بسم الله الرحمن الرحيم

Physiology lecture #20

Control of the tissue blood flow 2

Last time we start talking about the control of tissue blood flow, and we said that the aim of the whole circulation is to give the tissue it's blood need.

- The blood flow to the tissue is controlled **locally** in an **auto-regulation** process which means that the amount of blood flow to the tissue is exactly as its blood need "not more and not less"

- The blood flow to the tissue is proportional with it's **metabolic rate** → the more the metabolic rate and the activity to the tissue the more blood flow to this tissue.

These are the main ideas in controlling the blood flow to **most tissues.

- Regulation of the blood flow to the tissue is **local** regulation not by the autonomic nervous system but mainly by **local vasodilators** and **local vasoconstrictors**, so the tissue blood flow is not controlled by the MAP since the MAP which must be kept almost constant all the time and is controlled by too many factors, so changing the **radius** of the vessel "by **vasodilation** or **vasoconstriction**" will change the blood flow to the tissue much more than when we change the pressure.

The tissue blood flow auto-regulation theories:

1-**Metabolic theory**

2-**Myogenic theory**

- The tissue blood flow regulation includes:

1) short term regulation (Acute control) : which occurs mainly by **vasodilation** or **vasoconstriction**

- when the tissue needs **more** blood → **Vasodilation** of blood vessels will occur to increase the blood flow to this tissue in order to cover the tissue needs.

-when the tissue needs **less** than it's normal blood need → there will be **vasoconstriction** to decrease the blood flow to the tissue

2) long term regulation: includes :

A) **ANGIOGENESIS :** this occurs in the presence of a tumor which is uncontrolled growth of cells or hyperthyrodism, this needs more blood and more oxygen so there will be an increase in the vascularity by formation of new blood vessels, stimulated by tissue ischemia through humoral chemical mediators called angiogenic factors/ angiogenes.

B) **Opening of collaterals:** this occurs only when there is certain degree of vasoconstriction of the tissue blood vessels which causes decrease in the blood flow to the tissue. Many constrictions occur along with increasing in age which leads to open some collaterals in the tissue and this continues until certain age where these opened collaterals are able to compensate for the decrease in the blood flow to that tissue.

- Each tissue cotrolls it's own blood flow **locally** according to it's metabolic rate.. tissue needs blood for : 1) delivery of O2 to the tissue 2)delivery of nutrients to the tissue 3) removal of CO2 and other metabolites from the tissue 4) transport of hormo nes and other substrates to dfferent tissues

- The cardiac output and the O2 consumption go in parallel to each other → the more the O2 consumption the more the cardiac output since the cardiac output is the sum of all the tissues blood flows … so if a certain tissue has a higher metabolic rate this will increase the blood flow to it and the blood flow comes from the cardiac output . different tissues have different amounts of blood flow in terms of per 100g of tissues and also depending on their metabolic rate , O2 consumption, …

In the **<u>ACUTE (short-term) control</u>**:

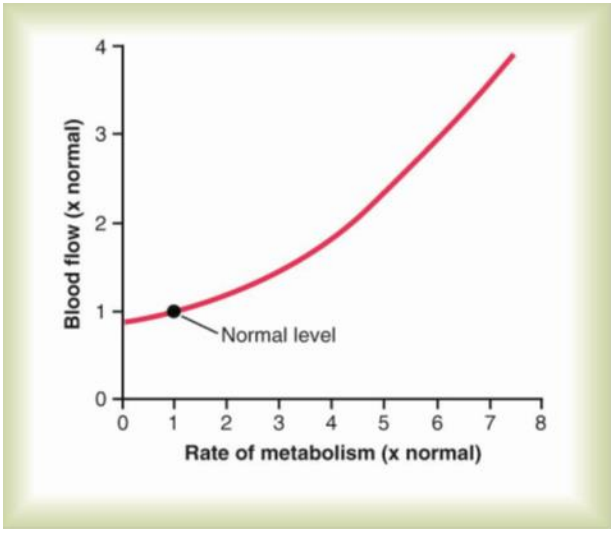
- increase in the tissue metabolism leads to increase the tissue blood flow ,,, while decrease in the tissue metabolism leads to decrease the blood flow.

