PHYSIOLOGY

بسم الله الرحمن الرحيم

Final | Lecture 4

Arterioles

وَلَقَدْ خَلَقْنَا الْإِنسَانَ وَنَعْلَمُ مَا تُوَسْوِسُ بِهِ نَفْسُهُ ۖ وَنَحْنُ أَقْرَبُ إِلَيْهِ مِنْ حَبْلِ الْوَرِيدِ

اللهم إنّا نعوذ بك من شرور أنفسنا ومن سيئات أعمالنا

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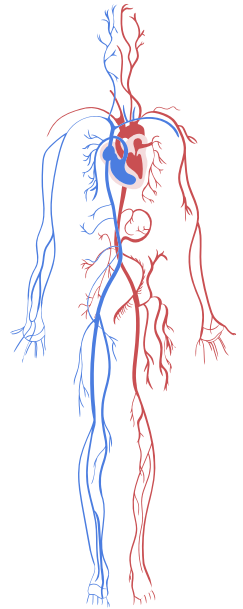

وَلِلَّهِ الْأَسْمَاءُ الْحُسْنَى فَادْعُوهُ بِهَا

المعنى: الذي له ملك السموات والأرض ومن فيهنّ، لا ملك فوقه، ولا شيء إلا دونه، له الملك المطلق، والتصرف في الكون كله، وهو المالك لكل شيء، والمليك دالٌّ على عظيم ملكه تعالى.

الورود: ورد اسم الملك (٥) مرات، أما اسم المليك فورد مرة واحدة، واسم المالك مرتان.

الشاهد: ﴿ٱلْمَلِكُ ٱلْقُدُّوسُ﴾ [الحشر:٢٣]، ﴿فِي مَقْعَدِ صِدْقٍ عِندَ مَلِيكٍ مُّقْتَدِرٍ﴾ [القمر:٥٥]، ﴿قُلِ ٱللَّهُمَّ مَٰلِكَ ٱلْمُلْكِ﴾ [آل عمران:٢٦].

اضغط هنا لشرحٍ أكثر تفصيلًا

Vascular Physiology

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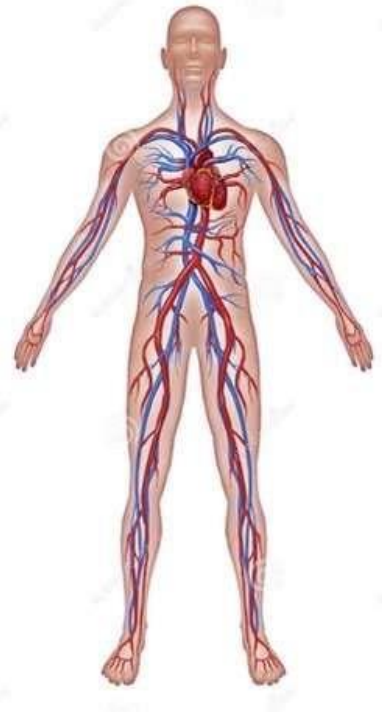


Arterioles

- Arterioles are **the main resistance vessels**.
  - → Most important function of arterioles is to control blood flow to tissues through resistance.
  - → Changing resistance can affect blood flow & pressure.
  - → Flow reaching tissue depends on metabolic needs. So it is variable and changes momentarily in the same organ depending on change of metabolic activity.
- arterioles are also **the site where resistance can be changed** by alterations in local, humoral, and neural factors.

Remember:

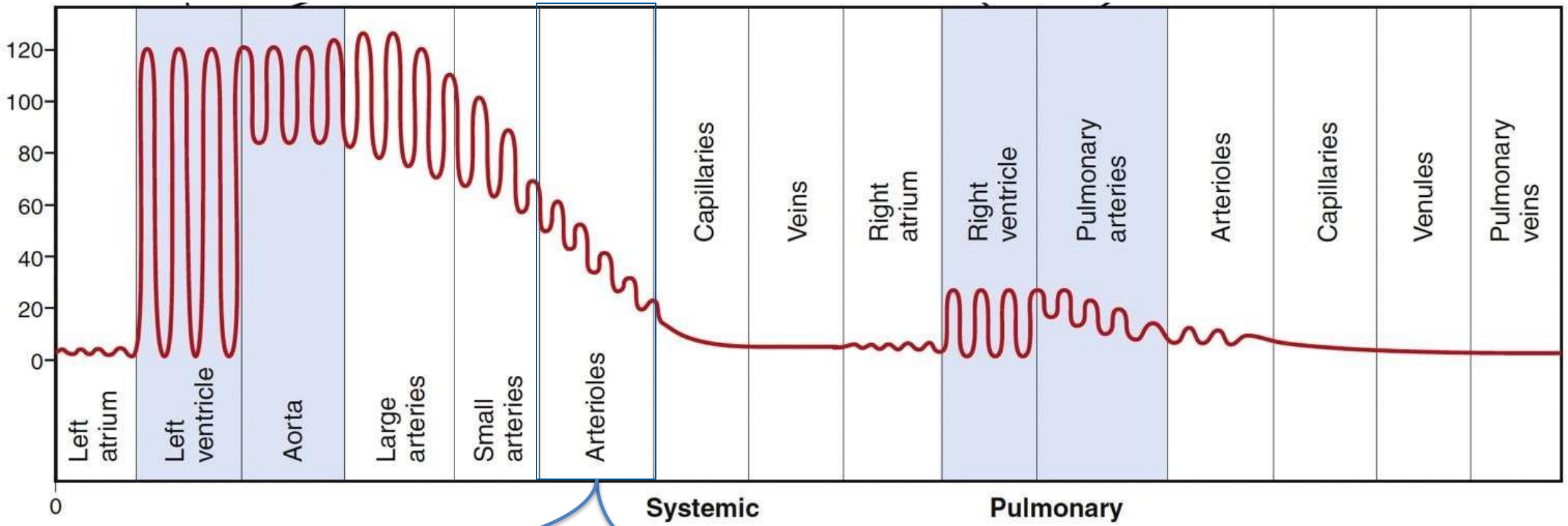
$$\text{Flow} = \frac{\text{Change in Pressure}}{\textbf{Resistances}}$$

→ Changing resistance will help us in controlling blood pressure and regulate blood flow reaching the tissue.

