The Cardiovascular System

The blood belong to the connective tissue, therefore it is also composed of:

Cellular elements (the **formed elements [Living blood cells]).** Constitute up to 45% of our blood composition.

Red blood cells (RBCs): Erythrocytes function in O_2 transport.
White blood cells (WBCs): Leukocytes function in immunity.
Platelets: Cell fragments function in clotting.

Extracellular matrix also called **plasma up to 55% of the blood.**
Makes the blood unique among connective tissues because it is fluid.
mostly water, perpetually suspends the formed elements and enables them to circulate throughout the body within the cardiovascular system.

Blood is about 8% of an adults body weight.
Supplies essential substances and nutrients such as sugar, oxygen, and hormones to cells and carries waste away from those cells (flushed out the body in urine, feces, sweat, and lungs (CO_2)).

Functions of Blood:
Transport of oxygen, nutrients and hormone to cells and removal of wastes.
Defense (fight infection).
Clotting to repair damaged vessels: Platelets and certain proteins dissolved in the plasma interact to block the ruptured areas of the blood vessels. This protects the body from further blood loss.

Distribution of heat. As blood passes through the vessels of the skin, heat would be dissipated to the environment, and the blood returning to your body core would be cooler. In contrast, on a cold day, blood is diverted away from the skin to maintain a warmer body core. In extreme cases, this may result in frostbite.

Maintenance of Homeostasis
Blood also helps to maintain the chemical balance of the body. Proteins and other compounds in blood act as buffers, which thereby help regulate the pH of body tissues. Blood also helps regulate the water content of body cells.

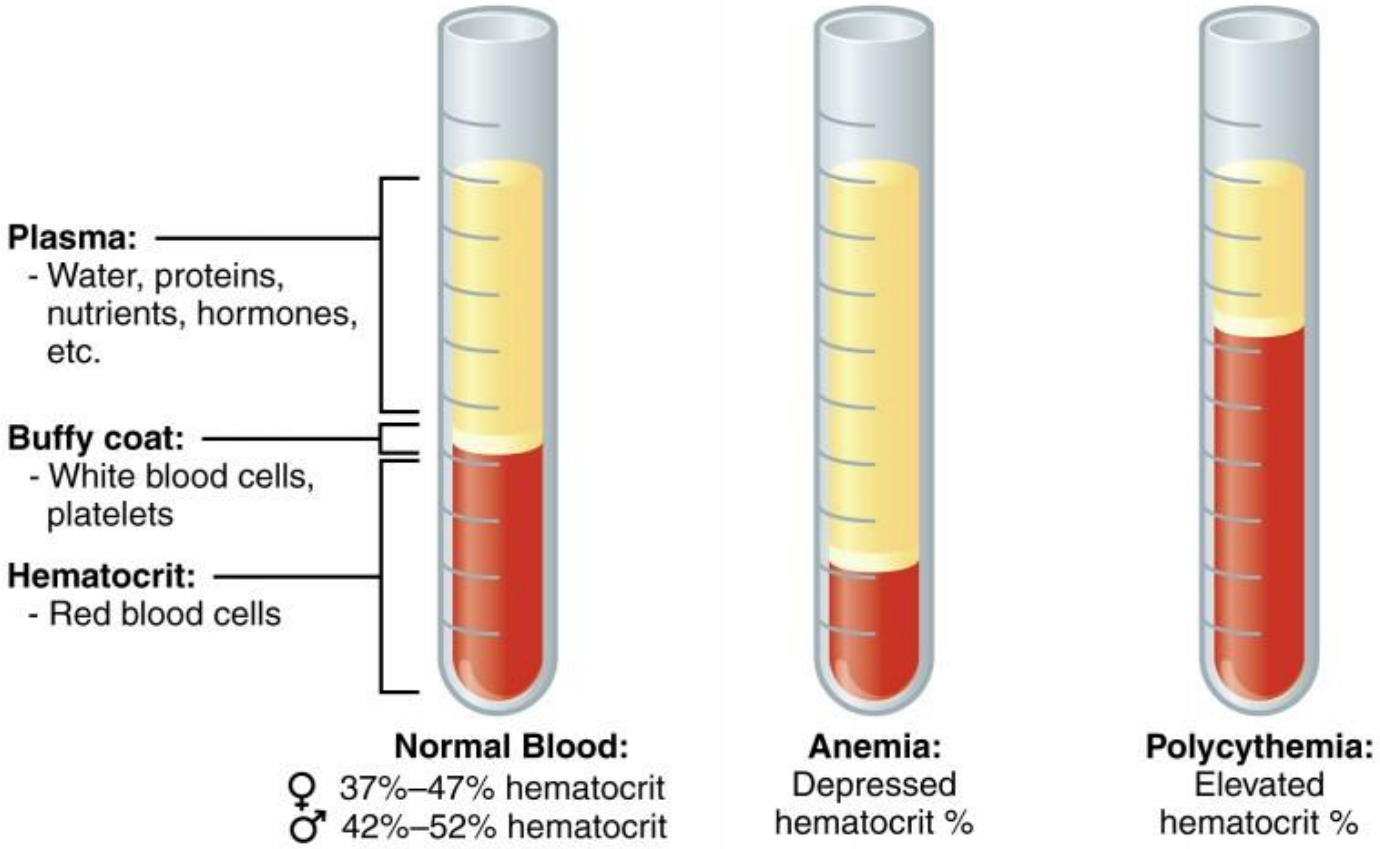
Composition of Blood

Blood can be separated into 3 layers:

Bottom: Erythrocytes(RBCs) give the **haematocrit** (volume of erythrocytes).

Middle: Thin white layer (**buffy coat)** consist in the leukocytes and platelets.

Top: The plasma



Characteristics of Blood:

5 fold more viscous than water and somewhat stickier.

Viscosity is a measure of a fluid's thickness or resistance to flow.

- Plasma proteins
- Formed elements.
- Dramatic impact on blood pressure and flow.

The normal temperature of blood **is 38 °C**.

Result from friction and resistance again wall of blood vessels.

The pH of blood averages about 7.4. The range is from 7.35 to 7.45 in a healthy person.

Blood constitutes approximately 8% of adult body weight.

5-6 liters in males.

4-5 liters in females.

Blood Plasma:
Plasma is composed up to 92% of water.
Dissolved or suspended within this water is a mixture of substances
Mostly proteins.

There are literally hundreds of substances dissolved or suspended in the plasma, many of them are found only in very small quantities.

Plasma Proteins represent 7% of plasma volume.
Several plasma proteins (proteins that are unique to the plasma)
Much smaller number of regulatory proteins (including enzymes and hormones).

There are three major groups of plasma proteins:

Albumin is the most abundant of the plasma proteins (54 %).

- Produced in the liver, albumin molecules serve as binding proteins
- Transport vehicles for fatty acids and steroid hormones.

- Most significant contributor to the osmotic pressure of blood which holds water inside the blood vessels and draws water from the tissues, across blood vessel walls into the bloodstream.

Globulins (approximately 38 percent of the total plasma protein).
They also contribute to osmotic pressure.
The α- and β-globulins transport iron, lipids, and the fat-soluble vitamins A, D, E, and K to the cells
The γ-globulins (or immunoglobulins) are involved in immunity.

Fibrinogen (7% of the total plasma protein). Essential for blood clotting,

Other Plasma Solutes

Various electrolytes (such as sodium, potassium and calcium ions).
Dissolved gases (oxygen, carbon dioxide and nitrogen); various organic
Nutrients (vitamins, lipids, glucose, and amino acids).
Metabolic wastes.

All of these nonprotein solutes combined contribute approximately 1 percent to the total volume of plasma.

Production of the Formed Elements

Erythrocytes, leukocytes, and platelets only live a few hours to a few weeks.
Rapid and continuous production of new blood cells.
Within 24 hours body can replace the 475 mL of plasma from a blood donation while it takes about 4 to 6 weeks to replace the blood cells.

The process by which blood cells are produced is called hemopoiesis.

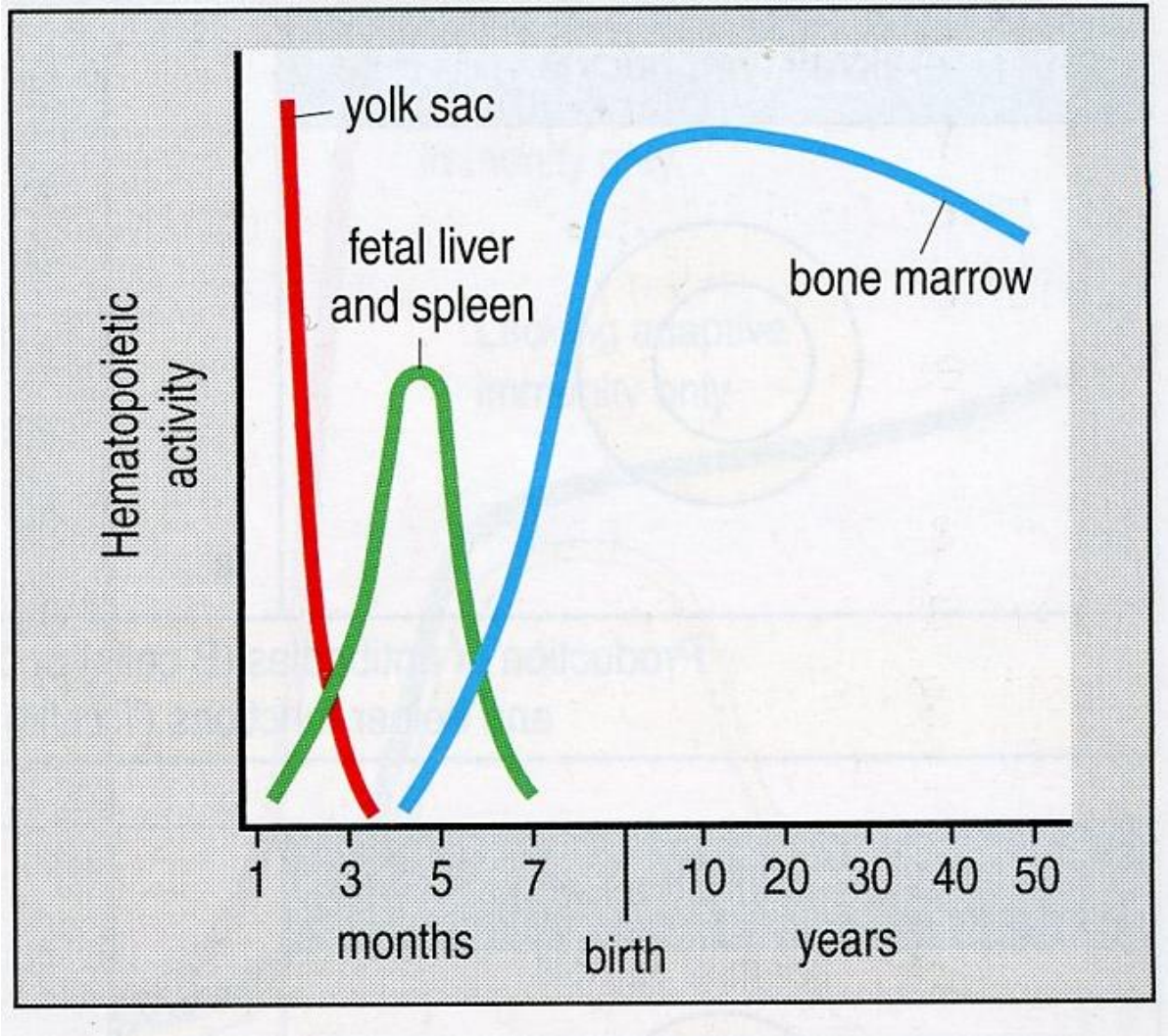
In children, hemopoiesis can occur in the medullary cavity of long bones
In adults, the process is largely restricted to the cranial and pelvic bones, the vertebrae, the sternum, and the proximal epiphyses of the femur and humerus.