- Decrease in the O2 availability to tissues "or increase in the CO2 availability" increases the tissue blood flow by vasodilation .

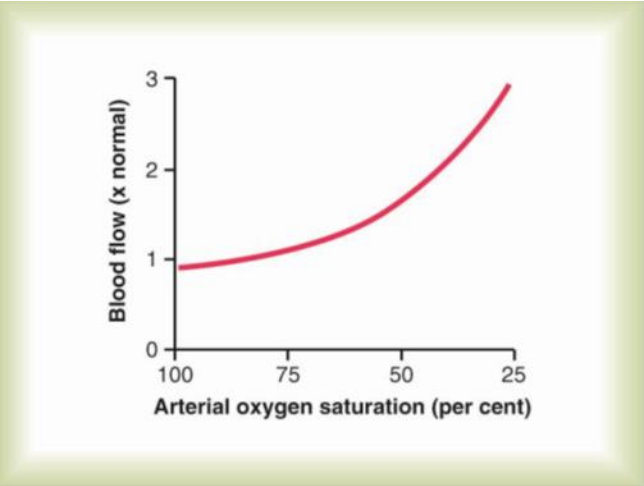
The 2 major theories for local blood flow are: **1) the vasodilator theory** : by release of local vasodilators

2) Oxygen demand theory.

As the tissue metabolic rate increases >> the blood flow to the tissue increases as you see in the following figure



We can show this relation in another way„ As PO2 "tissue O2 concentration" decreases → the tissue blood flow increases … O2 conc. In the tissue might decrease due to increase in the tissue metabolic rate and increase in the O2 consumption .



We can do the previous curve in another way round; we relate the blood flow to the PCO2 "conc. Of CO2" → the higher conc. Of CO2 the more the blood flow to the tissue and vice versa. So you have to understand the curves and relations not to memorize them as they are drawn in the figures .

F=▲P/R … so blood flow through a vessel is determined by :

1)the pressure difference between the two ends of the vessel

2) the resistance : this is factor which can be changed by either vasodilation or vasoconstriction to regulate the tissue blood flow while changing the first factor will not produce much difference on the tissue blood flow as we mentioned before .

*** Vasodilator (metabolic) theory** for blood flow control : when the tissue metabolism increases there will be vasodilation of the tissue vessels to increase the blood flow .. this occurs by local vasodilators that their conc. Increase with the increased metabolic rate in the tissue such as : CO2 but CO2 alone is not enough to cause much vasodilation so there are other local vasodilators that help to induce the vasodilation including : 1) Adenosine >> it's conc. increases since when there is increase in the metabolic rate there will be an increase in the ATP consumption so ATP will be converted to ADP then to AMP then to adenosine which will accumulate in the tissue 2) lactic acid 3) ADP compounds 4)histamine 5) K+ ions 6)H+ ions 7) Bradykinin 8)prostacyclin ... so the local vasodilator might be any substance that it's conc. Increases when the metabolic rate increases .

When they study the effect of each vasodilator alone they find that this vasodilator is not enough to induce much local vasodilation in the tissue vessels „ so local vasodilation occurs by

more than one local vasodilators that are present in higher conc. In the tissue when the metabolic rate of the tissue increases .

Some local vasodilators are more important in certain tissues for ex. Adenosine is more important in the skeletal muscles „ Bradykinin is more important in the heart „ CO2 is more important in the brain … but one vasodilator alone in the tissue can't explain the whole story and that's why they put the vasodilator theory .