Arterioles

the high degree of arteriolar **resistance causes a marked drop in mean pressure** as blood flows through these small vessels.

- Arteriolar resistance also **converts the pulsatile** systolic-to-diastolic pressure swings in the arteries into the **nonfluctuating pressure** present in the capillaries.



Largest drop in **mean arterial pressure** is at the level of arteriole

Pulse pressure (difference between systolic and diastolic pressure) will decrease.

So the aim of arterioles to:-

1. Lower pressure gradients by increasing resistance
2. Continuous flow as possible (to switch to complete continuous flow in capillaries).

Arterioles

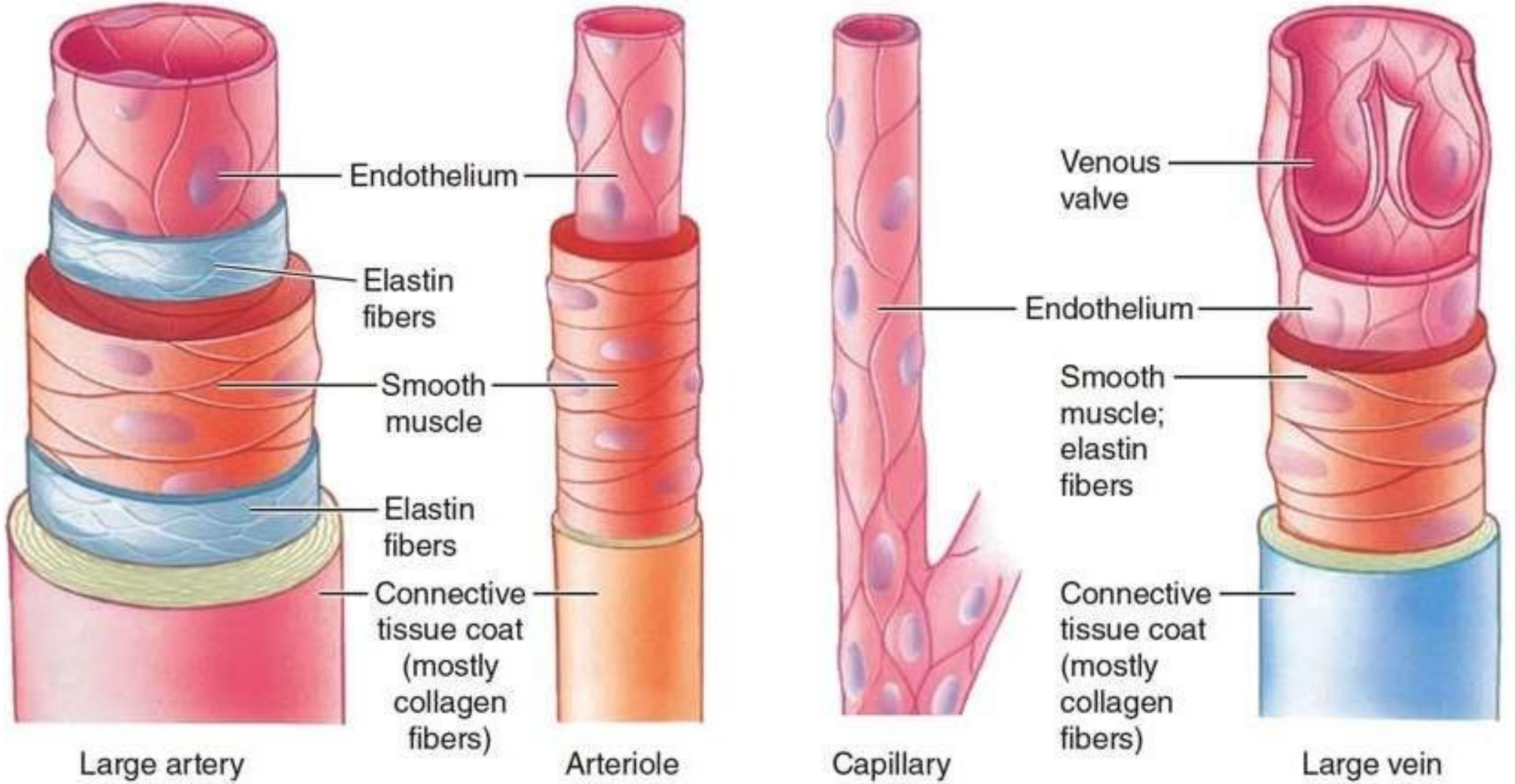
- The **radius can be adjusted** independently to accomplish two functions:

- (1) to variably distribute the cardiac output among the systemic organs, depending on the body's momentary needs,
- (2) to help regulate arterial blood pressure.

Arterioles

- little elastic connective tissue. → Doesn't need it due to no stretching and recoil.
- thick layer of smooth muscle
- richly innervated by sympathetic nerve fibers.
- The smooth muscle layer runs circularly around the arteriole; so when the smooth muscle layer contracts, the vessel's circumference (and its radius) becomes smaller, increasing resistance and decreasing flow through that vessel.

- Smooth muscle vasoconstriction will change the diameter of arterioles.
- Even at rest smooth muscles aren't fully relaxed they still have partial constriction called **"vascular tone"**
- The vascular tone can be due to continuous supply of sympathetic by norepinephrine or by intrinsic contractility (voltage-gated sodium channels a bit open in resting state).
- Certain situations can stimulate Smooth muscle to contract and vasoconstrict.



Small radius in arteriole means large effect on resistance.

