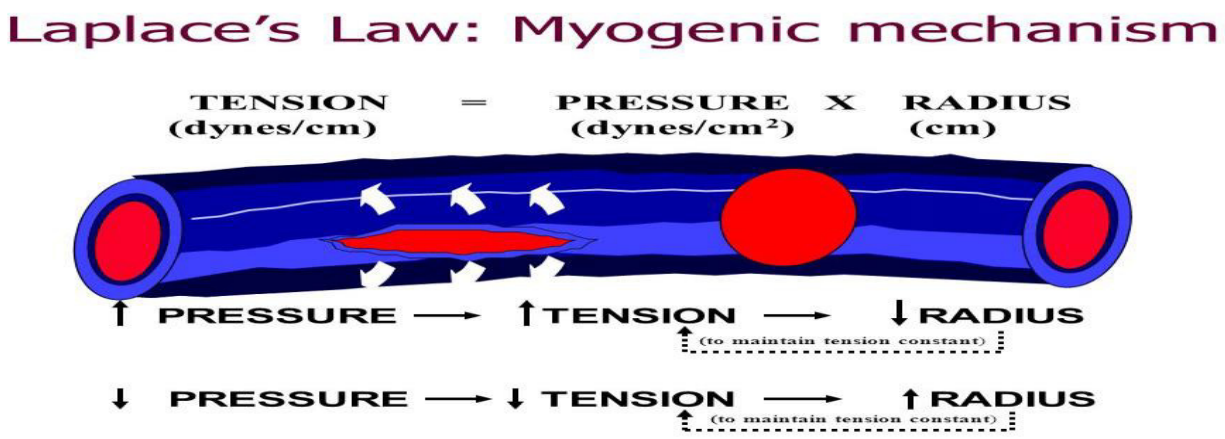
1- Metabolic theory : same as vasodilator theory , increase in the metabolic demand of the tissue increase there will be a release of vasodilator substances which increases the blood flow through decreasing the resistance .

2- Myogenic theory : when there is a decrease in the perfusion pressure (decrease in the flow) **the stretch of the wall of arteriole decreases** this decreases Ca+2 permeability to the arterioles leading to relaxation (vasodilation) -> decrease the resistance which increases the flow . On the other hand if the perfusion pressure increases the blood flow increase so the stretch on the wall of arterioles will increases which consequently increases Ca+2 permeability leading to contraction (vasoconstriction)

- So the myogenic theory can be explained based on **wall stretch** , high blood pressure -> increases stretch -> increases Ca+2 influx -> vasoconstriction . Low blood pressure -> decreases stretch -> low Ca+2 influx -> vasodilation .

  Note : the metabolic theory is more acceptable than myogenic theory , however both theories seem to work , for example the myogenic theory is mostly applied to the kidneys blood flow .

The relationship between Laplace's law and myogenic theory



- The myogenic theory can be explained by Laplace's law which is Tension=Distending pressure x Radius

  Increase in pressure : increases tension and in order to maintain the tension you decrease the radius which decreases the flow because of increased resistance.

  Decrease in pressure : decreases the tension so we increase the radius to maintain the tension which increases the flow .

Long term regulation of blood flow

- The previous mechanisms and theories were short term (acute) regulations , long term mechanisms are more effective in regulating blood flow that acute regulations .

- To understand long term regulations look at the following examples

  1- In case **hyperthyroidism** there is too much metabolism and O2 consumption , acute term regulations cannot maintain high blood flow

for long time so here there should be permanent mechanisms like **Angiogenesis** (increased vasculature) to increase blood flow

2- In case of **ischemic heart disease** : the blood flow to the heart decreases and I can't regulate it acutely so how can I regulate it permanently ? by increasing **anastomosis or collateral circulation** so when another ischemic episode happen the damage will be less catastrophic . **for this reason MI in young age is considered lethal compared to elderly since young people were not exposed to ischemia before so they have no collaterals compared to elderly .**

- **From those previous examples we concluded that long term regulation of blood flow is by changing the degree of vascularity of the tissue .**