Hematopoiesis site change during development.

Hematopoiesis during development

- Hematopoiesis site change during development
  - Yolk sac (embryonic stage)
  - Fetal liver and spleen
  - (3 - 7eme months)
  - Bone morrow (4th month)
    - Skull
    - Ribs
    - Sternum
    - Spine
    - Pelvis
    - Femur

- Active during all life
  - Continuous renewing of blood cells



Throughout adulthood, the liver and spleen maintain their ability to generate the formed elements in the process called extramedullary hemopoiesis.

When a disease such as bone cancer destroys the bone marrow, causing hemopoiesis to fail, extramedullary hemopoiesis may be initiated.

hemopoiesis is maintained by negative feedback.

During hypoxia kidneys and liver release erythropoietin.
    This hormone that stimulates haematopoiesis.
        RBCs count increase so does oxygen levels.
            Increased oxygen levels will decrease erythropoietin.

Hierarchy of the Stem cells.

1) **Totipotent stem cell** is the zygote, or fertilized egg gives rise to all cells of the human body.

2) Pluripotent stem cell, which gives rise to multiple types of cells of the body and some of the supporting fetal membranes.

3) Multipotent stem cell

- **Hemopoietic stem cell**, or hemocytoblast produces all the formed elements of blood.

- **Mesenchymal stem cell** develops only into types of connective tissue, (fibrous connective tissue, bone, cartilage, and blood) but not epithelium, muscle, and nervous tissue.

Structure and Function of Blood Vessels

Blood is carried through the body via blood vessels.

Artery carries blood away from the heart.
Branches into ever-smaller vessels. The smallest arteries are the arterioles.
They further branch into tiny capillaries, where nutrients and wastes are exchanged.

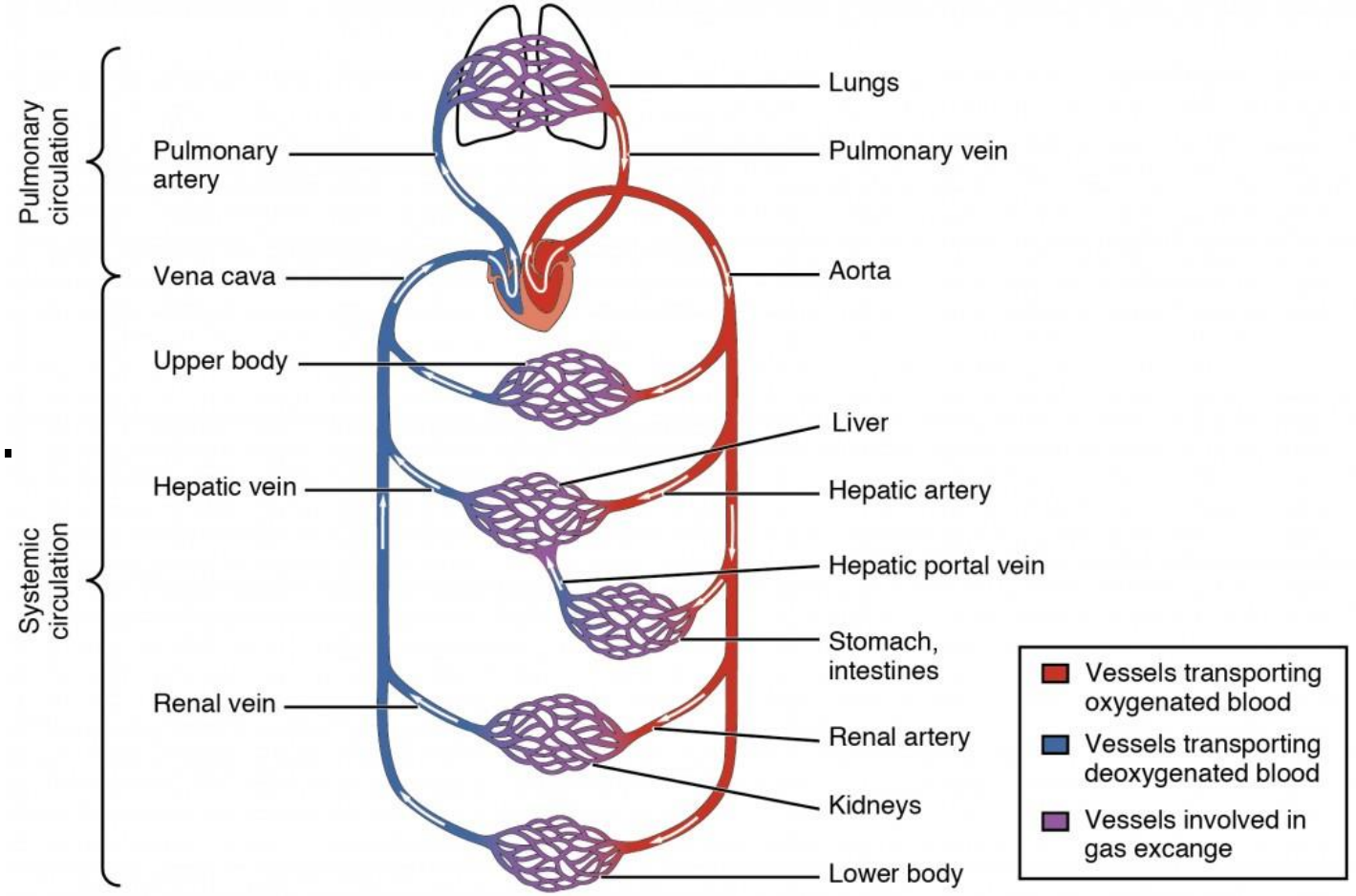
Then combine with other vessels that exit capillaries to form venules, small blood vessels that carry blood to a vein, a larger blood vessel that returns blood to the heart.

Structure and Function of Blood Vessels

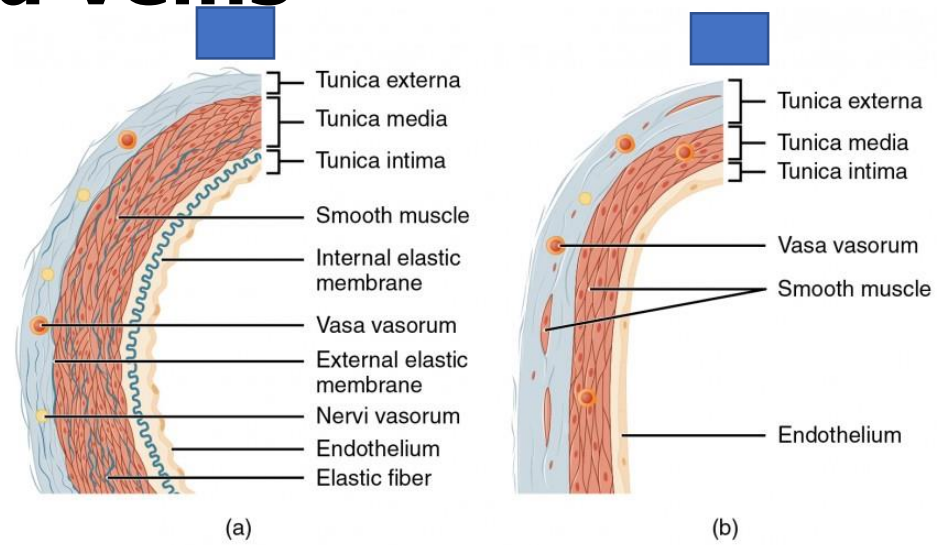
Arteries and veins transport blood in two distinct circuits: the systemic circuit and the pulmonary circuit.

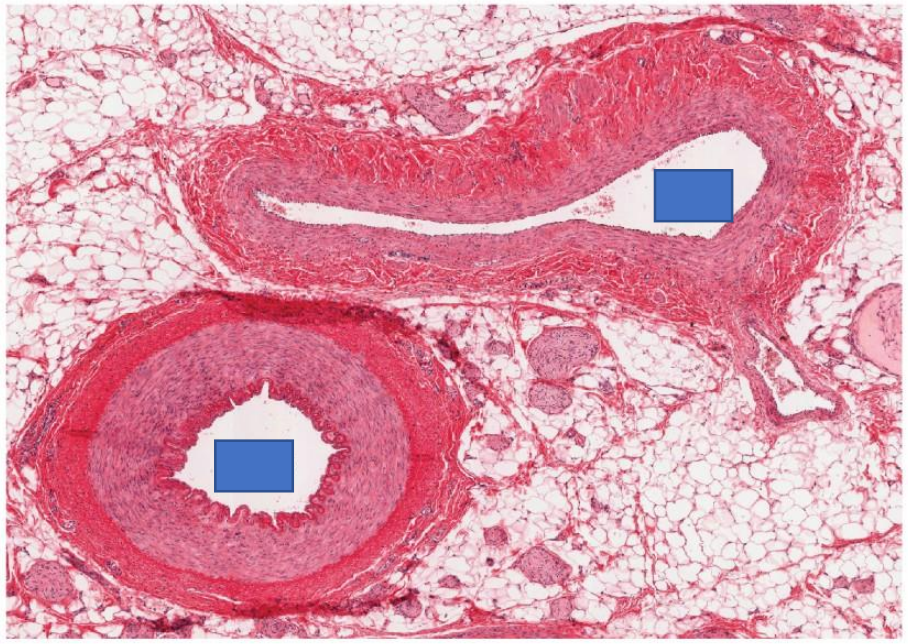
In the systemic circuit
Arteries provide blood rich in O_2 to the body's tissues.
The blood returning to the heart through systemic veins has less O_2.

In the pulmonary circuit:
Arteries carry blood low in O_2 exclusively to the lungs for gas exchange. Pulmonary veins then return freshly oxygenated blood from the lungs to the heart.



Shared Structures between artery and veins





(c)

Many veins of the body, particularly those of the limbs, contain valves that assist the unidirectional flow of blood toward the heart.

The walls of arteries and veins are largely composed of living cells and their products (including collagenous and elastic fibers).

Larger arteries and veins contain small blood vessels within their walls known as the **vasa vasorum.**
Because of the higher pressure within arteries, the vasa vasorum must function in the outer layers of the vessel to avoid collapsing.
The lower pressure within veins allows the vasa vasorum to be located closer to the lumen.

Nervi vasorum are minute nerves within the walls of both types of vessels that control the contraction and dilation of smooth muscle

Tunica Intima

Composed of epithelial (endothelium) and connective tissue layers.

- The endothelium is continuous throughout the entire vascular system including the lining of the chambers of the heart.

Damage to this endothelial lining is one of the primary causes of clot formation.