Arterioles

- Vasoconstriction is the term applied to such narrowing of a vessel.
- Vasodilation refers to enlargement in the circumference and radius of a vessel as a result of its smooth muscle layer relaxing.
- Vasodilation leads to decreased resistance and increased flow through that vessel.

Vascular tone

- Arteriolar smooth muscle normally displays **a state of partial constriction** known as vascular tone, which establishes a baseline of arteriolar resistance.

  → Allows for both ways (vasodilation & vasoconstriction) of regulating contractility of Smooth muscle.

- This ongoing tone **makes it possible to either increase or decrease contractile activity to accomplish vasoconstriction or vasodilation, respectively.**

Arterioles

- The smooth muscle in the arteriole is sensitive to:
- 1. local chemical changes.
- 2. circulating hormones.
- 3. mechanical factors such as stretch.

  → More blood pressure increases sheer stress which will induce vasoconstriction in blood vessels.
- 4. sympathetic nerve stimulation.

There are factors influencing contraction of Smooth muscle in arterioles:-

1. Intrinsic (local)
2. Extrinsic (neuronal or hormonal)

- **Intrinsic (control blood flow) vs extrinsic factors (control BP)**

Local blood flow control

- most tissues have the ability to control their own local blood flow in proportion to their specific metabolic needs.

- Local controls override sympathetic vasoconstriction.

  → **Local regulation of blood flow** overrides other mechanisms, whether extrinsic, sympathetic stimulation, blood pressure changes, etc.

Local blood flow control

- The fraction of the total F delivered to each organ is not always constant; it varies, depending on the demands for blood at the time.
- The share of CO received by each organ is determined by the number and caliber of the arterioles supplying that area.
- **Vasomotion**

CO: cardiac output

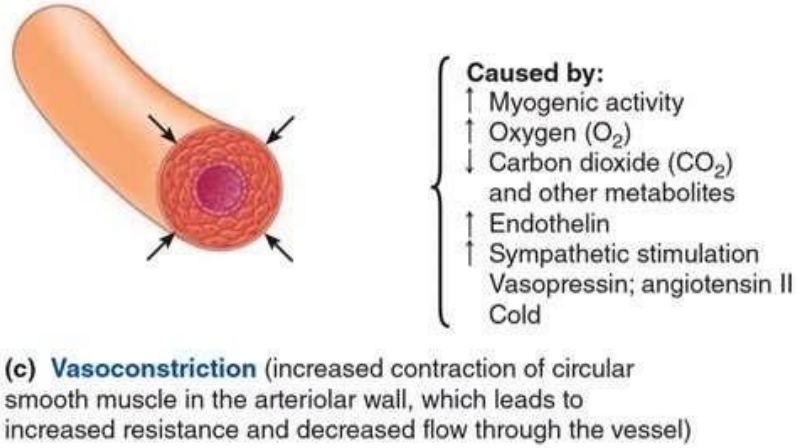
Local blood flow control

- Local blood flow control can be divided into two phases, acute control and long-term control. → Acute control takes seconds to minutes to adapt, like active hyperemia.

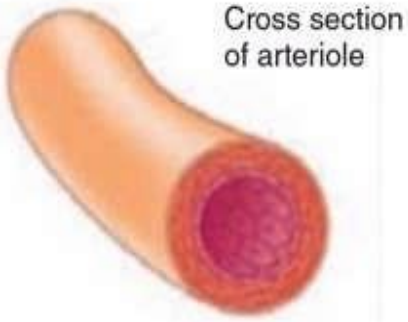
- Acute control is achieved by rapid changes in local vasodilation or vasoconstriction of the arterioles, metarterioles, and precapillary sphincters that occur within seconds to minutes to provide rapid maintenance of appropriate local tissue blood flow

- Long-term control means slow, controlled changes in flow over a period of days, weeks, or even months. In general, these long-term changes provide even **better control** of the flow in proportion to the needs of the tissues

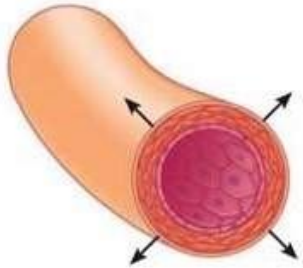
- These changes come about as a result of an increase or decrease in the physical sizes and numbers of blood vessels supplying the tissues.



(c) **Vasoconstriction** (increased contraction of circular smooth muscle in the arteriolar wall, which leads to increased resistance and decreased flow through the vessel)



(b) **Normal arteriolar tone**

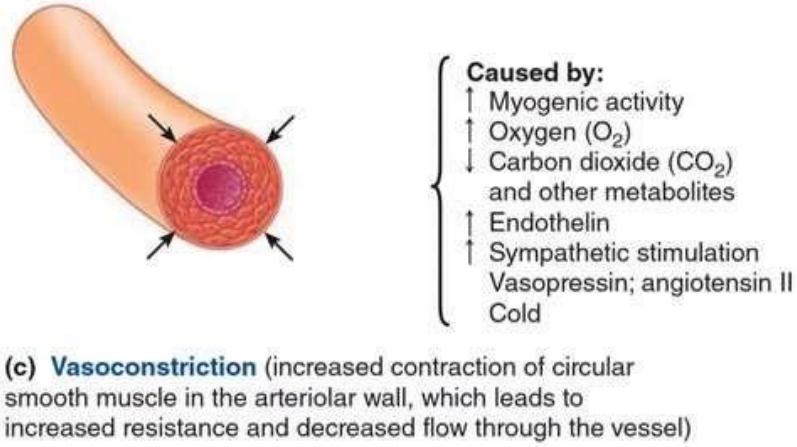


(d) **Vasodilation** (decreased contraction of circular smooth muscle in the arteriolar wall, which leads to decreased resistance and increased flow through the vessel)

→ Local factors can be chemical (from vascular cells themselves or from surrounding tissues when need of surrounding tissues changes) or mechanical.
→ These chemicals that affect arterioles are generally metabolic chemicals, for example, O2 being available in large amount in tissues indicates that the O2 level is enough & the tissue is not very active (as it doesn't consume the oxygen in high amounts). On the other hand, decrease in O2 concentration signals smooth muscle of arterioles to dilate to increase blood flow to tissues and lower resistance.
→ Other chemicals like CO2, adenosine, H+, K+, etc. (They increase with high metabolic activity of tissue) which causes more need of blood flow signals of vasodilation in arterioles.
→ Arterioles are efficient as they prioritize blood flow to metabolically active tissues.

