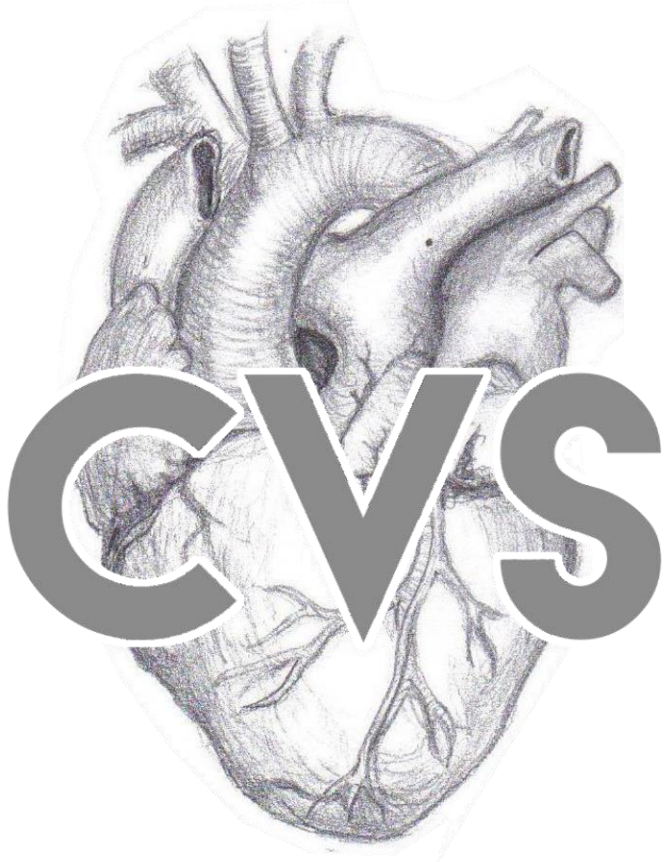

CVS

PHYSIOLOGY

✓Sheet ○Slide ○Handout

Number

18

Subject

Blood Flow

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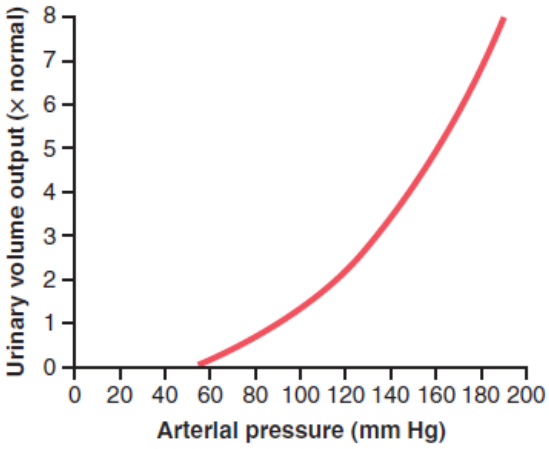
Date: 00/00/2016

Price:

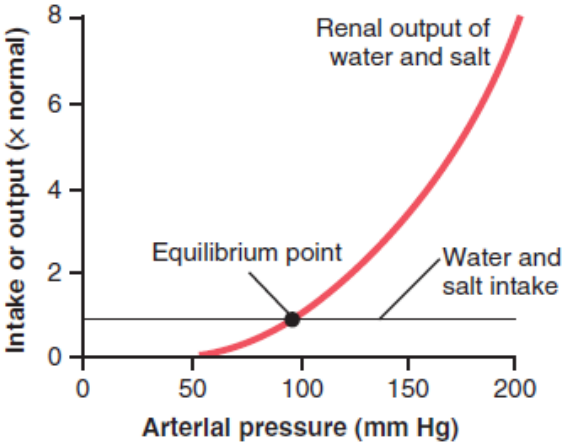
- As we said in the last lecture, the short-term regulators for blood pressure reset and adapt fast, so the body needs long-term regulators.
- This long-term control of arterial pressure is closely intertwined with homeostasis of body fluid volume, which is determined by the balance between the fluid intake and output.

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**.