The endothelium releases local chemicals called endothelins that can constrict the smooth muscle within the walls of the vessel to increase blood pressure.

The basement membrane binds the endothelium to the connective tissue. Provides strength while maintaining flexibility. It is permeable.

The thin outer layer of the tunica intima contains a small amount of areolar connective tissue.

- Elastic fibers to provide the vessel with additional flexibility,
- Collagen fibers to provide additional strength.

In larger arteries, there is also a thick distinct layer of elastic the **internal elastic membrane** at the boundary with the tunica media: Provides structure while allowing the vessel to stretch. It is permeated with small openings that allow exchange of materials between the tunics.

Tunica Media
Generally much thicker in arteries than it is in veins.
Layers of smooth muscle supported by elastic fibers most of which arranged in circular sheets.
On the outer portion of the tunic, there are also layers of longitudinal muscle.

Vasoconstriction: contraction of the smooth muscle in the walls of the tunica media to decrease blood flow but increasing blood pressure.
Vasodilation: relaxation of smooth muscle allowing the lumen to widen and blood flow to increase while pressure to drop

Both vasoconstriction and vasodilation are regulated in part **nervi vasorum** (generally sympathetic fibers)**.** Parasympathetic stimulation does trigger vasodilation for erection during sexual arousal in the external genitalia of both sexes.

Hormones and local chemicals also control blood vessels. Together, these neural and chemical mechanisms reduce or increase blood flow in response to changing body conditions, from exercise to hydration.
External elastic membrane separating the tunica media from the outer tunica.

Tunica Externa

Also called the tunica adventitia a substantial sheath of collagenous fibers. Some bands of elastic fibers are also found.

The tunica externa in veins also contains groups of smooth muscle fibers. This is normally the thickest tunic in veins and may be thicker than the tunica media in some larger arteries.

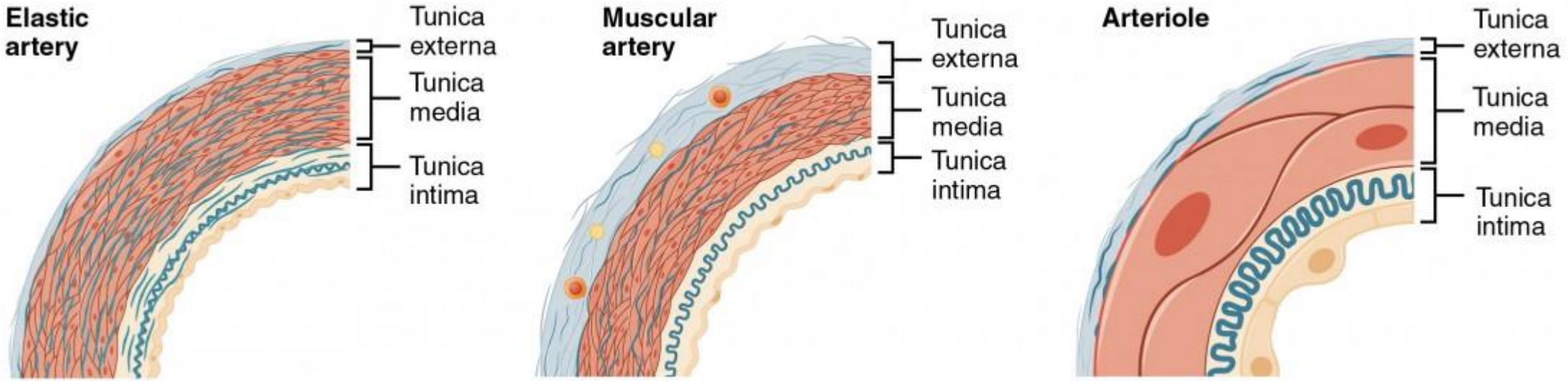
The outer layers of the tunica externa are not distinct but rather blend with the surrounding connective tissue outside the vessel, helping to hold the vessel in relative position.

Arteries

Must withstand the high pressure of blood ejected from the heart. The closer to the heart the thickest their walls (high percentage of elastic fibers in all three tunics), known as an **elastic artery (**larger than 10 mm). The elastic recoil of vessel maintain the pressure gradient that drives the blood through the arterial system. An elastic artery is also known as a conducting artery.

Farther from the heart, lesser the pressure % of elastic fibers decrease and amount of smooth muscle in its tunica media increase (**muscular arteries** 0.1-10 mm) (leading role in vasoconstriction).

There is a gradual transition as the vascular tree repeatedly branches. In turn, muscular arteries branch to distribute blood to the vast network of arterioles. For this reason, a muscular artery is also known as a distributing artery.



Arterioles

Very small artery that leads to a capillary. The critical endothelial lining of the tunica intima is intact. The tunica media is restricted to one or two smooth muscle cell layers in thickness. The tunica externa remains but is very thin.

Because lumen averaging 30 μm or less in diameter
Play critical role in slowing down blood flow
Causing a substantial drop in blood pressure.
Referred to as resistance vessels.
The muscle fibers in arterioles are normally slightly contracted (vascular tone).
Arterioles are the primary site of both resistance and regulation of blood pressure.

The precise diameter of the lumen of an arteriole at any given moment is determined by neural and chemical controls.

Vasoconstriction and vasodilation in the arterioles are the primary mechanisms for distribution of blood flow.

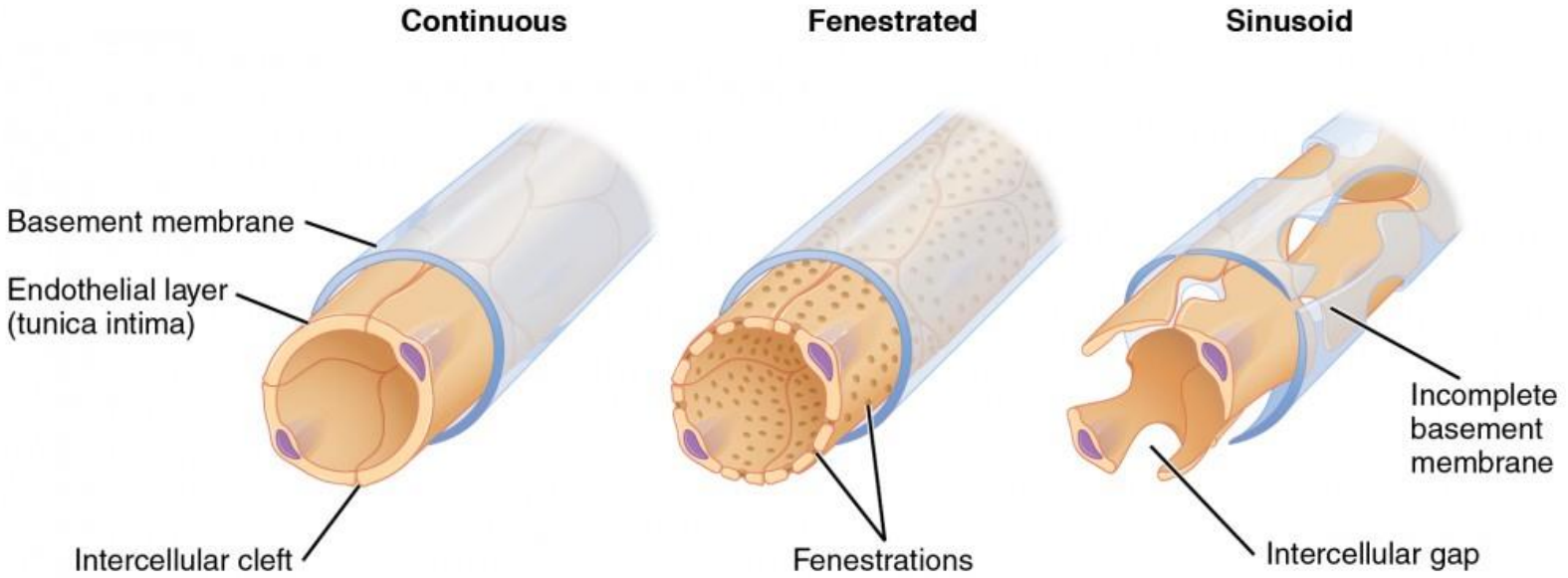
Capillaries

Microscopic channel (5–10 μm) that supplies blood to the tissues themselves (**perfusion)**. the smallest are just barely wide enough for an erythrocyte to squeeze through. capillaries is often described as **microcirculation.**

Exchange of gases and other substances occurs in the capillaries between the blood and the surrounding cells and their tissue fluid (interstitial fluid).

The wall of a capillary consists of the endothelial layer surrounded by a basement membrane with occasional smooth muscle fibers.

For capillaries walls must be leaky, allowing substances to pass through. There are three major types of capillaries, which differ according to their degree of "leakiness:"



Continuous Capillaries

The most common type is found in almost all vascularized tissues.
Characterized by a complete endothelial lining with tight junctions between endothelial cells.

Tight junction are often incomplete in capillaries, leaving intercellular clefts that allow for exchange of water and other very small molecules between the blood plasma and the interstitial fluid.
Substances that can pass between cells include metabolic products, such as glucose, water, and small hydrophobic molecules like gases and hormones, as well as various leukocytes.

Continuous capillaries not associated with the brain are rich in transport vesicles, contributing to either endocytosis or exocytosis.

Those in the brain are part of the blood-brain barrier where their tight junctions do not leave place for intercellular clefts, a thick basement membrane and astrocyte extensions called end feet.

Fenestrated Capillaries

Have pores (or fenestrations) in addition to tight junctions in the endothelial lining. These make the capillary permeable to larger molecules. The number of fenestrations and their degree of permeability vary depending on their location.

Fenestrated capillaries are common:

- The small intestine (the primary site of nutrient absorption).
-
- The kidneys, which filter the blood.

- The choroid plexus of the brain and many endocrine structures, including the hypothalamus, pituitary, pineal, and thyroid glands.

Sinusoid Capillaries

The least common type of capillary.

Flattened capillaries with extensive intercellular gaps and incomplete basement membranes in addition to intercellular clefts and fenestrations.

These very large openings allow for the passage of the largest molecules, including plasma proteins and even cells.

Blood flow through sinusoids is very slow allowing more time for exchange of gases, nutrients, and wastes.

Sinusoids are found in the liver and spleen, bone marrow, lymph nodes (where they carry lymph, not blood), and many endocrine glands including the pituitary and adrenal glands.