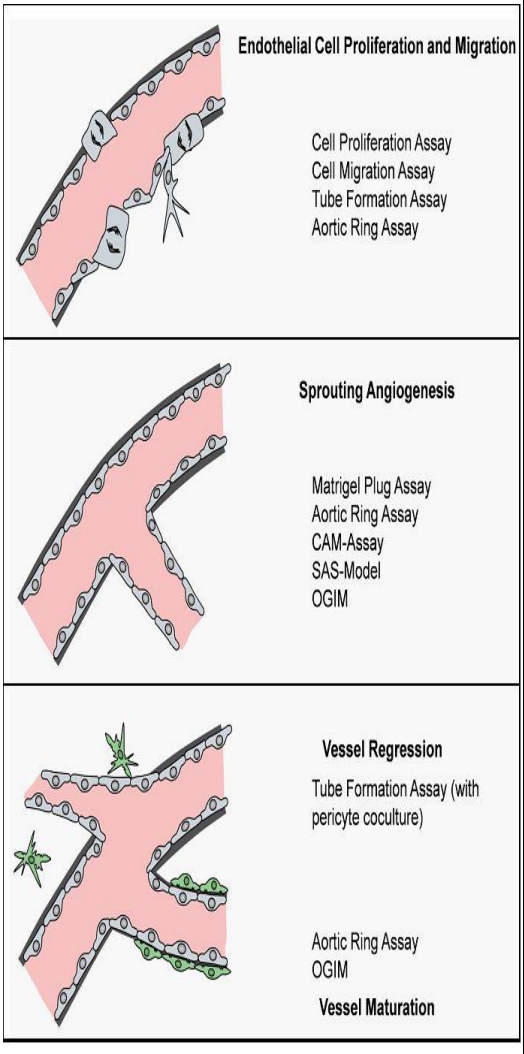
Angiogenesis

- Angiogenesis is defined as the formation of new blood vessels which increases blood flow . the main stimulus for angiogenesis is **ischemia (decrease in oxygen supply) .**

- Angiogenesis occur in response to angiogenic factors released from :

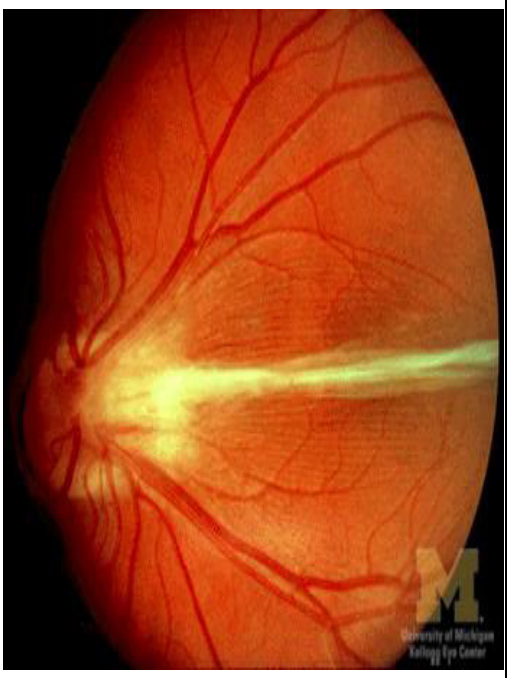
  1- Ischemic tissues
  2- Tissues with high metabolic rate
  3- Rapidly growing tissues

- Most of these Angiogenic factors are **small peptides** such as **Vascular endothelial cell growth factor** (VEGF) ,**Fibroblast growth factor** (FGF) and **angiogen**



- To know about the importance of angiogenesis read the following example : you know that newborns don't have ability to see when they are first born and their eye sight develops gradually overtime , the reason behind that is their retinal blood vessels are under developed at time of birth and needs time to develop by undergoing angiogenesis . In some cases where a baby is born prematurely , in this case he need to be put in an incubator in order to prevent **infantile respiratory distress syndrome** since the baby hasn't develop surfactants in the lungs .in the incubator the baby must be exposed to 100% O2 this means that retinal angiogenesis will be inhibited and his body will adapt to 100% O2 intake from the outside **.**