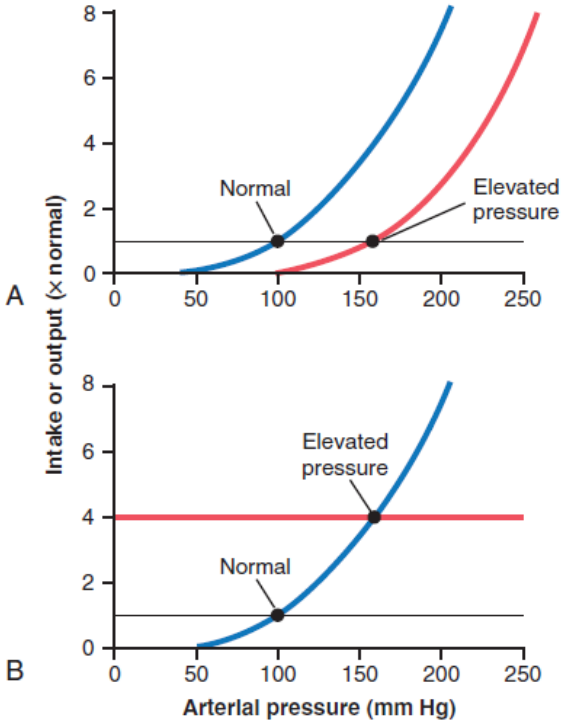
- *Over a long period, the water and salt output must equal the intake.*
- But if the pressure increased above normal, as seen in the figure, then the renal output will get higher than the intake. For instance, assume the pressure rises to 150 mmHg. At this level, the renal output of water and salt is 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**.

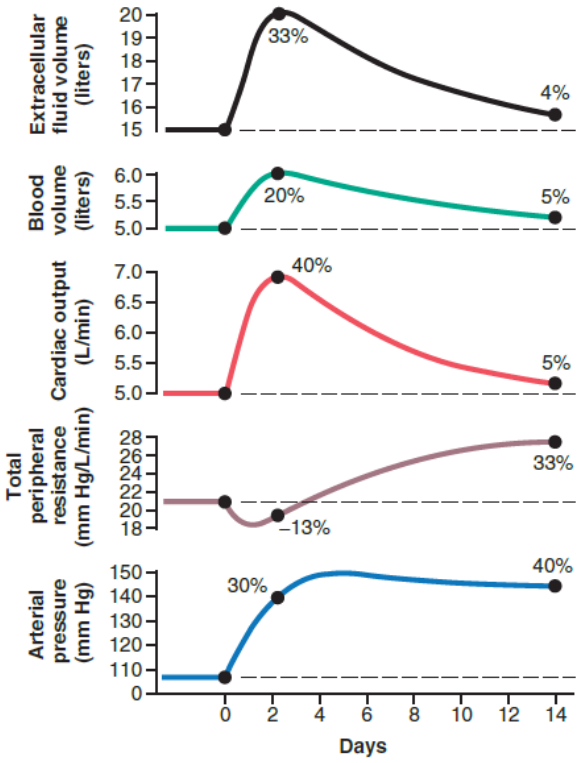
A) Some abnormality of the kidneys has caused the renal output curve to shift 50 mmHg in the high-pressure direction (to the right). Note that the equilibrium point has also shifted to 50 mmHg higher than normal. And here the intake stayed normal and did not increase.

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.

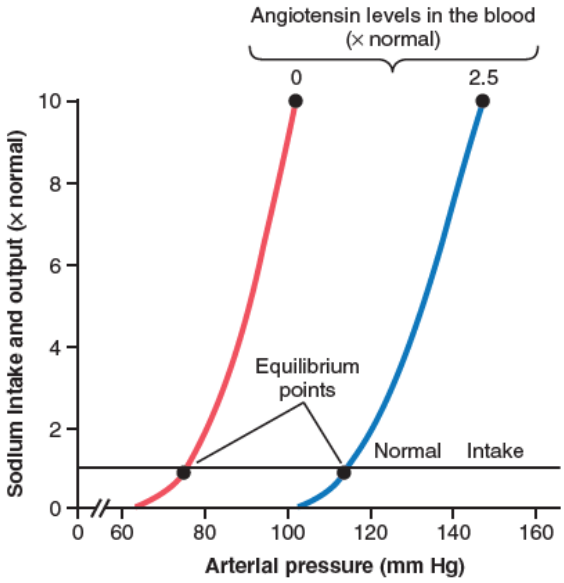


- The volume-leading hypertension:
  - Look at the figure to the right and notice the sequential changes in circulatory function during progressive development of volume-loading hypertension.
  - From the up down; if you increase the extracellular volume, you increase the blood volume, then the cardiac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