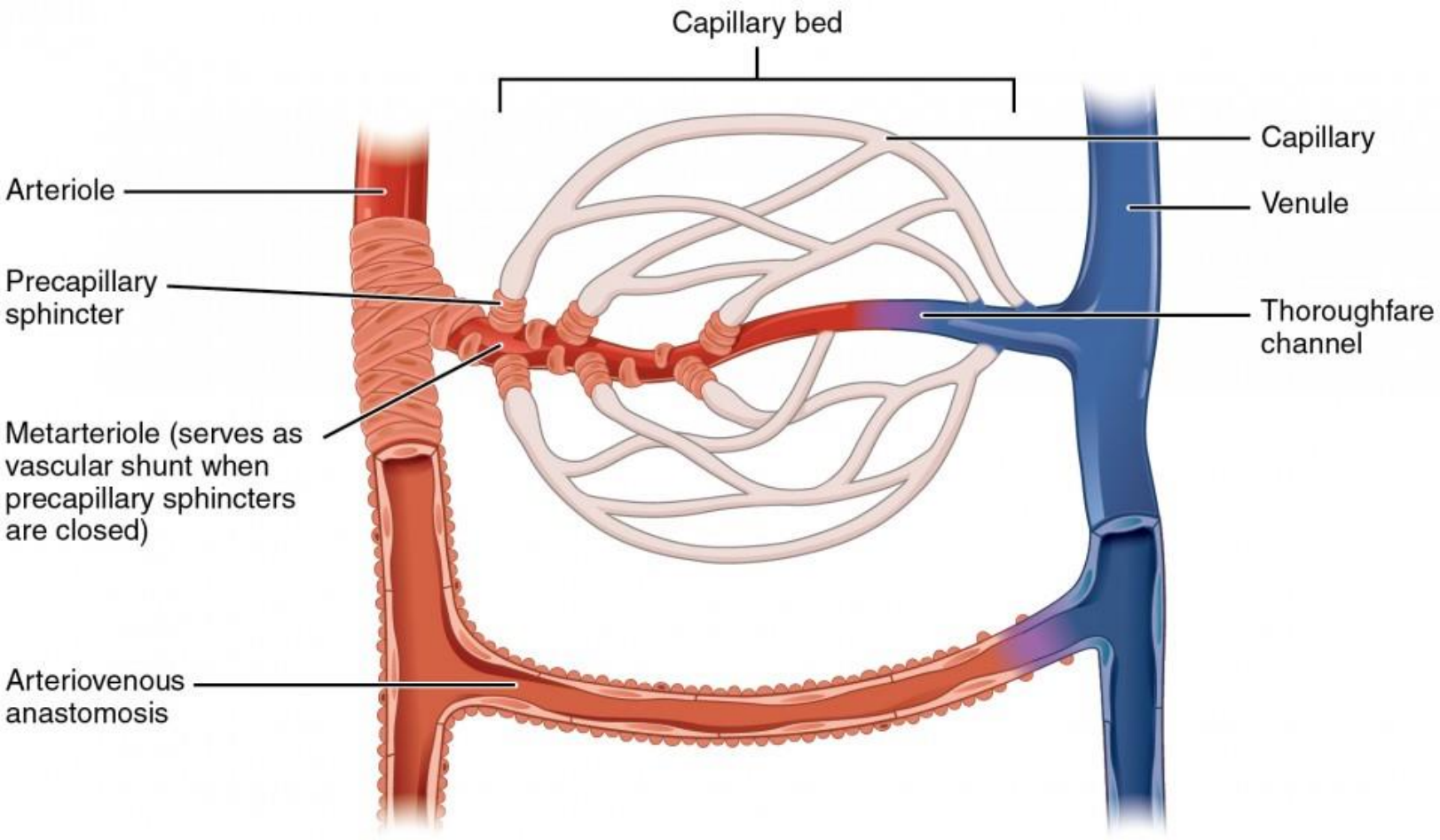
Metarterioles and Capillary Beds

A **metarteriole** has structure characteristics of both an arteriole and a capillary.
Slightly larger than the typical capillary, the smooth muscle of the tunica media of the metarteriole is not continuous but forms rings of smooth muscle (sphincters) prior to the entrance to the capillaries.

Each metarteriole arises from a terminal arteriole and branches to supply blood to a **capillary bed** that may consist of 10–100 capillaries.

The **precapillary sphincters**, circular smooth muscle cells that surround the capillary at its origin with the metarteriole.
Tightly regulate the flow of blood from a metarteriole to the capillaries.
Their function is critical to prevent all of the capillary beds in the body to open simultaneously.
Normally, the precapillary sphincters are closed and only open when the surrounding tissues need oxygen and have excess waste products.

Metarterioles and Capillary Beds



When all precapillary sphincters in a capillary bed are closed, blood flows through **thoroughfare channel** to reach the venous circulation.

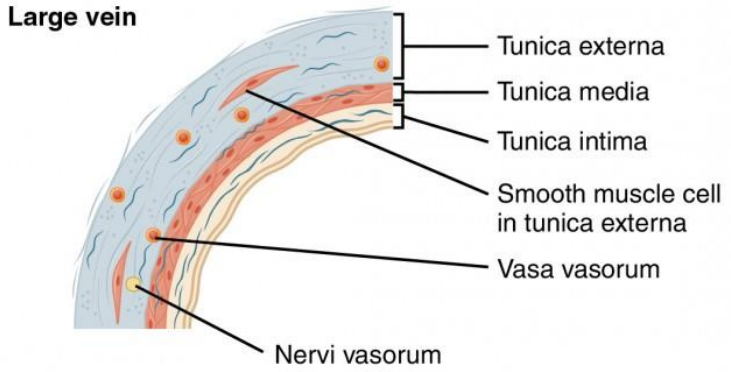
Arteriovenous anastomosis may bypass the capillary bed and lead directly to the venous system.
Blood flow through a capillary bed with an irregular, pulsating flow.
This pattern is called **vasomotion** and is regulated by chemical signals that are triggered in response to changes in internal conditions, such as oxygen, carbon dioxide, hydrogen ion, and lactic acid levels.

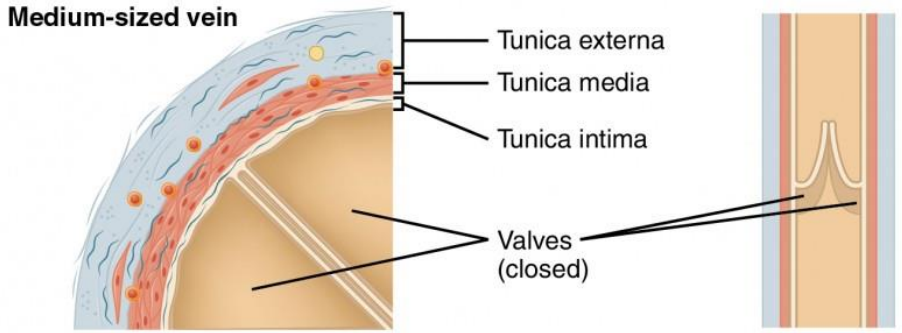
During strenuous exercise when oxygen levels decrease and carbon dioxide, hydrogen ion, and lactic acid levels all increase, the capillary beds in skeletal muscle are open.
Same in the digestive system when nutrients are present in the digestive tract.

During sleep or rest periods, vessels in both areas are largely closed. They open only occasionally to allow oxygen and nutrient supplies to travel to the tissues to maintain basic life processes.

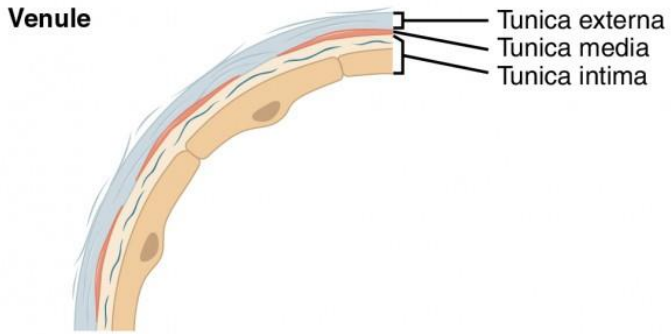
A **venule** is an extremely small vein (8–100 μm) . Postcapillary venules join multiple capillaries exiting from a capillary bed while multiple venules join to form veins.

The walls of venules consist of endothelium with a few muscle cells and elastic fibers plus an outer layer of connective tissue fibers forming the very thin tunica externa.
Venules as well as capillaries are the primary sites of diapedesis to enter the tissue fluid.





Veins
Conducts blood toward the heart. They are low-pressure vessels and are commonly equipped with valves to promote unidirectionality of flow toward the heart, preventing backflow toward the capillaries caused by low blood pressure in veins as well as gravity.



Veins as Blood Reservoirs

Veins may be considered blood reservoirs, since systemic veins contain approximately 64 % of the blood volume at any given time.

Their high **capacitance (**capacity to distend/expand) allow veins to store a high volume of blood even at a low pressure. They are said to be **capacitance vessels**.

To redistributed blood to other portions of the body, the vasomotor center located in the medulla oblongata sends sympathetic stimulation to the smooth muscles in the walls of the veins, causing constriction.

This increases pressure on the blood within the veins, speeding its return to the heart.

Approximately 21 percent of the venous blood is located in venous networks within the liver, bone marrow, and integument. This volume of blood is referred to as **venous reserve**. Through venoconstriction this reserve can get back to the heart more quickly for redistribution to other parts of the circulation.

Components of Arterial Blood Pressure

Arterial blood pressure in the larger vessels consists of several distinct components:

- Systolic pressure.
- Diastolic pressures.
- Pulse pressure.
- Mean arterial pressure.

Systolic and Diastolic Pressures

- The systolic pressure reflects the arterial pressure resulting from the ejection of blood during ventricular contraction (systole).

- The diastolic pressure represents the arterial pressure of blood during ventricular relaxation (diastole).

Pulse Pressure:

- Difference between systolic and diastolic pressure.
- Should be at least 25 % of the systolic pressure. A pulse pressure below this
- < 25% (a low stroke volume, congestive heart failure, stenosis of the aortic valve, or significant blood loss following trauma).
- > 25% sign of excessive resistance in the arteries.

Mean Arterial Pressure:

- Average pressure of blood in the arteries (statistical concept).
- Σ of the values/number of values.
- Can be approximated by adding the diastolic pressure to 1/3 of the pulse pressure or systolic pressure minus the diastolic pressure.

Variables Affecting Blood Flow and Blood Pressure:

Cardiac output: Measurement of blood flow from the heart through the ventricles.

Compliance: Ability of vessel to expend to facilitate blood flow.

Blood volume: Volume decreases, pressure and flow decrease (ok up to 10–20%).

Blood viscosity: thickness (resistance to flow).

Blood vessel length and diameter.

Variables Affecting Blood Flow and Blood Pressure:

Blood vessel length and diameter.

Length:

- Longer the vessel, greater the resistance the lower the flow.
- Vessel length increases throughout childhood as we grow.
- Is unchanged in adults under normal physiological conditions.
- Half kg of adipose tissue contains about 322km of vessel.
- Half kg of skeletal muscle contains more than twice that.
- Vessels length decrease during loss of mass or amputation.
- A 68kg individual has about 96561 km of vessels.
- Gaining about 4.5 kg adds from 3219 to 6437 kms of vessels.

Diameter:

- Change from large to small vessels throughout the body.
- Depends on vascular tone (vasoconstriction or vasodilatation).
- Smaller the diameter greater the resistance and lower is the flow.
- Small variation have huge impact on resistance ($R = 1/r^4$).