➢ What are the mechanisms by which chemicals can affect the diameter of arterioles?

- **Theory #1:** Chemicals (adenosine, K+, H+) changing diameter of blood vessels may be due to acting as vasodilators.
- **Theory #2:** Enough O2 in tissues means there is also enough O2 in the smooth muscles of arterioles to contract which means vasoconstriction happens.



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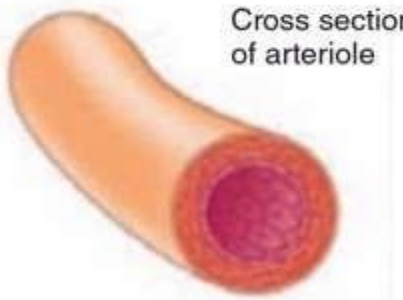
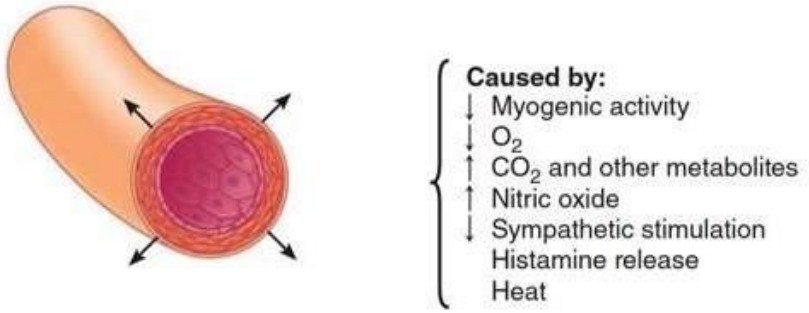


(b) **Normal arteriolar tone**



(d) **Vasodilation** (decreased contraction of circular smooth muscle in the arteriolar wall, which leads to decreased resistance and increased flow through the vessel)

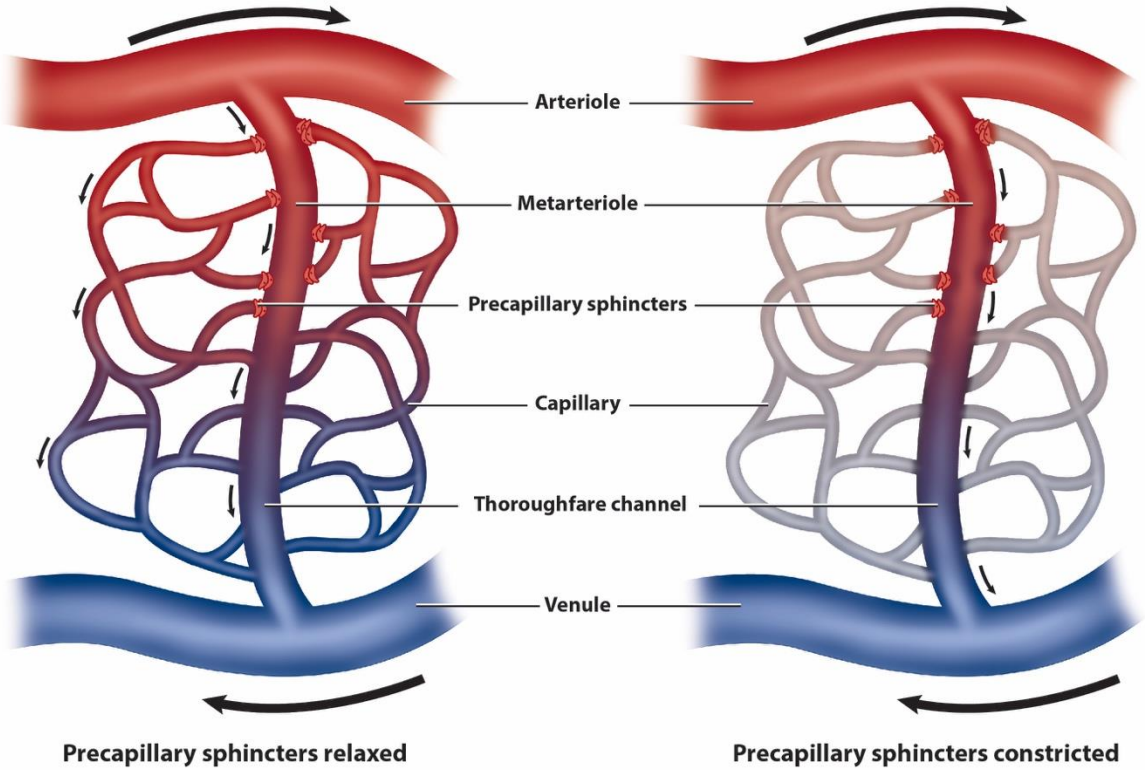
➢ **Other factors that affect arterioles include:**

- **Heat** (induces dilation in blood vessel) & **Cold** (induces vasoconstriction).
- Chemicals like **histamine** cause vasodilation during inflammatory or allergic reactions (not physiological).
- **Sympathetic** stimulation usually causes vasoconstriction, depending on the receptor; Alpha-1 & Beta-2
  Activation of α1 receptors (found in most blood vessels) will cause vasoconstriction while the activation of β2 receptors (found in smooth muscles of coronary arteries & arteries supplying skeletal muscles) causes vasodilation.
- Some chemicals are within vascular walls, mainly endothelium, like **NO** (induce vasodilation by acting locally as a paracrine factor, used in anginas and erectile dysfunction). Another chemical is endothelin (most potent vasoconstrictor released from endothelial cells). **Endothelin** is usually released from injured endothelial cells and works to vasoconstrict blood vessels and decrease bleeding/loss of blood, in conditions like hypertension endothelin levels are high to cause vasoconstriction & maintain the vascular tone.