After the baby gets well by developing surfactants and get out from the incubator , he will become exposed to 21 % O2 from the air , **this 21% O2 to the body of the baby indicates ischemia since his body is adapted to 100% O2 (which inhibited angiogenesis), this will cause a very high increase in level of angiogenesis <u>especially</u> in retinal blood vessels because they are under developed , this excessive angiogenesis will cause the retinal vessels to grow so fast to the extent that they completely cover the retina impairing the ability to see** (in order for vision to take place light must hit the retina where vision receptors are found) this condition is called **<u>Retrolental Hyperplasia .</u>**



How to prevent retrolental fibroplasias ? by **gradually** decreasing the O2 concentration the baby is exposed to in the incubator and not suddenly removing him from the incubator once he develops surfactants .

<u>Blood flow to special organ</u>

<u>Blood flow to Skeletal muscles</u>

- Controlled mainly by local metabolites

From slides

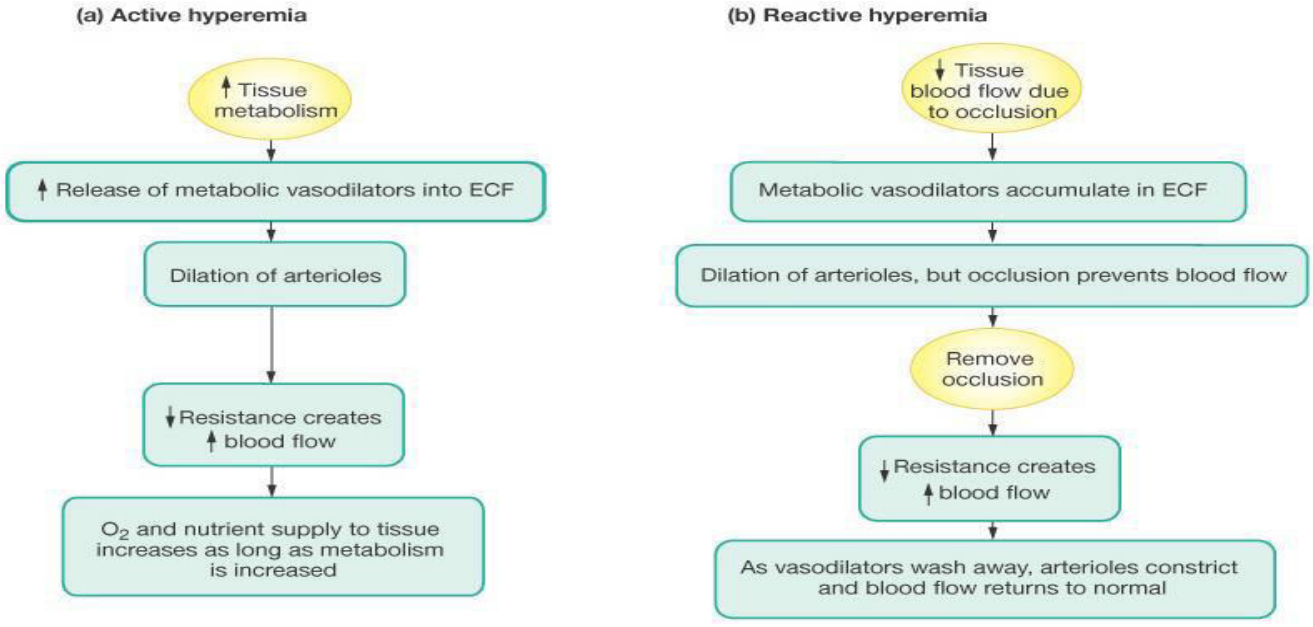
Muscle blood flow can increase tenfold or more during physical activity as vasodilation occurs

- Low levels of epinephrine bind to β receptors

- Cholinergic receptors are occupied
- Intense exercise or sympathetic nervous system activation result in high levels of epinephrine
- High levels of epinephrine bind to α receptors and cause vasoconstriction
- This is a protective response to prevent muscle oxygen demands from exceeding cardiac pumping ability

- In general there is two main types of increase in blood flow **(hyperemia)** :