Pulse:

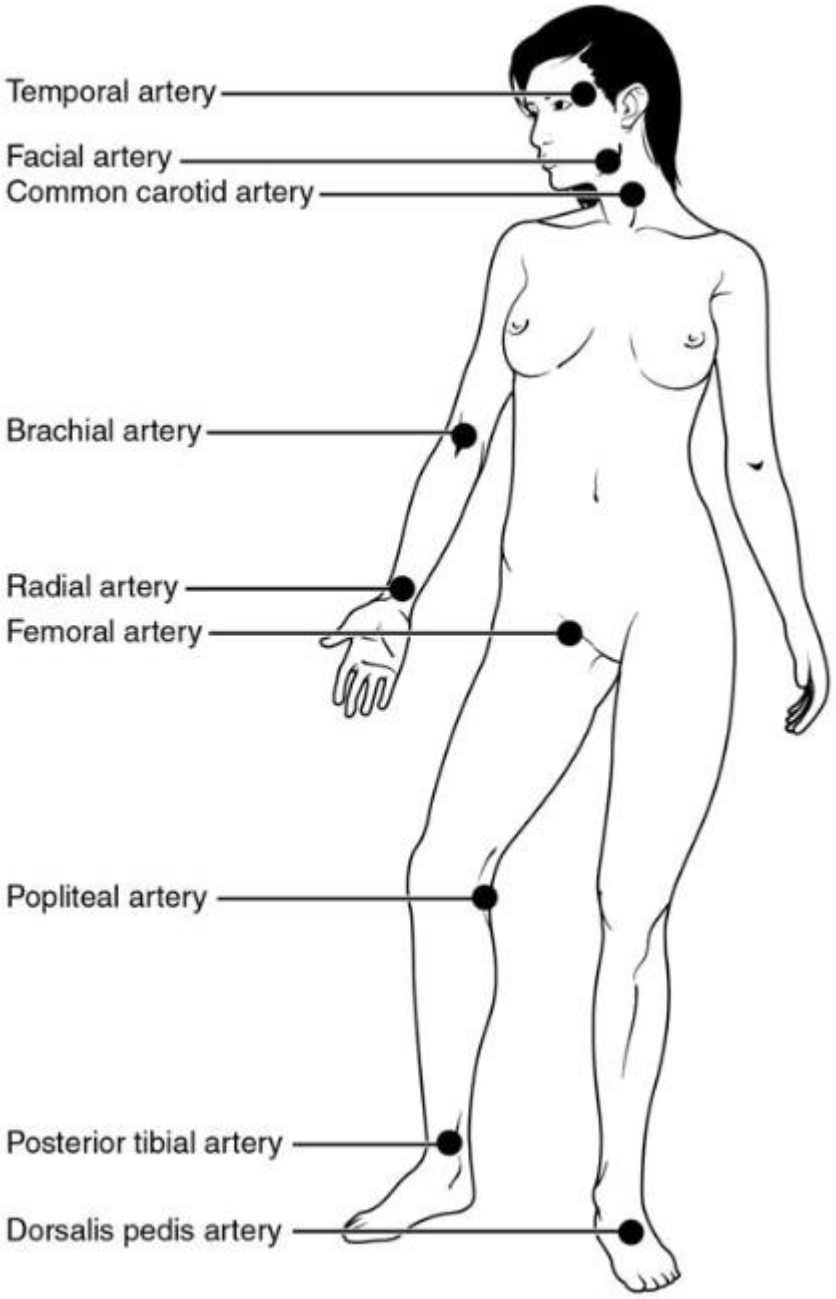
- Expansion and recoiling of the arteries during the blood flow.

- Can be palpated manually or measured electronically.

- Effect diminishes over distance from the heart, elements of the systolic and diastolic components of the pulse are still evident down to the level of the arterioles.

- Measuring the pulse rate gives indication of the heart rate.

- The pulse strength indicates the strength of ventricular contraction (cardiac output).
- Strong pulse, systolic pressure is high.
- Weak pulse, systolic pressure has fallen (bad).



Venous System:

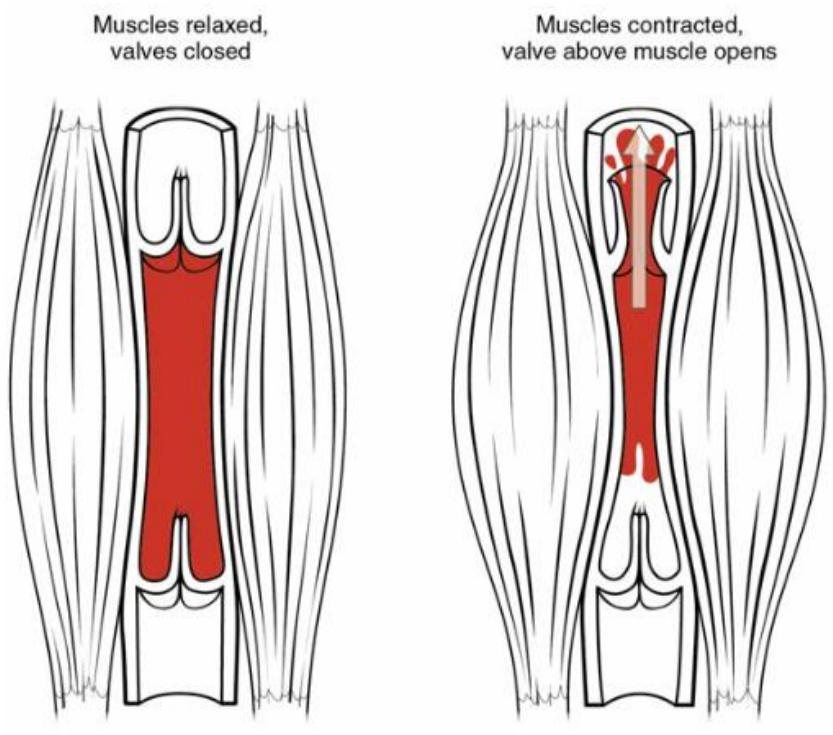
For blood to flow from the veins back into the heart, the pressure in the veins must be greater than the pressure in the atria of the heart.

1. During diastole the pressure in the atria is very low (near zero). When the atria are relaxed (atrial diastole).

2. Two physiologic "pumps" increase pressure in the venous system.

   Skeletal Muscle Pump

   Muscle contraction increase the vein pressure.



Respiratory Pump:

- During inhalation, diaphragm contraction increases the volume of the thorax.
- External intercostal muscles contraction also increasing thorax volume.
- Air pressure decrease allowing inhalation.
- Blood pressure in the thoracic veins also decreases below the pressure in the abdominal veins.
- Blood flows from veins outside the thorax into the thoracic region.
- This in turn promotes the return of blood from the thoracic veins to the atria.
- During exhalation, air pressure increases within the thoracic cavity.
- Pressure in the thoracic veins increases, speeding blood flow into the heart.
- Valves in the veins prevent blood from flowing backward.

Pressure Relationships in the Venous System:

- Diameter increases from smaller venules to the larger veins to venae cavae.
- Total cross-sectional area decreases (more venules than large veins).
- As blood moves from venules to veins pressure drops but velocity increases.
- This pressure gradient drives blood back toward the heart.
- One-way valves + the skeletal muscle and respiratory pumps facilitate flow to heart.
- 64% of the total blood is in systemic veins. Any action that increases the flow in veins increase blood return to the heart.
- Vascular tone of veins prevents the veins from distending.

The Role of Venoconstriction in Resistance, Blood Pressure, and Flow

- Vasoconstriction of arteries or arterioles decreases the radius, increasing resistance and pressure, but decreasing flow.
- Vein walls are thin but irregular, during vasoconstriction lumen becomes rounded. The rounded the lumen, less surface area, less resistance, higher flow. Vasoconstriction increases pressure within veins but in veins this increases flow.

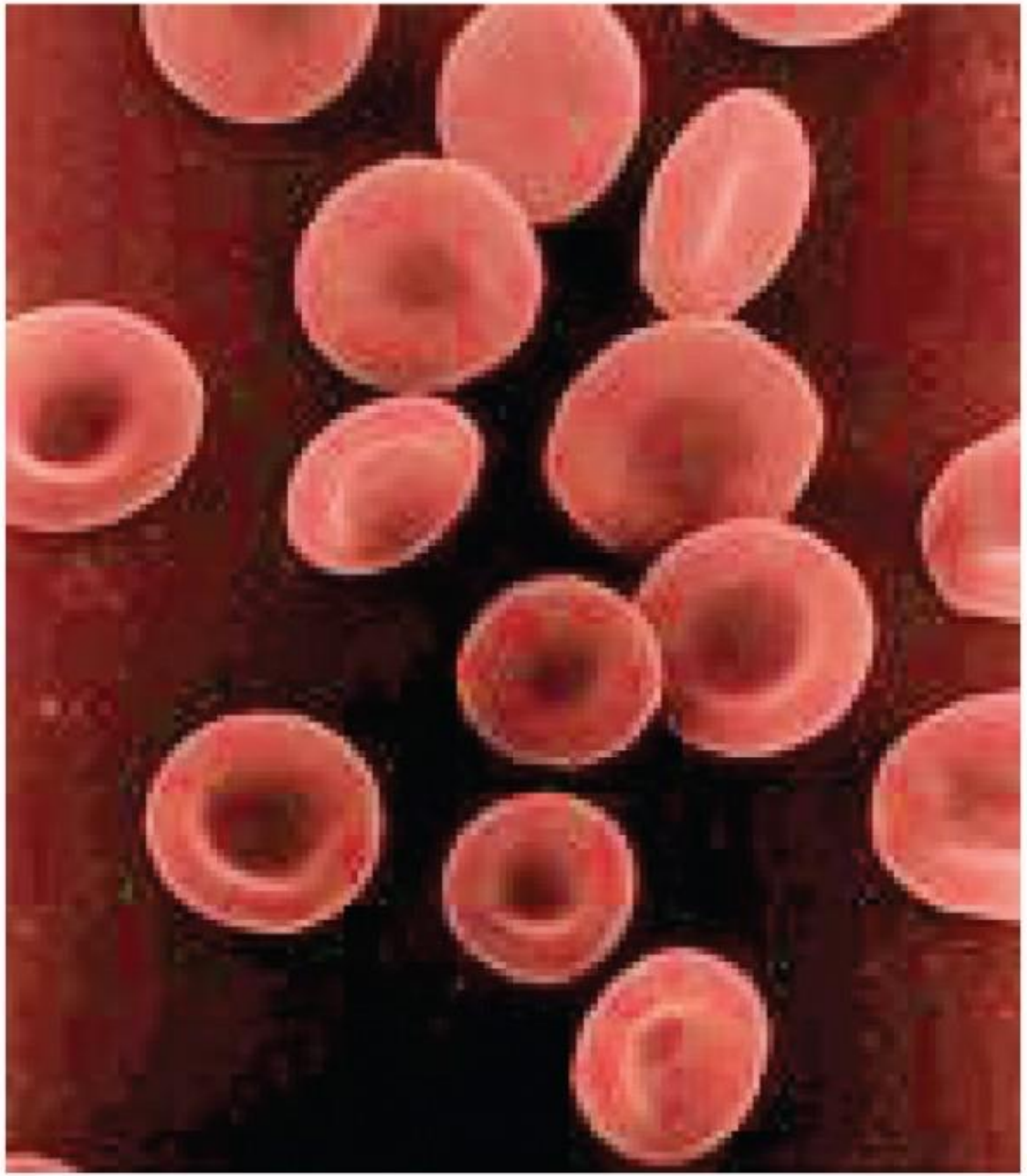
Erythrocytes (RBC).

Main function is to carry oxygen from lungs.
Pick up about 24% of CO2 waste at tissues.