Arterioles → Metarterioles → pre-capillary sphincters → Capillaries

- Usually, these vessels are not all open at the same time, they open or dilate only in the regions of tissue that actually need more blood flow. Otherwise, they remain mostly closed until demand increases.
- There is always continuous dynamic adjustment of local blood flow within tissues.
- This process is called **vasomotion**

~ Added picture



Acute control of local blood flow

- Active hyperemia: → When you exercise, you need more metabolic products and higher metabolic demand, this induces vasodilation and increases local blood flow
- When a tissue becomes highly active, such as an exercising muscle the rate of blood flow through the tissue increases.
- The increase in local metabolism causes the cells to devour tissue fluid nutrients rapidly and release large quantities of vasodilator substances.
- The result is dilation of local blood vessels and increased local blood flow.
- In this way, the active tissue receives the additional nutrients required to sustain its new level of function.

Acute control of local blood flow

- Reactive hyperemia: → For example, What happens after removing tourniquet when taking blood sample.

- When the blood supply to a tissue is blocked for a few seconds to as long as 1 hour or more and then is unblocked, blood flow through the tissue usually increases immediately to four to seven times normal.

→ After temporary blockage of blood supply to certain tissues, metabolic by-products will accumulate which will stimulate an increase of blood flow many folds more than actual need.

Blood flow autoregulation

- **Blood flow autoregulation** means arterioles regulate blood flow and keep it constant despite changes in arterial pressure. When pressure rises, blood flow initially increases and stretches the smooth muscle, but then local control overrides & senses that the tissues don't need the extra flow, so vasoconstriction occurs and flow returns to normal. Autoregulation works mainly between about **70–170 mmHg,** where the curve becomes a **plateau**. Different tissues vary in their strength, with the **brain** having the strongest autoregulation. Above roughly **175 mmHg,** local autoregulation can't compensate, so control shifts back to **central** mechanisms.

- The ability of each tissue to adjust its vascular resistance and to maintain normal blood flow during changes in arterial pressure between approximately 70 and 175 mm Hg is called blood flow autoregulation .

- Blood flow changes rarely last for more than a few hours in most tissues, even when increases in arterial pressure or increased levels of vasoconstrictors are sustained.

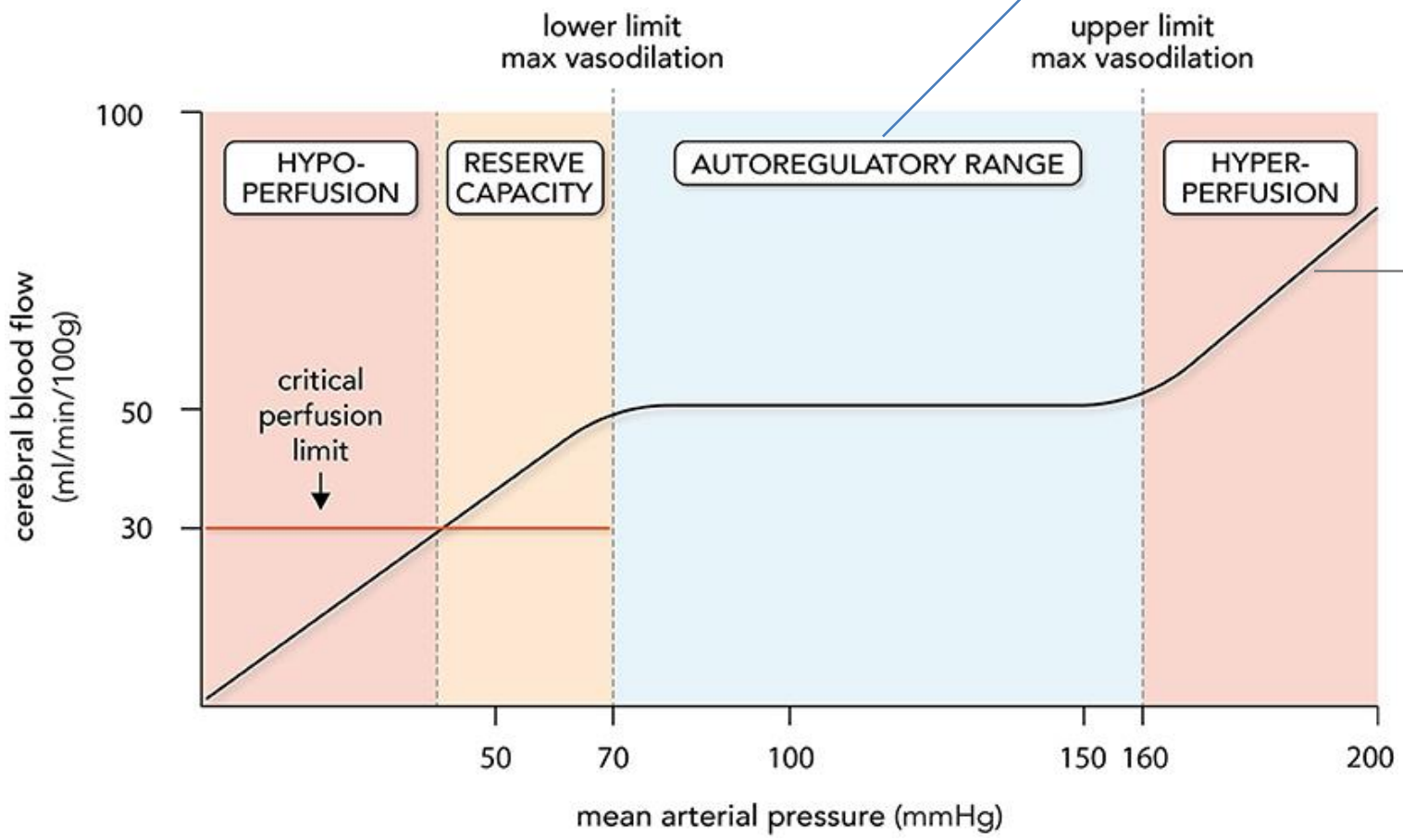
- The reason for the relative constancy of blood flow is that each tissue's **local autoregulatory mechanisms eventually override most of the effects of vasoconstrictors** to provide a blood flow that is appropriate for the needs of the tissue.