**What we can understand from this theory ??

⬆ Tissue metabolism → ⬆ release of local vasodilators "causing local vasodilation" → ⬇ arteriolar resistance → ⬆ blood flow

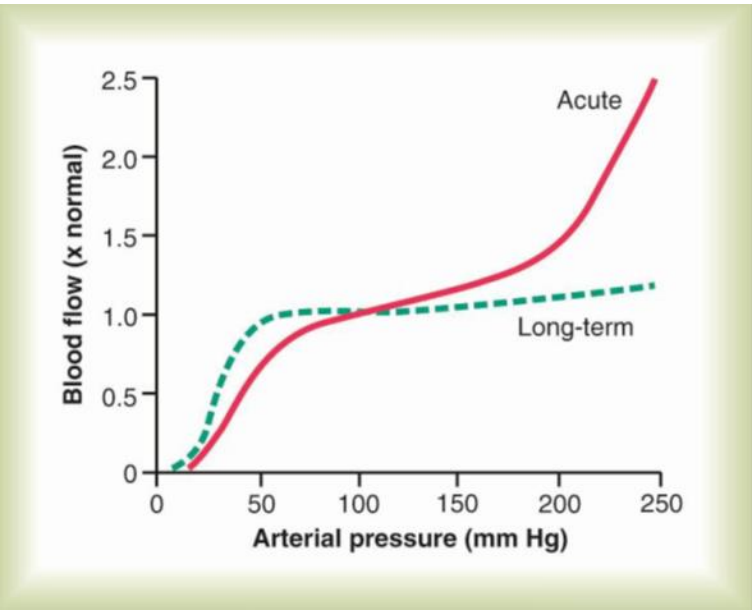
<u>Oxygen demand theory</u> for blood flow control:

Increase in metabolism (decrease in O2 delivery) → Less O2 in the tissues, more demand → pO2 is low → arteriolar resistance decreases due to local vasodilation → increased blood flow to tissues

**** vice versa is true in both previous theories : when tissue metabolism decreases there will be local vasoconstriction causing decrease in the blood flow ...**

The tissue blood flow is auto-regulated mainly by local vasodilation or vasoconstriction according to it's blood need so **<u>AUTO-REGULATION</u>** means :the ability of the tissue to maintain the blood flow relatively constant over a wide range of arterial pressure … MAP is regulated by too many factors and if the tissue blood flow depends on the pressure then the blood flow to the tissue will be changed continuously without following the tissue needs but this of course will not happen since the blood flow to the tissue should be exactly as much as the tissue needs so again the blood flow to the tissue is auto-regulated by the tissue itself by either vasodilation or vasoconstriction to be maintained relatively constant and cover the tissue needs only without being affected by the MAP ..

if the MAP INCREASES much this will increase the blood flow but if the tissue doesn't need that much flow the tissue will induce a local vasoconstriction to decrease the blood flow to .match it's needs exactly



A question was asked : when the tissue induces local vasoconstriction this will increase the pressure what will affect the tissue blood flow more :the increase in the pressure or the vasoconstriction?? This is true when vasoconstriction occurs it will increase the pressure but there is not much increase in the pressure so usually the effect of the vasoconstriction will appear causing a decrease in the tissue blood flow … actually this depend on which factor is increases more : vasoconstriction will decrease the blood flow while increasing the pressure will increase the blood flow , so one of them will dominate … if vasoconstriction causes much increase in the pressure in a certain case this will cause an increase in the blood flow even that there is a local vasoconstriction and this is called a **positive feedback** which is dangerous that's why the pressure is regulated by a variety of factors other than vasoconstriction or vasodilation to prevent this positive feedback and mostly local vasoconstriction will dominate decreasing the blood flow to the tissue to match it's needs …

Theories of blood flow auto-regulation : 1) **Metabolic theory : it's the same as the vasodilator theory → when the metabolic rate increases there will be release of many local vasodilators within the tissue by auto-regulation and this will induce local vasodilation and increase in the blood flow to the tissues. Most of the tissues have their blood flow controlled locally except for the skin which is controlled through the nervous system.

If we study the heart blood flow: the sympathetic effect will increase the contractility which will increase the metabolic rate to the heart (HR) and this will increase the blood flow. at the same time the sympathetic will increase the vasoconstriction of the coronary arteries directly, but the indirect way of sympathetic innervation is that will cause an increase of the release of local vasodilators, these local vasodilators will also induce vasodilation of the coronary arteries which overrides the effect of the vasoconstriction. To sum up: the blood flow to the heart is controlled locally by local metabolites not by the nervous system