The most abundant formed element:
5.4 x 10^6/ μL in males.
4.8 x 10^6/ μL in females.
25% of the total cells in the body.

Very small 7–8 μm Ø
biconcave disks (bags of haemoglobin),
enucleate, contain very
few organelles.

Erythrocytes do not extravasate.



Shape and Structure of Erythrocytes

During maturation in the red bone marrow erythrocytes extrude their nucleus and most of their other organelles.

Reticulocytes: Immature erythrocytes still contain remnants of organelles.
1-2% of the RBCs.
Provide an estimate of the rate of RBC production.

Mature, circulating erythrocytes have few internal cellular structural components.
Rely on anaerobic respiration. They do not use any of the O_2 they are transporting.

Erythrocytes still contain some structural proteins to maintain their unique structure and enable them to change their shape to squeeze through capillaries. This includes the protein spectrin, a cytoskeletal protein element.

They lack most organelles: more interior space for haemoglobin molecules.
The biconcave shape provides a greater surface area for gas exchange.

Capillary beds are extremely narrow, slowing the passage of the erythrocytes and providing an extended opportunity for gas exchange to occur.

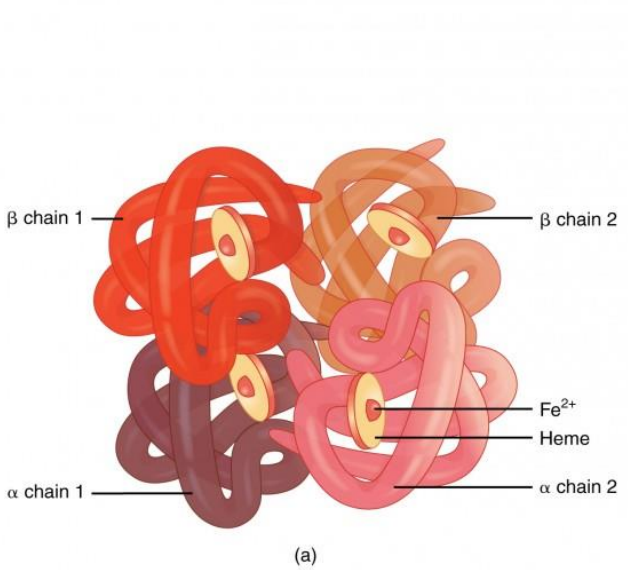
Hemoglobin

Four chains of globin, designated $\alpha 1$, $\alpha 2$, $\beta 1$ and $\beta 2$. Each of these globin molecules is bound to a red pigment molecule called **heme**, containing iron (Fe^{2+}).
Each Fe^{2+} can bind to one O_2 molecule: each hemoglobin molecule can transport four O_2 molecules (oxyhemoglobin bright red).

An individual erythrocyte may contain about 300 million haemoglobin molecules and transport up to 1.2 billion oxygen molecules.

In tissues haemoglobin releases some of the oxygen molecules (darker red deoxyhemoglobin.
O_2 release depends on the need in the tissues.

In the capillaries, CO_2 enters the bloodstream.
76% dissolves in the plasma where the majority forming bicarbonate ion.
23–24% of CO_2 binds to the amino acids in haemoglobin (carbaminohemoglobin).
In the lungs CO_2 is exchange for O_2.



Anemia: reduction in RBC count affects the ability to effectively deliver oxygen to the tissues.
Polycythemia: overproduction of RBCs increased viscosity of the blood (difficult for the heart to circulate the blood).

In patients with insufficient hemoglobin, the tissues may not receive sufficient oxygen.

Hypoxemia is a low blood oxygen content.

The kidneys filter about 180 liters (~380 pints) of blood in an average adult each day or about 20 percent of the total resting volume. It is the ideal sites for receptors that determine oxygen saturation. In response to hypoxemia less O_2 exits the vessels supplying the kidney. Resulting in hypoxia (low oxygen concentration) in the tissue fluid of the kidney, which trigger kidney interstitial fibroblasts to secrete EPO to increase erythrocyte production and restoring oxygen levels. As oxygen saturation rises EPO secretion falls.

At high altitude, the lower levels of O_2 in the atmosphere, naturally maintain a hematocrit higher.

Lifecycle of Erythrocytes:

Production rate of erythrocytes in the marrow is $2x10^6$ cells/second.
Enormous need of raw materials:
Glucose, lipids and amino acids as for any cells.

Specific to erythrocyte production requires several trace elements:

- **Iron:** 4 x Fe^{2+}/ haemoglobin molecules.
  Less than 20 percent of the iron is absorbed (hemes from meat, poultry, and fish, is absorbed more efficiently than non-heme iron from plant foods).

The bone marrow, liver, and spleen can store iron in **ferritin** and **hemosiderin**.
Ferroportin transports iron across the enterocyte plasma membranes and from its storage sites into tissue fluid where it enters the blood.

When EPO stimulates the production of erythrocytes, iron is released from storage, bound to transferrin, and carried to the red marrow where it attaches to erythrocyte precursors.

•**Copper:** Enter the formation of two plasma proteins, hephaestin and ceruloplasmin essential for the adequate production of haemoglobin.

Located in intestinal villi, hephaestin enables iron to be absorbed.

Ceruloplasmin transports copper.

Both enable the oxidation of iron from Fe^{2+} to Fe^{3+}, a form in which it can be bound to its transport protein, **transferrin**, for transport to body cells.

Copper deficiency lead to decrease of the transport of iron for heme synthesis, iron accumulate in tissues leading to organ damage.

•**Zinc:** A co-enzyme that facilitates the synthesis of the hemes.

•**B vitamins**. The vitamin B_9 (folate) and vitamin B_{12} (cobalamin) function as co-enzymes that facilitate DNA synthesis. Thus, both are critical for the synthesis of new cells, including erythrocytes.

Erythrocytes live up to 120 days in the circulation, after which they are removed by **macrophage**, in bone marrow, liver, and spleen.

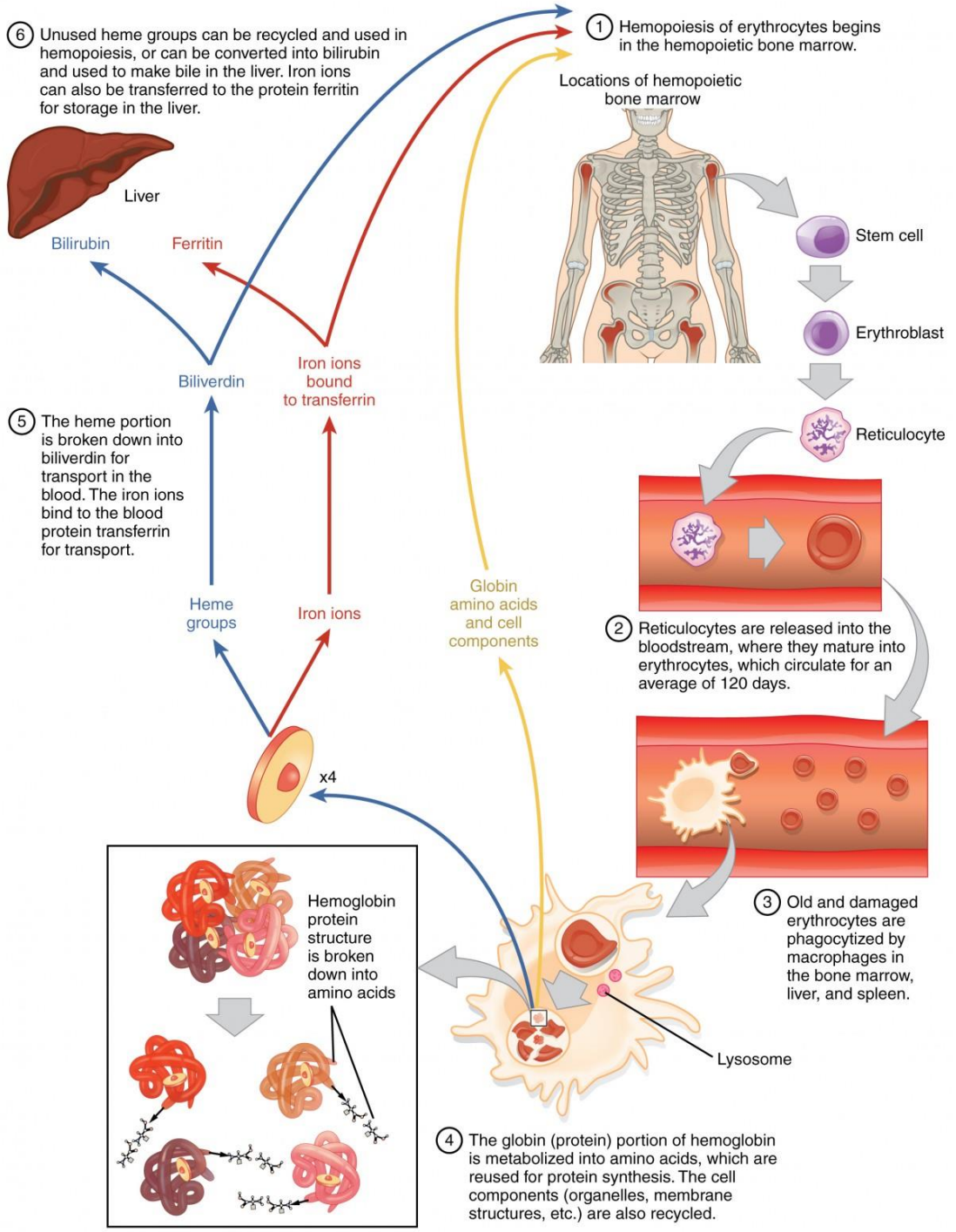
Recycling of RBC contents:

Contents of RBCs are recycled to produce new RBC each day.

•Globin, the protein portion of hemoglobin, is broken down into amino acids.

Hemoglobin that is not phagocytized is broken down in the circulation, releasing α and β chains that are removed from circulation by the kidneys.

•The iron contained in the heme is stored in the liver or spleen bound to ferritin or hemosiderin or carried through the bloodstream by transferrin to the red bone marrow for recycling into new erythrocytes.



•The non-iron portion of heme is degraded into **biliverdin** (a green pigment) and then into **bilirubin**, (a yellow pigment).

Bilirubin binds to albumin to travel in the blood to the liver where it is used to manufacture bile to emulsify dietary fats in the intestines.

In the large intestine, bacteria break bilirubin apart from the bile and converts to urobilinogen and then into stercobilin which is then eliminated in the feces.

The kidneys also remove any circulating bilirubin and other related metabolic by products such as urobilins and secrete them into the urine.

At the site of an injury, biliverdin from damaged RBCs produces some of the dramatic colours associated with bruising.

In condition of liver failure, bilirubin accumulate in circulation causing the body to be yellowish (jaundice).

Stercobilins give the typical brown color associated feces.
Urobilins give the yellow color of the urine.

Disorders of Erythrocytes:

The size, shape, and number of erythrocytes, and the number of hemoglobin molecules can have a major impact on a person's health.

Deficiency in RBCs or hemoglobin are causes of **anemia (>**400 types of anemia).

Three major groups of anemia depending of their ethiology.

- Blood loss.
- Faulty or decreased RBC production.
- Excessive destruction of RBCs.