Blood flow autoregulation

- Autoregulation Attenuates the Effect of Arterial Pressure on Tissue Blood Flow:
- One might expect an increase in arterial pressure to cause a proportionate increase in blood flow through the body's tissues.
- However, the effect of arterial pressure on blood flow in many tissues is usually far less than one might expect.
- This is because an increase in arterial pressure not only increases the force that pushes blood through the vessels, but also initiates compensatory increases in vascular resistance within a few seconds through activation of the local control mechanisms,

Additional figure !

Note the autoregulatory plateau; blood flow remains constant despite changes in the MAP



Shifting to central mechanisms (increase in blood flow with further increase MAP) flow becomes pressure-dependent again

Local control :endothelial derived factors: NO

- Clinicians used nitroglycerin and other nitrate derivatives to treat patients who had **angina pectoris**—that is, severe chest pain caused by ischemia of the heart muscle. These drugs cause dilation of blood vessels throughout the body, including the coronary blood vessels.

- Other important applications of NO is the clinical use of drugs (e.g., sildenafil) that inhibit cGMP-specific phosphodiesterase- 5 (PDE-5), an enzyme that degrades cGMP. By preventing the degradation of cGMP, the PDE-5 inhibitors effectively prolong the actions of NO to cause vasodilation.

- The primary clinical use of the PDE-5 inhibitors is to treat **erectile dysfunction**.

Local control :endothelial derived factors: endothelin

- Endothelial cells also release vasoconstrictor substances.
- The most important of these is endothelin that requires only minute amounts (nanograms) to cause powerful vasoconstriction.
- This substance is present in the endothelial cells of all or most blood vessels but greatly increases when the vessels are injured.
- After severe blood vessel damage, local release of endothelin and subsequent vasoconstriction helps prevent extensive bleeding from arteries.
- Increased endothelin release is also believed to contribute to vasoconstriction when the endothelium is damaged by hypertension.

Long term blood flow regulation: changes in tissue vascularity

- A key mechanism for long-term local blood flow regulation is to change the amount of vascularity of the tissues.

Changing the amount of vascularity refers to structural changes in a tissue's blood vessels, and this can go in both directions:

1) increasing the number of vessels.
2) changing their structure, or decreasing them.

- For example, 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.

➢ The chronic changes in **functional demands** of each organ are one of the causes of changes in vascularity.

Long term blood flow regulation: changes in tissue vascularity

Vascularity changes depend on the age of tissues, whether they are young or older.

- Aging→ vascular remodeling and adaptation to changes in blood flow or metabolic needs become less efficient and take more time.
- Children → better vascular remodeling and long-term metabolic control.

- the time required for long-term regulation to take place may be only a few days in the neonate or as long as months in older adults.
- Furthermore, the final degree of response is much better in younger than in older tissues; thus, in the neonate, the vascularity will adjust to match almost exactly the needs of the tissue for blood flow, whereas in older tissues, vascularity frequently lags far behind the needs of the tissues.

Long term blood flow regulation

- long-term regulation gives far more complete control of blood flow.

Examples of long term regulations:

1) Long-term regulation of blood flow is especially important when the metabolic demands of a tissue change. Thus, if a tissue becomes chronically overactive and requires increased quantities of oxygen and other nutrients, the arterioles and capillary vessels usually increase both in number and size within a few weeks to match the needs of the tissue, unless the circulatory system has become pathological or too old to respond.

Long term blood flow regulation: changes in tissue vascularity

2) In **premature babies**, who are born at 30 weeks instead of 38 weeks, are put in incubators, one of the tissues that haven't been fully developed is the retina, so any excess oxygen causes almost immediate cessation of new vascular growth in the retina of the premature baby's eyes (because the excessive oxygen signals the retina to stop it's own neovascularization resulting in incomplete maturation) and even causes degeneration of some of the small vessels that already have formed.

Long term blood flow regulation: changes in tissue vascularity

- When the infant is taken out, **explosive** overgrowth of new vessels then occurs to make up for the **sudden** decrease in available oxygen
  because the oxygen in room air is lower, causing relative hypoxia, which triggers strong neovascularization.
- Often, so much overgrowth occurs that the retinal vessels grow out from the retina into the eye's vitreous humor, eventually causing blindness, a condition called **retrolental fibroplasia**.

➢ Since vascularity changes in neonates are easier and faster in infants, many new but fragile vessels grow, and they can extend into the vitreous humor and rupture, leading to blindness. So the oxygen supplied in the incubator should be precisely calculated.

Long term blood flow regulation: changes in tissue vascularity

- Vascular growth factors like the vascular endothelial growth factor (VEGF)
- Steroid hormones decrease vascularity
- Antiangiogenic factors

- **Vascularity Determined by Maximum Blood Flow Need, Not by Average Need.**

Long term blood flow regulation: changes in tissue vascularity

3) Collateral circulation

- An important example of the development of collateral blood vessels occurs after thrombosis of one of the coronary arteries. By the age of 60 years, many people have experienced closure or at least partial occlusion of at least one of the smaller branch coronary vessels, but they are not aware of it because collateral blood vessels **(by neoangiogenesis)** have developed rapidly enough to prevent myocardial damage.
- When collateral blood vessels are unable to develop quickly enough to maintain blood flow because of the rapidity or severity of the coronary insufficiency, serious heart attacks can occur.