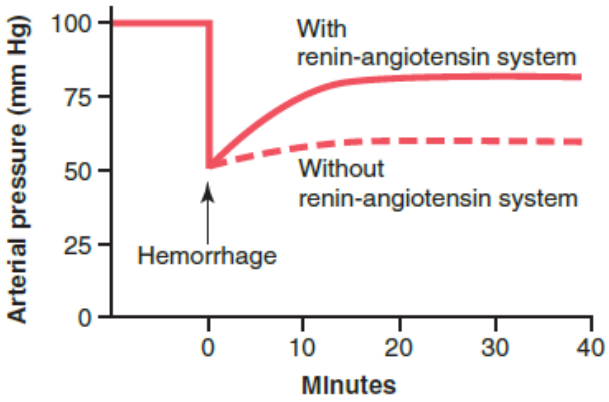
The renin-angiotensin system:

- 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.

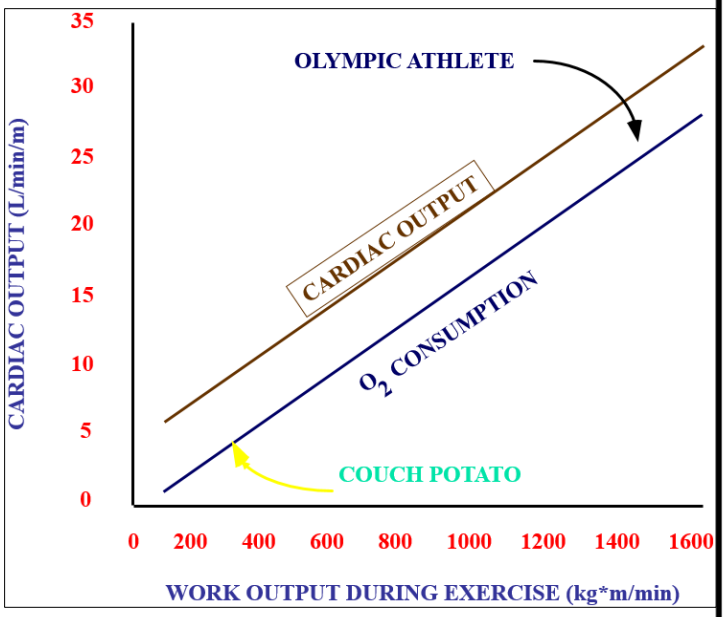
  Nitric oxide is a local vasodilator.

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.

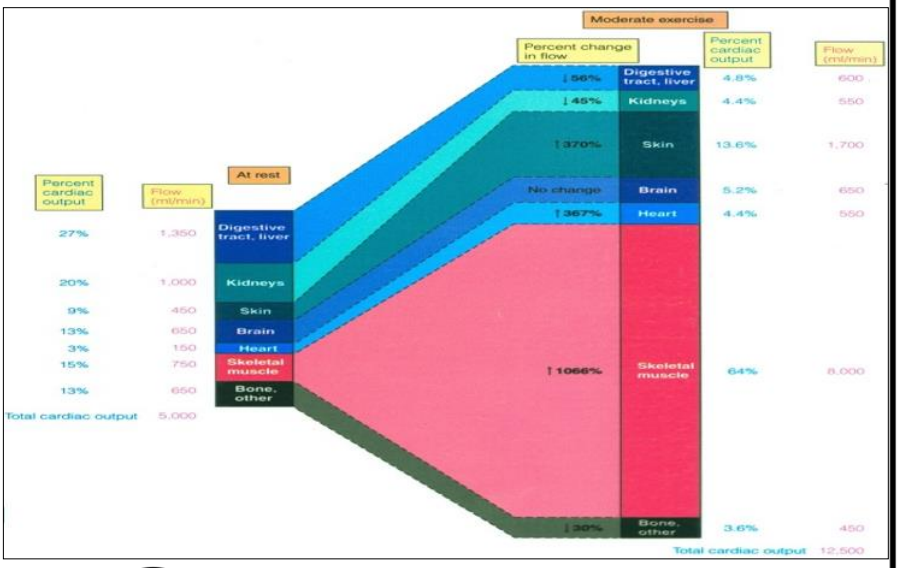
- As we talked in a previous lecture, when relating the change in cardiac output to the change in the work output during exercise, we see there is a positive relationship, but why is that?