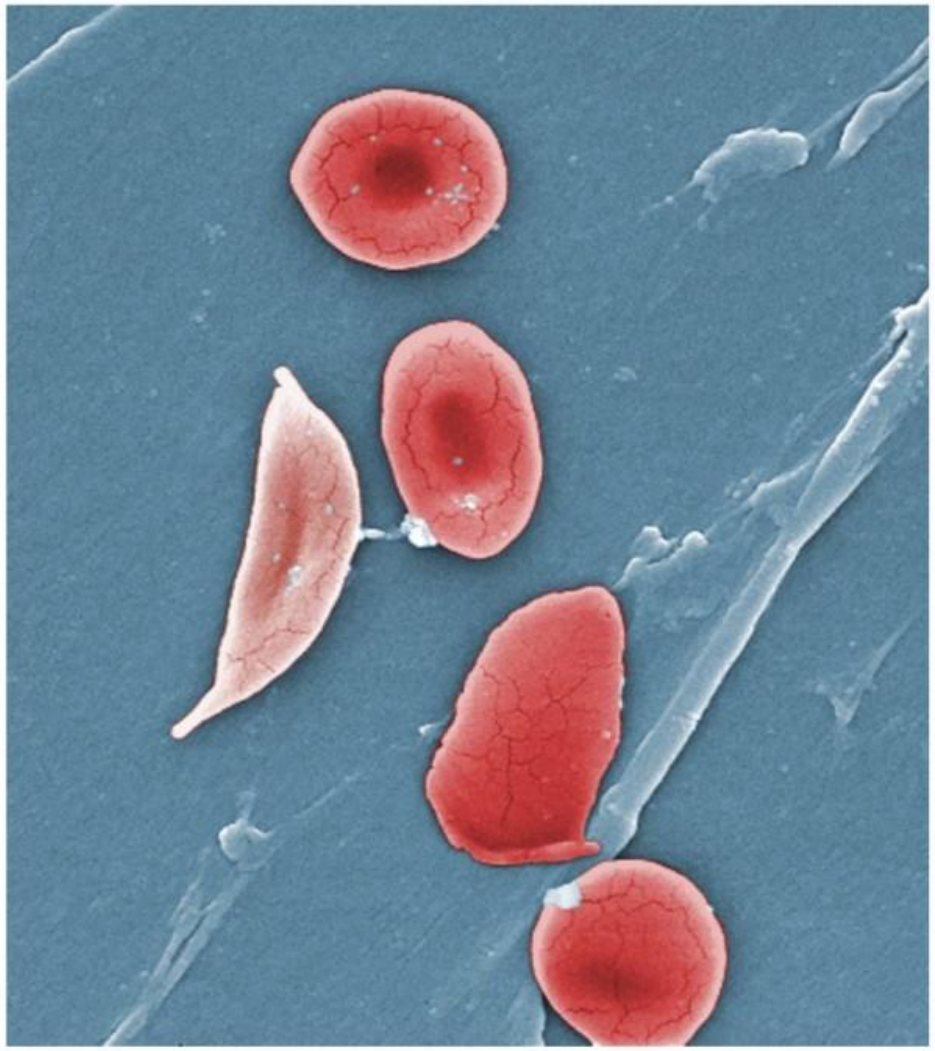
Mean corpuscle volume (MCV) measures size.

- Normocytic: normal-sized. cells are referred to as, and
- Microcytic: smaller-than-normal.
- Macrocytic: larger-than-normal.

Reticulocyte counts are also important and may reveal inadequate production of RBCs.

Anemias caused by faulty or decreased RBC production:

- Sickle cell anemia.
- Iron deficiency anemia.
- Vitamin deficiency anemia.
  - •Megaloblastic anemia deficiency of vitamin B12/B9.
    - Lack of meat or a viable alternative
    - Overcooking or eating insufficient amounts of vegetables may lead to a lack of folate.
  - •Pernicious anemia absorption of vitamin B12
    - In patients with Crohn's disease.
    - Surgical removal of the intestines or stomach. Intestinal parasites.
    - AIDS.
  - •Pregnancies, some medications, excessive alcohol consumption, celiac disease.



•Hemolytic anemia- results from premature rupture of the RE so that hemoglobin is released in the plasma.

Hemostasis:

Process by which the body seals a ruptured blood vessel.

- Platelets are key players in **hemostasis.**

Although rupture of larger vessels usually requires medical intervention, Hemostasis is quite effective in dealing with small, simple wounds.

- **Vascular spasm.**
- **Formation of a platelet plug.**
- **Coagulation (blood clotting).**

Failure of any of these steps will result in **hemorrhage**—excessive bleeding.

Vascular Spasm:

- When a vessel is severed or punctured.
- when the wall of a vessel is damaged.
  - Vessels constrict in response to damaged to reduce blood loss.
  - Platelets release serotonin (causes vasoconstriction).

Smooth muscle in the walls of the vessel contracts dramatically (both circular and longitudinal layers).

Endothelins released by endothelium and by pain receptors in response to vessel injury. Lasts for up to 30 minutes, although it can last for hours.

Formation of the Platelet Plug:

Platelets are exposed to underlying connective tissue and collagenous fibers.

- Platelets "stick to the fibers" forming a plug.
  - Clump together.
  - Become spiked and sticky.
  - Bind to the exposed collagen and endothelial lining.

This process is assisted by the von Willebrand factor, which stabilize the growing **platelet plug**.

As platelets collect, they simultaneously release chemicals from their granules into the plasma that further contribute to hemostasis.

- Adenosine diphosphate (ADP), which helps additional platelets to adhere to the injury site, reinforcing and expanding the platelet plug.
- Serotonin, which maintains vasoconstriction
- Prostaglandins and phospholipids to maintain vasoconstriction and activate further clotting chemicals, as discussed next

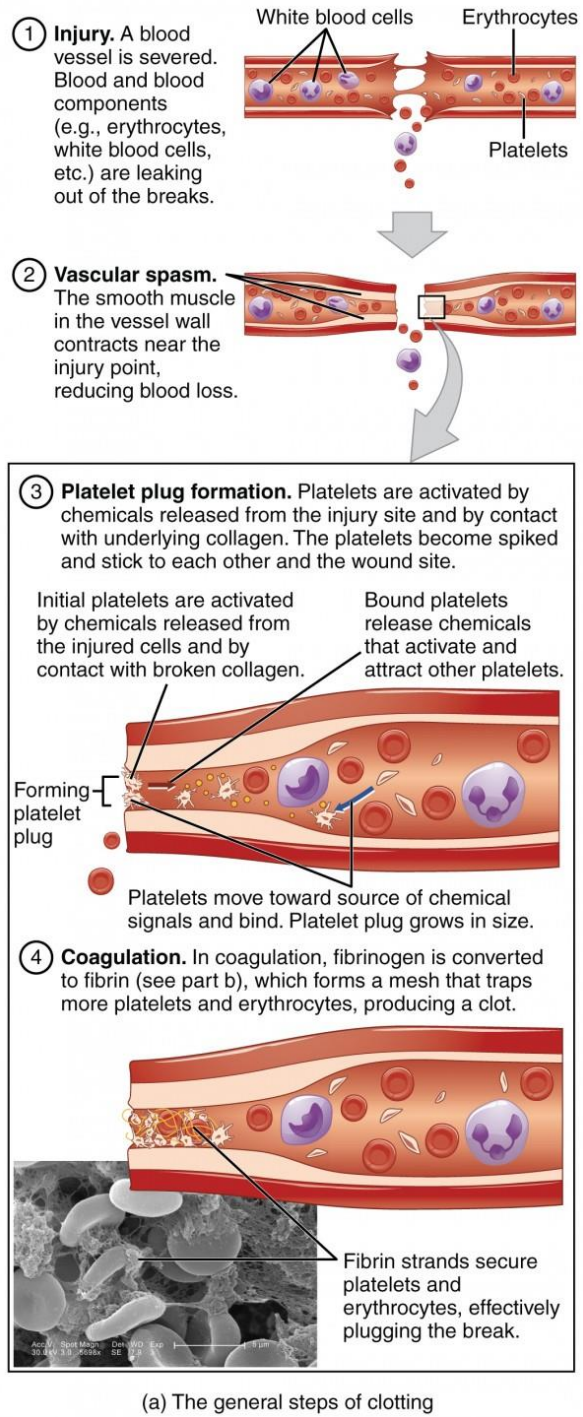
A platelet plug temporarily seal a small opening in a blood vessel to buy time while more sophisticated and durable repairs are being made.

Coagulation:

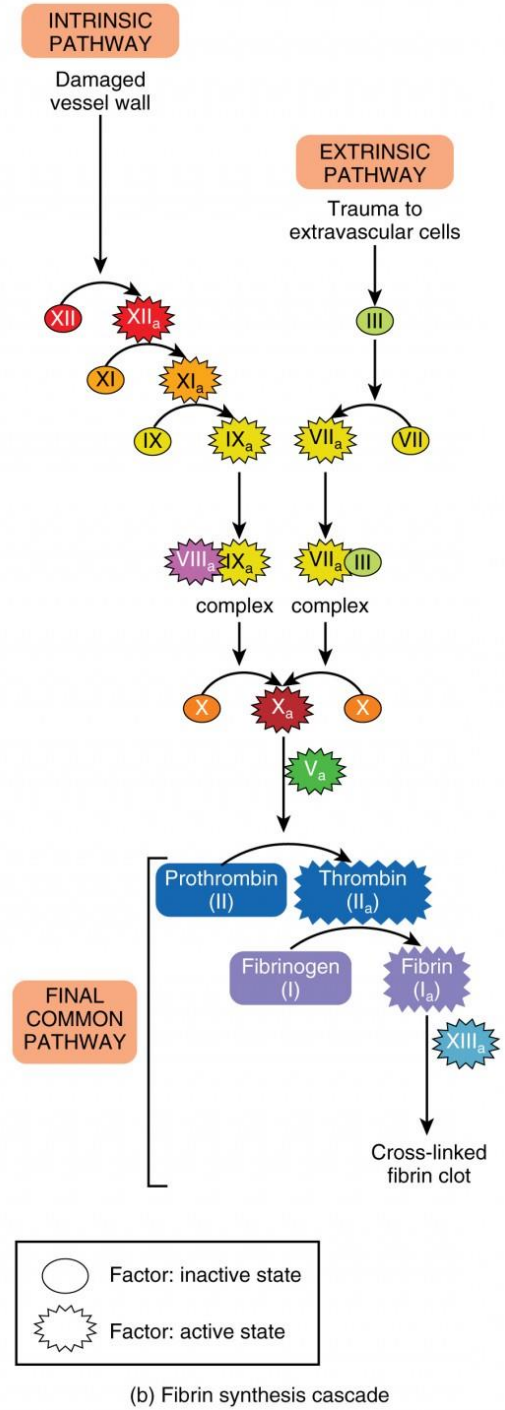
1. Injured tissue (vessel) releases <u>thromboplastin</u>
    - Collected platelets release platelet factors.
    - Both thromboplastin and platelet factors react with clotting factors in the plasma to produce <u>prothrombin activator</u>.
2. In the presence of calcium, prothrombin activator converts <u>prothrombin</u> into <u>thrombin.</u>

3. In the presence of <u>calcium</u>, <u>thrombin</u> converts <u>fibrinogen</u> into hair-like insoluble fibrin to forms the meshwork that traps RBCs and forms the basis of the clot.