➢ **Acute coronary artery thrombosis → no room for neovascularization → no collateral circulation → ischemia and infarction of myocardium**

Long term blood flow regulation: vascular remodeling

Vessels do not just change in vascularity; they also undergo **remodeling**. This remodeling can change the diameter (affecting cross-sectional area) and wall thickness according to tissue needs.

A. In small arteries and arterioles, chronic stress like hypertension initially will lead to vasoconstriction that reduces vessel radius to lower wall tension (tension ∝ radius)* → if this occurs chronically, smooth muscle cells & endothelial cells rearrange themselves into a smaller lumen in a process called **inward eutrophic remodeling**

(This structural change reduces lumen size permanently, instead of relying on continuous vasoconstriction)

B. In contrast, large arteries experience higher pressure and higher wall tension, so the vascular wall undergoes thickening (no vasoconstriction), resulting in one of these types of remodeling:

1) **Hypertrophic remodeling**
2) **Outward remodeling**
3) **Outward hypertrophic remodeling**

* Tension = pressure × radius

Long term blood flow regulation: vascular remodeling

- In addition to changes in capillary density, there may also be **changes in the structure of large blood vessels** in response to long-term changes in blood pressure and blood flow.

- When blood pressure is chronically elevated above normal, for example, the large and small arteries and arterioles remodel to accommodate the increased mechanical wall stress of the higher blood pressure.

- In most tissues, the small arteries and arterioles rapidly respond (within seconds) to increased arterial pressure with vasoconstriction, which helps autoregulate tissue blood flow.

- The vasoconstriction decreases lumen diameter, which in turn tends to normalize the vascular wall tension (T), which, according to Laplace's equation, is the product of the radius (r) of the blood vessel and its pressure (P): $T = r \times P$

Long term blood flow regulation: vascular remodeling

- In small blood vessels that constrict in response to increased blood pressure, the vascular smooth muscle cells and endothelial cells gradually—over a period of several days or weeks—rearrange themselves around the smaller lumen diameter. A process called inward eutrophic remodeling, with no change in the total cross-sectional area of the vascular wall.

- In larger arteries that do not constrict in response to the increased pressure. the vessel wall is exposed to increased wall tension that stimulates a hypertrophic remodeling response and an increase in the cross-sectional area of the vascular wall.

- The hypertrophic response increases the size of vascular smooth muscle cells and stimulates formation of additional extracellular matrix proteins, such as collagen and fibronectin, that reinforce the strength of the vascular wall to withstand the higher blood pressures.

- However, this hvpertrophic response also makes the large blood vessels stiffer, which is a hallmark of chronic hypertension.

Long term blood flow regulation: vascular remodeling

- Another example of vascular remodeling is the change that occurs when a large vein (often the saphenous vein) is implanted in a patient for a coronary artery bypass graft procedure.
- Veins are normally exposed to much lower pressures than arteries and have much thinner walls, but when a vein is sewn onto the aorta and connected to a coronary artery, it is exposed to increases in intraluminal pressure and wall tension.
- The increased wall tension initiates hypertrophy of vascular smooth muscle cells and increased extracellular matrix formation, which thicken and strengthen the wall of the vein; as a result, several months after implantation into the arterial system, the vein will typically have a wall thickness similar to that of an artery.

The vein here is chronically exposed to higher pressure leading to structural remodeling

Long term blood flow regulation: vascular remodeling

- Vascular remodeling also occurs when a blood vessel is exposed chronically to increased or decreased blood flow.
- The creation of a fistula connecting a large artery and large vein, thereby completely bypassing high-resistance small vessels and capillaries, provides an especially interesting example of remodeling in the affected artery and vein.
- In patients with renal failure who undergo dialysis, an arteriovenous (A-V) fistula directly from the radial artery to the antecubital vein of the forearm is created to permit vascular access tor dialysis. The blood flow rate in the radial artery may increase as much as 10 to 50 times the normal flow rate, depending on the patency of the fistula.

Long term blood flow regulation: vascular remodeling

- As a result of the high flow rate and high shear stress on the vessel wall the endothelial cells stretch & the luminal diameter of the radial artery increases progressively, (outward remodeling), whereas the thickness of the vessel wall may remain unchanged, resulting in an increase in cross-sectional area of the vascular wall.
- In contrast, wall thickness, lumen diameter, and cross-sectional area of the vascular wall on the venous side of the fistula increase in response to increases in pressure and blood flow (outward hypertrophic remodeling).
- This pattern of remodeling is consistent with the idea that long-term increases in vascular wall tension cause hypertrophy and increased wall thickness in large blood vessels, whereas increased blood flow rate and shear stress cause outward remodeling and increased luminal diameter to accommodate the increased blood flow.