2)Myogenic theory: when the arterial pressure increases there is an increase in stretch on the wall of the artery → stretching the wall of the vessel will increase the permeability of the wall to Ca+ → more intracellular Ca+2 → causing contraction of the muscle and constriction of the vessel → increasing the resistance and decreasing the flow back to the tissue needs even that the pressure increases

When the pressure decreases it will decrease the blood flow but the tissue needs more blood than what reaches it → so when pressure decreases → the stretch on the vessel wall decreases → the permeability for Ca+2 decreases → less intracellular Ca+2 → the smooth muscles of the wall relax (vasodilate) → decrease in the resistance → increasing the blood flow to the tissue to cover it's needs even that there is a decrease in the pressure

** this theory means that there is a danger since when the pressure increases this will cause vasoconstriction according to this theory , this vasoconstriction will increase the pressure more , increasing the pressure will cause more and more vasoconstriction and finally there will be no blood flow to the tissue and this might kill the person … on the other hand decrease in the pressure will cause vasodilation according to this theory → vasodilation will decrease the pressure more which causes more vasodilation and so on finally the tissue will have much blood flow more than it's own needs and this might lead to shock.

** Metabolic theory explains the blood flow to most tissues but certain tissues have other mechanisms for blood flow control :1- the kidneys follow the Myogenic theory in which they have a feedback system between the tubules and arterioles" glomerular feedback" .
2- the brain blood flow is controlled by CO2 mainly …

****Laplace's low** : it explains the **Myogenic mechanism** as following :

Tension = pressure *radius

-when the pressure increases >> tension increases >> radius decreases in order to maintain the tension constant .

- when the pressure decreases >> tension decreases but the radius increases to maintain the tension constant .

If you remember when we talked about the critical closing pressure we said that there might be no flow but there is much tension and much resistance which causes much pressure and that's what we called the critical closing pressure .. this will be discussed later Insha'Allah in the respiratory system " when there is much tension around the bronchioles there will be critical closing pressure" …

** these are the short term regulators „ now we will explain the long term reg.

LONG TERM regulation : this type occurs when the tissue needs more blood flow for **a long period** of time „ this reg. occurs in one of two mechanisms :

1) **Angiogenesis** : the tissue will increase the formation of blood vessels in this process . - this is stimulated by **ischemia** to the tissue (less O2 delivery to tissues), so there will be release of peptides called **growth factors** which will stimulate the growth of the endothelial cells to grow stimulating the angiogenesis . these growth factors include : Endothelial cell growth factors, epithelial cell GF, fibroblast growth factors…

2) opening of collaterals : stimulated only when there is a **block** or much constriction , so they will open to compensate the decrease in the tissue blood flow .

** long term reg. is **more effective** than the short term reg.

**in long term reg. the tissue blood flow is maintained relatively constant for a long period of time even if there is a change in the pressure…

***Retina of the eye will be completely developed 3-4 weeks after birth ,so after birth the retina is still developing and the baby can't see until the retina has continued it's development , so retinal blood vessels will continue their development after birth by angiogenesis ..but sometimes this might occur abnormally as following :

as we know that pregnancy period takes about 40 weeks , but if a baby is born premature at the 30th week of pregnancy his lungs are still collapsed due to absence of the surfactant which is very important .. they will put this baby in an incubator under 100% saturation of O2 but this will inhibit the angiogenesis since it's stimulated by decrease in the O2 availability.. after one month for example this baby is okay and his lungs continue maturation so he will get out from the incubator and he will be exposed to the atmospheric air in which the O2 saturation is only 21% , the normal for this baby is 100% saturation of O2 therefore t 21% causes ischemia to his tissues which will stimulate the angiogenesis and the retinal vessels will grow very fast and encroach underneath the retina and behind the lens and this is called **Retrolental hyperplasia** which will cause **permanent blindness**.