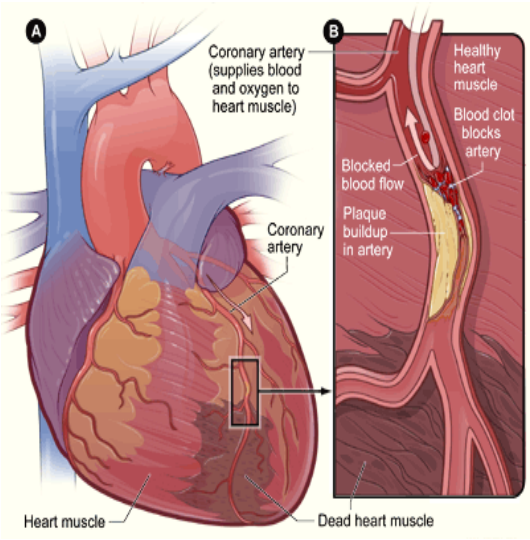
1- Active hyperemia : this occurs when the tissue is active releasing high levels of local vasodilators which dilate arterioles and increase blood flow . Active hyperemia happen is **isotonic muscular exercise** .
2- Reactive hyperemia : it is an increase in blood flow to the tissue which occurs following a brief period of ischemia (arterial occlusion) . for example when you put a cuff that exerts pressure on your hand stopping the blood supply and then you remove the cuff you can feel the rapid flow of blood .



- What is the cause of reactive hyperemia ? when there is occlusion or ischemia to the tissue metabolic wastes like CO2 accumulates in the tissue since there is no blood flow to wash them away , this will cause dilation of the vessels in the ischemic tissue and when the obstruction is removed the blood will flow very rapidly through dilated vessels manifesting as hyperemia . It is important to know the active hyperemia continues as long as the metabolism of the tissue is increased ,however in reactive hyperemia the blood flow returns to normal as local vasodilators are washed away .

Myocardial reperfusion injury (Clinical application):

In case of obstruction of the coronary artery by a thrombus the heart will undergo myocardial infarction and accumulation of metabolic vasodilators , after a while the thrombus will undergo dissolution by plasmin consequently blood will flow very rapidly to the ischemic area to compensate for the ischemia , this is called **hyperperfusion reaction and it's a type of reactive hyperemia** . Hyperperfusion reaction is one of the most important consequences after MI and can even lead to death .



Blood flow the brain

- The blood flow to the brain is almost entirely dependent local control since the neurons are intolerant to ischemia , This local control is mainly maintained by the metabolic theory through **CO2 vasodilator** .

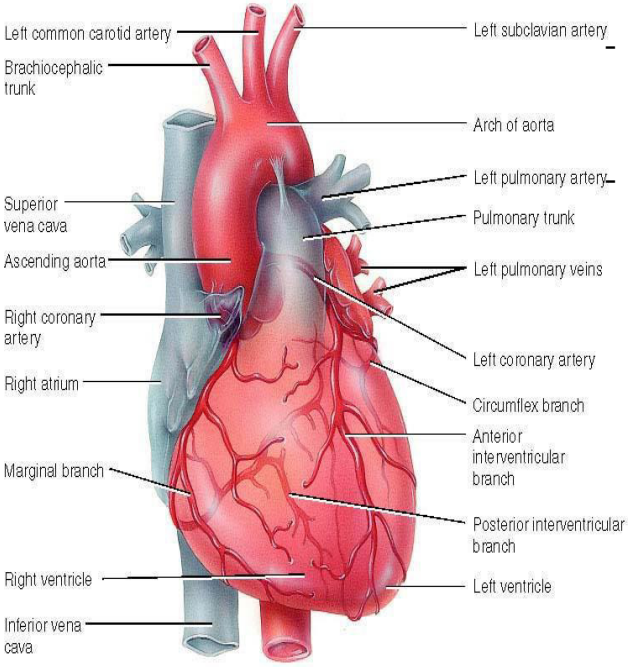
- Blood flow to the brain is kept constant between **60 -180 mmHg** , that's why we said in the previous lecture that hypotension below 60 mmHg is very critical since it can trigger **CNS ischemic response** due to ischemia .
- If the blood pressure decreases below 60 mmHg -> Syncope (fainting), if the blood pressure increase above 180 mmHg -> Cerebral edema and hemorrhage . This indicates the important of autoregulation of the blood flow to the brain as it is very sensitive to changes in blood flow.