Examples on vascular remodeling

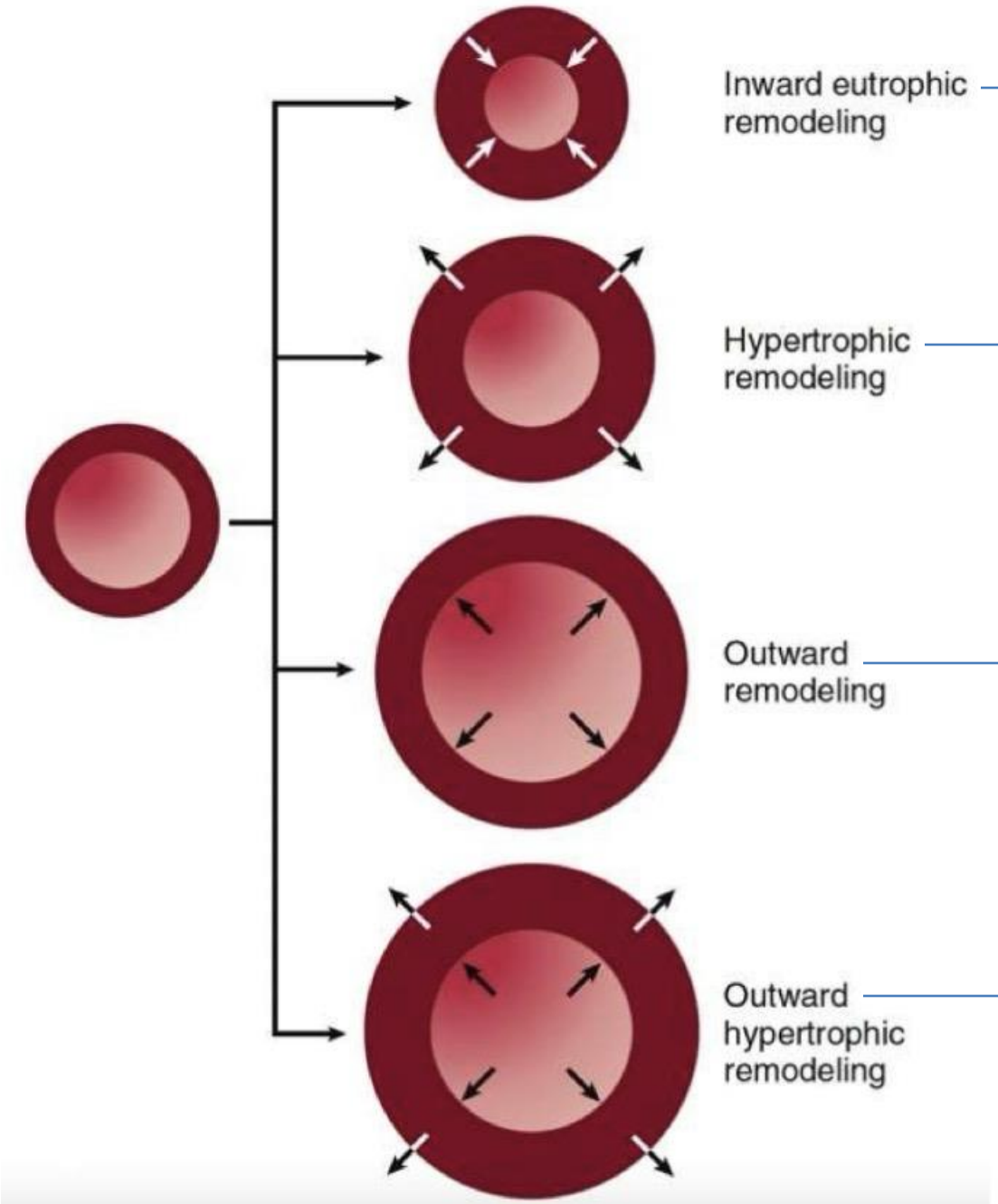
1) CABG (Saphenous Vein Used as an Arterial Bypass)

•A vein (e.g., saphenous vein) is placed into the high-pressure, high-flow arterial circulation.
•Because the vein is not normally exposed to this environment:
•High pressure → wall hypertrophy
•High volume → outward dilation
•Result: **Outward Hypertrophic Remodeling**

2) AV Fistula for Hemodialysis

Arterial side (e.g., radial artery):
•Flow/volume increases significantly.
•Pressure remains relatively normal.
•Result: **Outward remodeling** (dilation due to high volume).

Venous side:
•Vein receives higher pressure than normal
•And much higher volume/flow
• hypertrophy + outward dilation
•Result: **Outward Hypertrophic Remodeling**



High pressure in arterioles & small arteries

High pressure in large vessels

High volume in large vessels

High pressure & volume in large vessels

Additional table

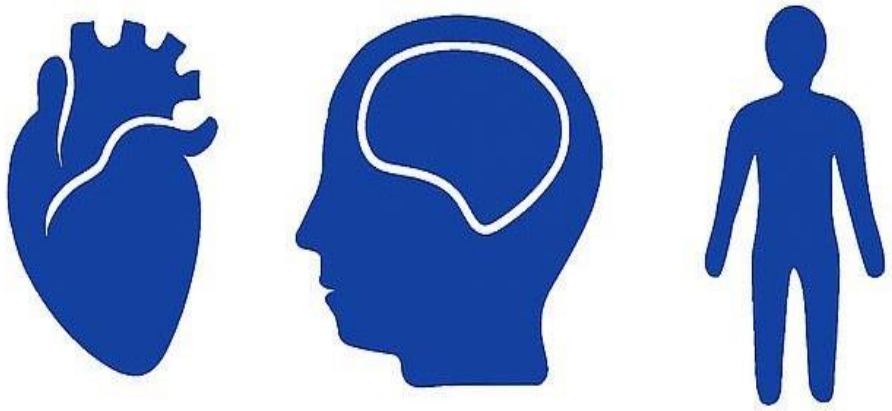
Type of remodeling	Stimulus	Site
Inward eutrophic remodeling	High blood pressure	Small arteries and arterioles
Outward remodeling	High blood volume	Large vessels
Hypertrophic remodeling	Increased blood pressure	Large vessels
Outward hypertrophic remodeling	Increased blood pressure + volume	Large vessels

So the type of remodeling depends on the stimulus & the affected vessel

Long term blood flow regulation

- When blood flow is greatly reduced, the diameter of the vascular lumen is also reduced and, when blood pressure is reduced, the thickness of the vascular wall usually decreases. Thus, vascular remodeling is an important adaptive response of the blood vessels to tissue growth and development, as well as to physiological and pathological changes in blood pressure and blood flow to the tissues.

Thank you



PHYSIOLOGY QUIZ LECTURE 4

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Versions	Slide # and Place of Error	Before Correction	After Correction
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