… to prevent this the must **wean** this baby from O2 gradually when he is in the incubator within the last 2 weeks of the incubation → in the first day we decrease the O2 saturation to 95% „in the second day to 89% and so on until the O2 saturation is as the atmospheric value at the end of the 2 weeks and now he will be taken out from the incubator without any problem …

wean: يفطم**

*Retrolental hyperplasia is the risk in angiogenesis that might occur if the doctor gets the baby out from the incubator without decreasing the O2 saturation gradually so be careful for that our doctors ☺

Myocardial infarction is lethal in young person's since the person doesn't suffer from ischemia before so no opening of the collaterals and if MI occurs the person will die since he has no opened collaterals that are enough to compensate for the stopped blood flow,, while older persons have ischemia many times during their life and opening of collaterals , by the age of 60 this person has enough opened collaterals to compensate so if he suffers from MI at this age he might remain alive since these opened collaterals will act as a protective mechanism that will compensate for the stopped blood flow

So DON'T ignore any compressive sternal chest pain or any ST segment elevation or depression since this indicates emergency and it might be a pain from the heart and it's a risk factor for MI, so don't ignore it in young persons and also in old persons .

HUMORAL REGULATION of blood flow :

1) Vasoconstrictors:

Systemic such as : **Epinephrine, NE**, **Angiotensin**, and **Vasopressin**

Endothelin: it's a local vasoconstrictor produced by the endothelial cells which indicates the importance of these cells since they don't cause only protection like the epithelial cells they also release substances like **endothelin** which help to regulate the tissue blood flow

2) Vasodilators: ex : **Bradykinin** it's important in the heart, **serotonin, Histamine**,

Prostaglandins → important in kidneys

Nitric oxide: it's alocal vasodilator that is released by the endothelial cells ,, it was called **the endothelial cell derived relaxing factor** but after that they discover it's components and they called it nitric oxide

Regulation of the blood flow of certain tissues:

1) Skeletal muscle blood flow regulation:

The blood flow to the skeletal muscle is regulated **locally** → when the muscle needs more blood flow there will be increased release of local vasodilators and the most important one in the skeletal muscle is **Adenosine** "also it's important in the heart as we said before that some local vasodilators are more important in certain tissues".

-the skeletal muscle has 2 types of exercise:

A) Iso-metric contraction: contraction that includes increasing the tension while the length is constant, when you push a wall

B)Iso-tonic contraction : there is shortening of the muscle but the tension is constant,, like in jogging there is much contraction and relaxation which will increase the release of local vasodilators due to increased metabolic rate and these vasodilators will cause local

vasodilation of the muscle arterioles so more blood flow to this muscle due to the increase in its metabolic rate .

in this type there is **active hyperemia there will be an increase in the tissue blood flow due to increased activity , this occurs actually when the muscle exercise increases → mainly the iso-tonic type

when iso-metric contraction occurs this will push the wall of the muscle or in the case of applying a tourniquet →the blood flow to the tissue decreases although the tissue is still metabolizing and needs more blood! So it releases the local vasodilators which collect but are unable to increase the blood flow to the muscle since there is constriction. When the pressure is released → there is too much increase in blood flow due to the excessive vasodilation by these vasodilators that collected. This increase in blood flow after removal of the obstruction is called **Reactive hyperemia which occurs as a reaction to the constriction, so it's not active it is reactive, occurs as a reaction to constriction and occlusion