  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

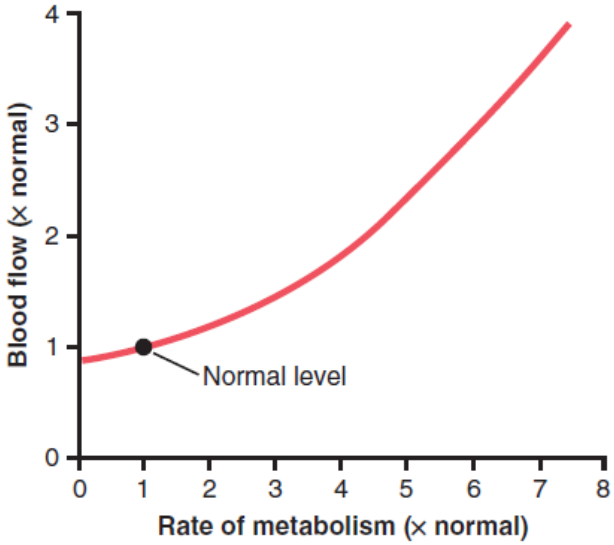


second; the percentage of that blood going to the skeletal muscles increases to about 64%, and also, the blood going to the GI decreases.

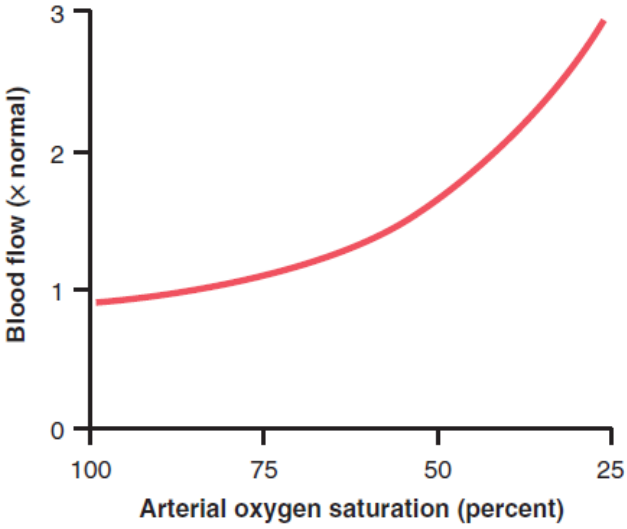
- So the cardiac output redistributes when there's exercise, but why?
  Well, the skeletal muscles are now metabolizing too much, so they need more blood.

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.

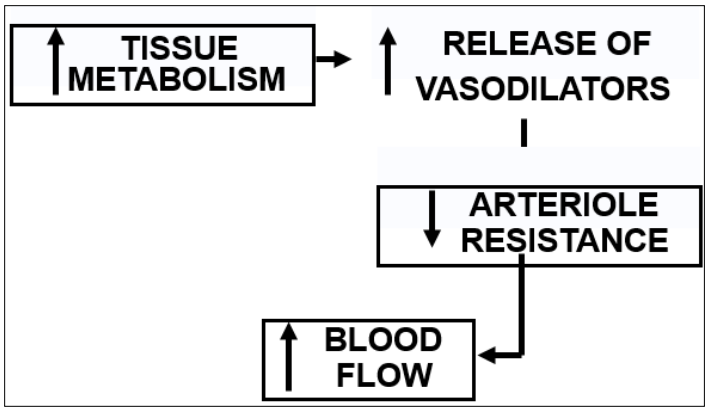


- For the millionth time, and the last time of this system, $\boldsymbol{F = \Delta P / R}$.
- Now the $\boldsymbol{\Delta P}$ is almost kept constant.
- So to play with the flow we cause vasodilation or vasoconstriction, affecting the resistance ($\boldsymbol{R}$).