Blood flow to the Skin

- The blood flow to the skin is different because its mainly controlled neutrally (by sympathetic) not locally. The blood flow to the skin is mainly important for **temperature regulation** .

- During summer when there is so much heat -> there will be vasodilation of the blood vessels of the skin in order to lose heat ,in cold weather the vessels of the skin will be constricted in order to reserve heat . This temperature control is mainly maintained by sympathetic stimulation .

Blood flow to the heart (important)



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- The blood flow to the heart is mainly controlled **locally** .

- When there is increase sympathetic stimulation to the heart this will **increase the blood flow to the heart** , How ?? Don't be confused , it is true that sympathetic stimulation causes vasoconstrictor to the coronary arteries , however sympathetic stimulation also increase the heart metabolic activity which elevates the level of local vasodilators like Adenosine and CO2 and H+ , those local vasodilators dilate the coronary arteries increasing blood flow and overriding the sympathetic stimulation on the coronary arteries .

- As if the sympathetic nervous system has a direct and indirect effects on the coronary arteries . the direct effect is vasoconstriction and the indirect effect is vasodilation by increasing the heart metabolic rate .

- What about the parasympathetic stimulation on the heart ? remember that the parasympathetic nervous system has NOOO direct effect on coronary arteries since it doesn't supply it , However parasympathetic nervous system activation causes indirect vasoconstriction of the coronary blood vessels by decreasing the metabolic activity of the heart and the amount of local vasodilators.

Sympathetic nervous system	Parasympathetic nervous system
Direct effect on coronary arteries : vasoconstriction	NO DIRECT EFFECT ON CORONARY ARTERIES
Indirect effect : Vasodilation which overrides the direct effect by the metabolic theory	Indirect effect : vasoconstriction by decreasing local vasodilators

- Skeletal muscles get 20ml of oxygen, they take out 5 ml, however cardiac muscle at rest take 15ml leaving out 5ml. The extraction ratio of the cardiac muscle at rest is 75% but for skeletal muscle its 25% at rest but can reach 75%. So the only way to increase blood supply to the heart is by increasing the blood flow as we can't increase extraction ratio above 75% because it's very high.

Coronary blood flow during cardiac cycle

- During systole the coronary arteries blood flow decreases compared to diastole because during systole there is too much compression on the coronary arteries .

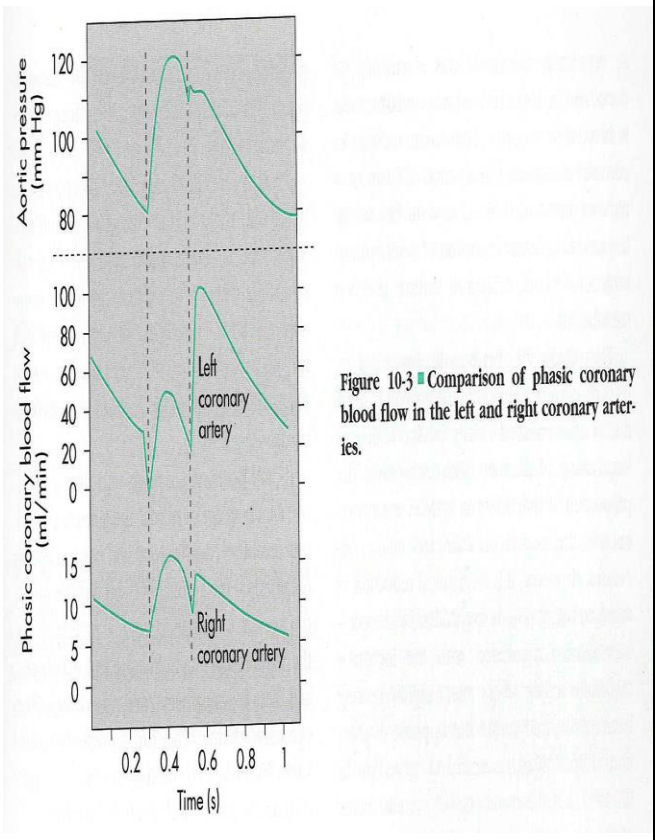


Figure 10-3 ▪ Comparison of phasic coronary blood flow in the left and right coronary arteries.