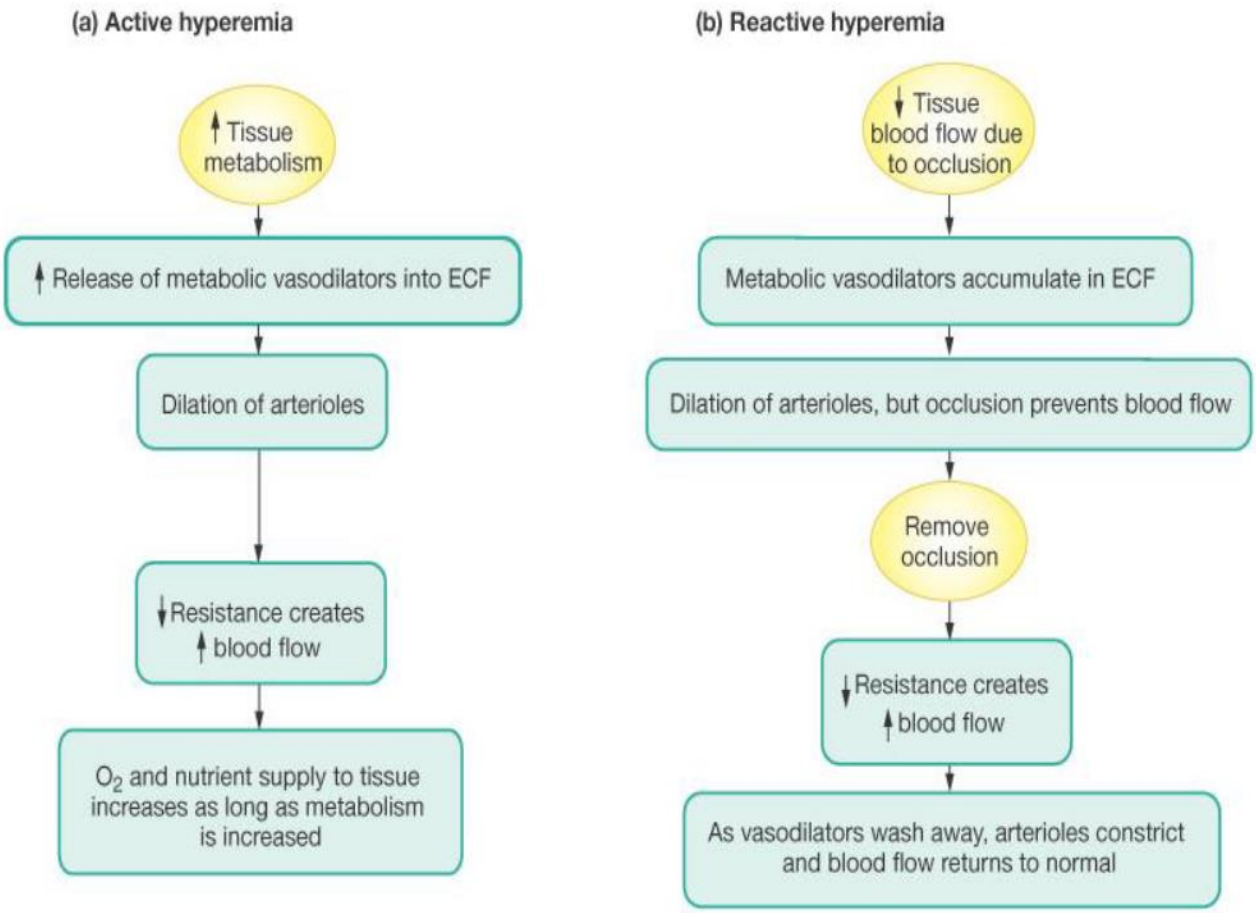
-Reactive hyperemia might occur in the heart in case of **reperfusion injury**: there will be vasoconstriction of the coronary arteries which causes decrease in the blood flow to areas they supply, but the tissue is still metabolizing and needs more flow so it releases local vasodilators, but still these vasodilators are unable to increase the blood flow due to the constriction. The thrombus that causes the constriction will be eventually dissolved by the fibrinolytic activity (plasmin). Once the clot is dissolved, there will be now excessive blood flow to the area that was constricted → so it's called reperfusion injury since the increase in the blood flow occurs after removal of the occlusion and after the injury of the tissue has started for example the sacrolemma may have increased permeability to Ca+2

SLIDE #18:

**the skeletal muscle blood flow increases 10 or more during exercise „ we explained this in previous lectures : in normal conditions the blood flow to the muscle is 1L/min while during exercise it increases to 8 or 10 L/min .

** Low levels of epinephrine bind to beta receptors especially in animals not humans. It causes vasodilation in skeletal muscles. It occupies cholinergic receptors. When there is intense exercise or sympathetic nervous system activation this will result in high levels of epinephrine. High levels of epinephrine bind to alpha receptors causing vasoconstriction. This is a protective response to prevent the muscle O2 demands from exceeding the cardiac pumping activity since cardiac output has certain limits, this allows the heart to cover the O2 demand of other tissues not only to the skeletal muscles demand

The doctor read slide #19:



Sorry for any mistake

تم بحمد الله و فضله ـ

بالتوفيق يا رب ولا تنسونا من دعواتكم ☺