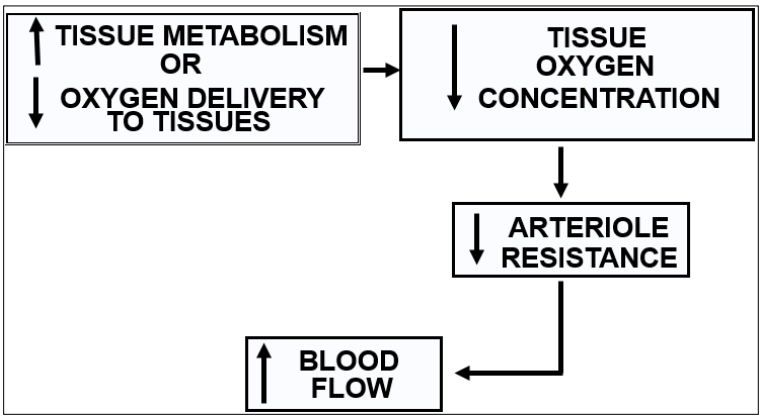
Theories for acute local blood flow regulation:

- 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:

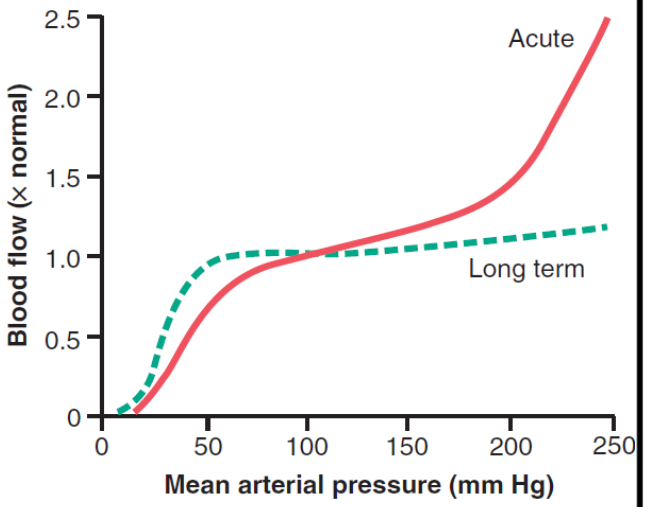
1. <u>The vasodilator theory</u>:
    - When the tissue is metabolizing too much it produces local vasodilators, these local vasodilators cause vasodilation of the arterioles that supply this tissue, which increases blood flow.
    - These **local vasodilators** are: Adenosine, CO_2, Lactic acid, ADP 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.

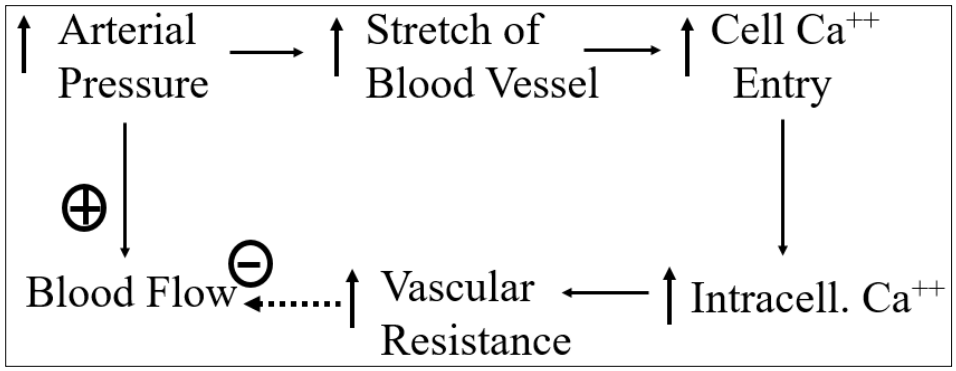


Autoregulation of blood flow during changes in arterial pressure:

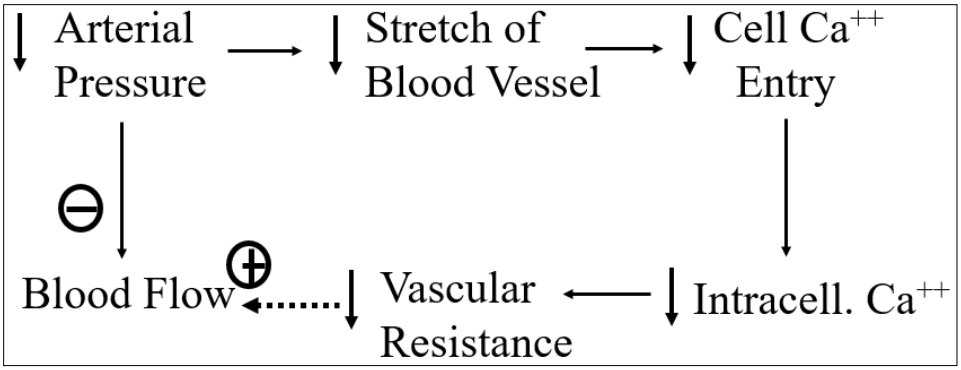


- Look at the continuous (red) curve in the figure, as we will talk about the dashed soon.
- As we can see, the blood pressure can change, and this affects the blood flow to the tissues. But the blood flow to the tissues <u>has to stay constant</u>.
- So the tissue autoregulates its blood flow; if there's 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)

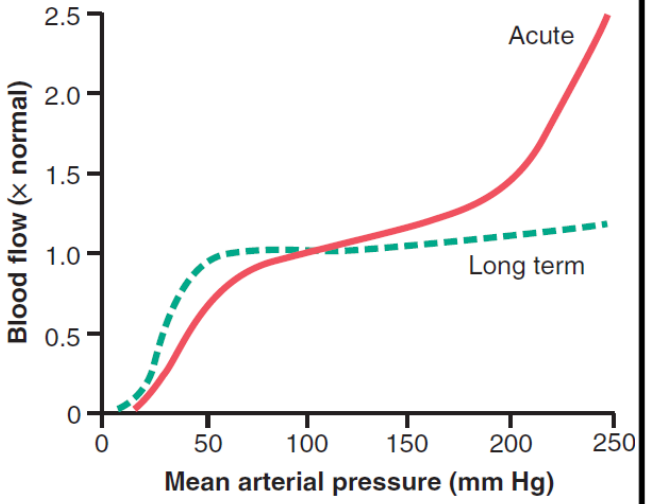
- As you might have noticed, this all seems a bit odd. Like when discussing those two theories we said:
    - When the pressure increases in a vessel, we induce vasoconstriction.
        - But vasoconstriction actually increases the pressure even more, so it's like a positive feedback; we keep increasing 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

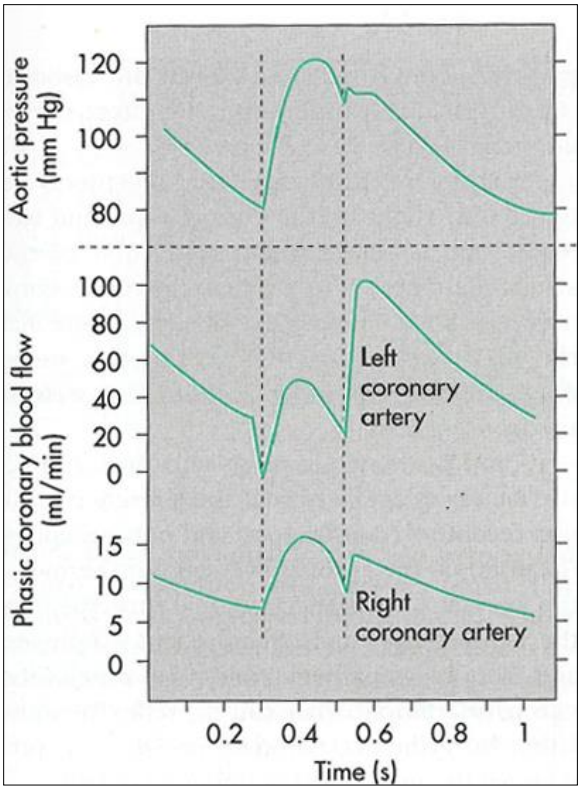
  } They're very important in the heart
  - Serotonin
  - Histamine
  - Prostaglandins
- Note: adenosine is an important vasodilator in skeletal muscles.