- This can be explained by the concept of reactive hyperemia , how ? since during systole the coronary arteries (especially the left) is under very high tension that might obstruct it , this will cause accumulation of metabolic local vasodilators which dilate the coronary and then when **early diastole** (isovolumetric relaxation) occurs the compression is relieved then the blood will flow very fast through the dilated coronary artery . **This variation is mainly in the blood supply of left ventricle** .

- According to dr faraj : in the right coronary , the blood flow is almost the same in both systole and diastole since the compression exerted by the right ventricle on the right coronary is very low compared to the left ventricle .

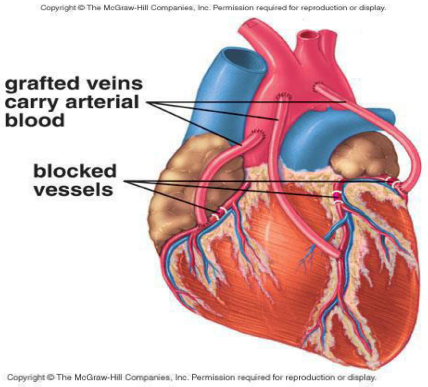
- Since the blood flow to the left coronary is dependent on early diastole , this means that the driving force for blood to flow through the left coronary is the **aortic diastolic pressure** so in case of **aortic regurgitation** in which people have a very low diastolic blood pressure (might reach 0) this is catastrophic for the left ventricle coronary supply , that's why when

someone have an aortic regurgitation he should never ever do exercise because it can lead to death (IMPORTANT)

Cardiac surgeries

1- Coronary bypass surgery

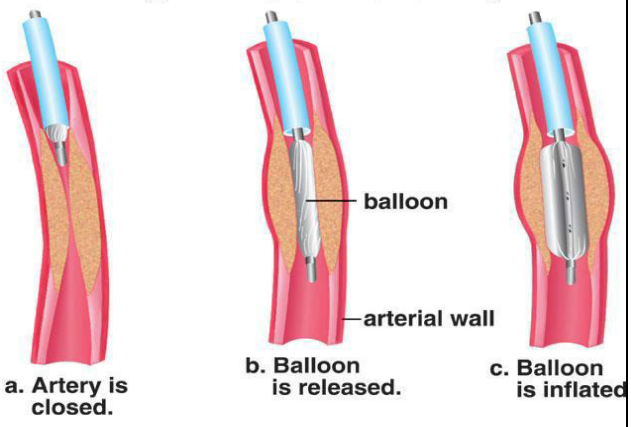
It is done by removing the great saphenous vein or the internal thoracic artery bypassing the area of coronary occlusion to restore myocardial perfusion



2- Angioplasty

It is an endovascular procedure to widen atherosclerotic coronary arteries by inserting a balloon catheter and then inflate the balloon once we reach the atherosclerotic area

3- Stents



Pulmonary circulation

- All the venous blood that comes from the systemic circulation goes into the pulmonary circulation
- The only difference between the pulmonary and systemic circulation is the pressures , the pressure in right ventricle is 25/0 while in the left is 120/0 , the pressure in the pulmonary artery is 25/8 while in the aorta is 120/80 , the MAP in the systemic circulation is 100 mmHg while in the MAP in the pulmonary circulation is 15 mmHg
- The cause of these differences in pressures is the difference in the RESISTANCE since the systemic circulation TPR is 6 times higher than the pulmonary circulation resistance
- **The pulmonary vessels are very special compared to systemic vessels since elevation of intra alveolar O2 causes vasodilation of pulmonary vessels and elevation of intra alveolar CO2 causes vasoconstriction of pulmonary**

vessels (while in systemic circulation CO2 is a local vasodilator) and this is logic if there is O2 in the alveoli it must be delivered to the blood while we don't want to deliver CO2 to the blood, this will be emphasized in more details in the respiratory system .

That's the end of the sheet good luck for everyone in the finals

Dedicated to Q