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:

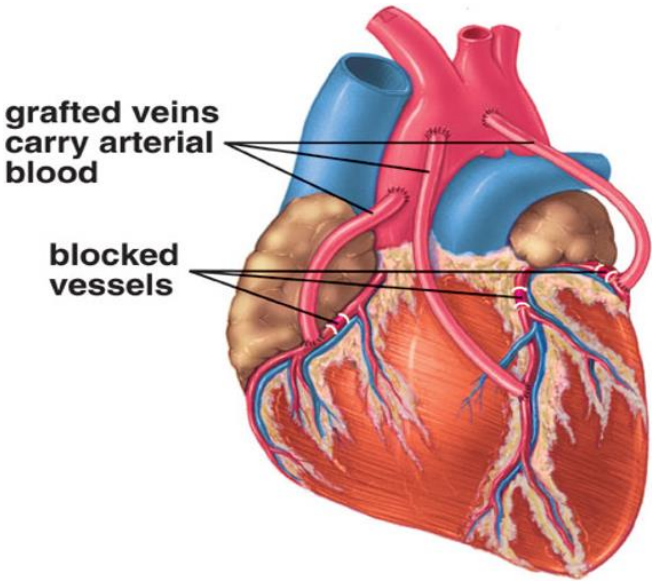
- Now as we took in anatomy, the coronary arteries are superficial, and they're compressed during systole, so the blood flow to the heart is reduced during contraction, *especially the left ventricle*.
- So during systole there's no much blood going through the coronary arteries, and this will result 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.



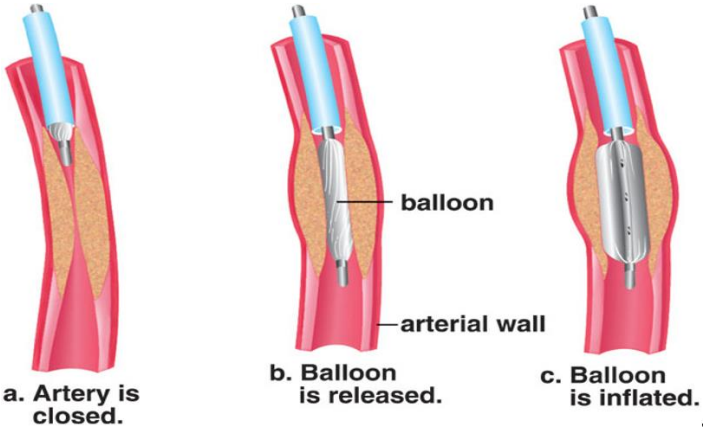
- This is important in certain cases, for instance, if someone has aortic regurgitation, his diastolic pressure is low, and since the coronary arteries originate from the aorta and their blood flow is mainly during diastole, then this patient could suffer from ischemia if he exercised. So you have to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

Blocked coronary arteries:

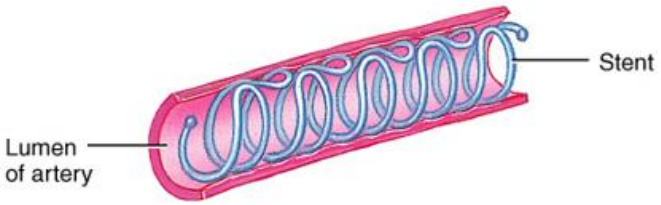
- If we have coronary obstruction, and there're at least three vessels that are blocked, then the patient needs a bypass operation; the surgeons take a part of a vein (e.g., saphenous vein), they bypass the block in the coronary artery and they supply the blood from the aorta, as seen in the figure.



- 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.



The Sheet is Over