Coagulation is a more sophisticated and more durable repairs.



(a) The general steps of clotting



(b) Fibrin synthesis cascade

Clotting Factors Involved in Coagulation:

Chemicals called **clotting factors** (or coagulation factors) prompt reactions that activate still more coagulation factors.

Two basic pathways:

- The extrinsic pathway, which normally is triggered by trauma.
- The intrinsic pathway, which begins in the bloodstream and is triggered by internal damage to the wall of the vessel.

Both of these merge into the common pathway.

All three pathways are dependent upon:

- 12 clotting factors secreted by the liver and platelets (requires vitamin K).
- Ca^{2+} From diet and from bone resorption.
- Vitamin K (from diet or synthesized by bacteria in the large intestine).

The 12 clotting factors are numbered I through XIII according to the order of their discovery. Factor VI was once believed to be a distinct clotting factor, but is now thought to be identical to factor V. Rather than renumber the other factors, factor VI was allowed to remain as a placeholder and also a reminder that knowledge changes over time.

Extrinsic Pathway:

- Very rapid (seconds) and more direct pathway known as the **tissue factor** pathway. Damage to the surrounding tissues (e.g. traumatic injury).

- Contact with blood plasma, the damaged extravascular cells release factor III (thromboplastin).

- Sequentially, Ca^{2+} then factor VII (proconvertin activated by factor III)

- Formation of an enzyme complex.

- Activation of factor X (Stuart–Prower factor)

- Activation of the common pathway. discussed below.

Intrinsic Pathway

- The contact activation pathway is longer and more complex.
- The factors involved are intrinsic to the bloodstream.

- Damage to the tissues, resulting from internal factors such as arterial disease.
- Factor XII is activated by negatively charged molecules (inorganic polymers and phosphate).
- Cascade of reaction leading to the activation of factor XI (anti-hemolytic factor C or plasma thromboplastin antecedent).
- Activation of Factor IX (anti-hemolytic factor B or plasma thromboplasmin).

- Chemicals released by the platelets increase the rate of these activation reactions.

- Factor VIII (anti-hemolytic factor A) from the platelets and endothelial cells combines with factor IX (anti-hemolytic factor B or plasma thromboplasmin).

- Formation of an enzyme complex that activates factor X (Stuart–Prower factor or thrombokinase). Activation of the common pathway. The events in the intrinsic pathway are completed in a few minutes.

Common Pathway:

- Fibrin is produced to seal off the vessel.
- Factor X activated by either the intrinsic or extrinsic pathway.
- Prothrombinase converts factor II, (inactive prothrombin) into **thrombin**.
-
- Thrombin converts factor I, the insoluble fibrinogen, into the soluble fibrin protein strands.
- Factor XIII then stabilizes the fibrin clot.

Disorders of Clotting:

Insufficient or an excessive production of platelets (severe disease or death).

Thrombocytopenia: Insufficient number of platelets results in the inability of blood to form clots (excessive bleeding, even from minor wounds).

Hemophilia: Inadequate production of functional amounts of one or more clotting factors (group of disorders).

- Hemophilia A: accounting for 80 percent of cases (factor VIII).
- Hemophilia B: accounting for 20 percent of cases (factor IX).
  - Both are X-linked.

Hemophilia C: a rare condition (factor XI)

Autosomal.

Not a true recessive condition, since even individuals with a single copy of the mutant gene show a tendency to bleed.

Regular infusions of clotting factors isolated from healthy donors can help prevent bleeding in hemophiliac patients. At some point, genetic therapy will become a viable option.

Thrombocytosis: excessive numbers of platelets
Increases the risk for excessive clot formation (**thrombosis)**.

A **thrombus** (plural = thrombi): an aggregation of platelets, erythrocytes, and WBCs trapped in a mass of fibrin strands.

Thrombi can form within an intact or only slightly damaged blood vessel.
In large vessels, a thrombus will adhere to the vessel wall and decrease blood flow. Mural thrombus.
In small vessels: Totally block blood flow (occlusive thrombus).

Caused by damage to the endothelial lining.
Venous stasis (static blood in the veins) (long airplane flights).

Thrombophilia: Hypercoagulation high tendency to form thrombosis.

- May be familial (genetic).
- Acquired.
  lupus, immune reactions to heparin, polycythemia vera, thrombocytosis, sickle cell disease, pregnancy, and even obesity.

Embolus: portion of a thrombus breaks free and enters the circulation.
Can be large enough to block a vessel critical to a major organ (embolism).

- Heart: Heart attack.
- Brain: Brain stroke.
- Lungs: pulmonary embolism.

These are medical emergencies.
Aspirin play role as an anticoagulant, is very effective at inhibiting the aggregation of platelets.

Thrombolytic agents can speed up the degradation of an abnormal clot.

If administered to a patient within 3 hours following a thrombotic stroke. patient's prognosis improves significantly.

Some strokes are not caused by thrombi, but by hemorrhage.

Tissue plasminogen activator convert plasminogen to plasmin (primary enzyme that breaks down clots). It is released naturally by endothelial cells but is also used in medicine. Venom of vipers and cobras, may have therapeutic value as thrombolytic agents.

The ABO Blood Group

Two glycoprotein antigens, A and B expressed at the surface of the erythrocytes.

- Blood type A only express antigen A.
- Blood type B only express antigen B.
- Blood type AB express antigen A and B.
- Blood type O express neither antigen A nor B.

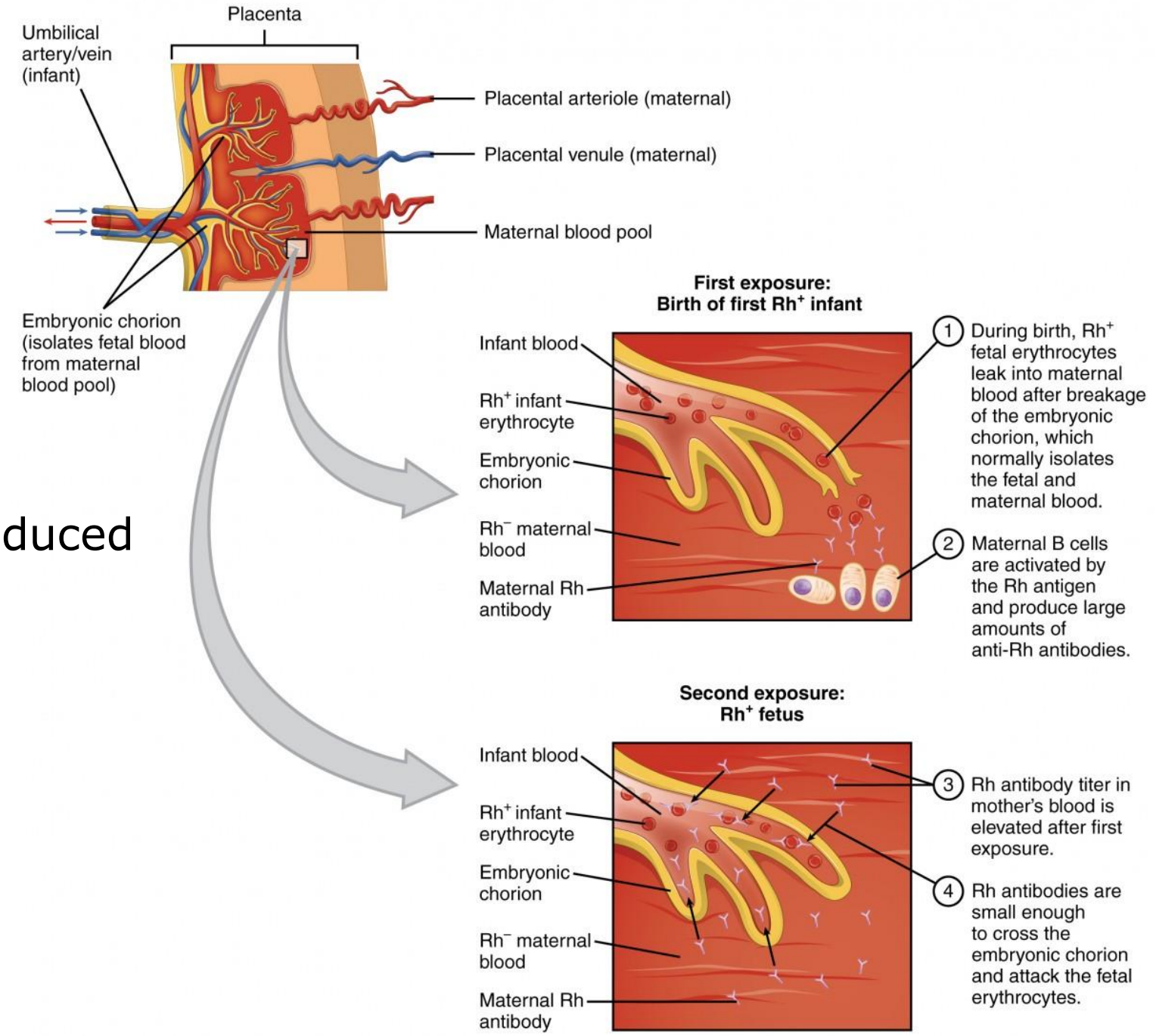
Individuals with type A blood have preformed antibodies to the B antigen
Individuals with type B blood have preformed antibodies to the A antigen.
Individuals with type AB blood do not have preformed antibodies to A & B antigens.
Individuals with type O blood have both anti-A and anti-B antibodies.

Rh Blood Groups

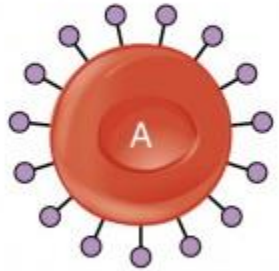
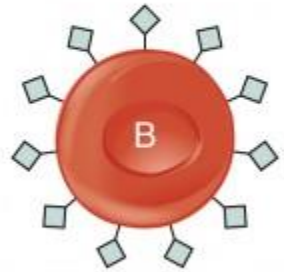
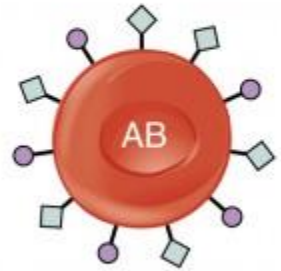
Classified according to the presence or absence of a second erythrocyte antigen identified as Rh.

Although dozens of Rh antigens have been identified, only one, designated D, is clinically important. Those who have the Rh D antigen are Rh positive (Rh^+) and those who lack it are Rh negative (Rh^-).

Antibodies to the Rh are produced only in Rh$^-$ individuals after exposure to Rh-D antigen.



Blood Type

	A	B	AB	O
Red Blood Cell Type				
Antibodies in Plasma	 Anti-B	 Anti-A	None	 Anti-A and Anti-B
Antigens in Red blood Cell	 A antigen	 B antigen	 A and B antigens	None
Blood Types Compatible in an Emergency	A, O	B, O	A, B, AB, O (AB^+ is the universal recipient)	O (O is the universal donor)

The Heart: Some facts.

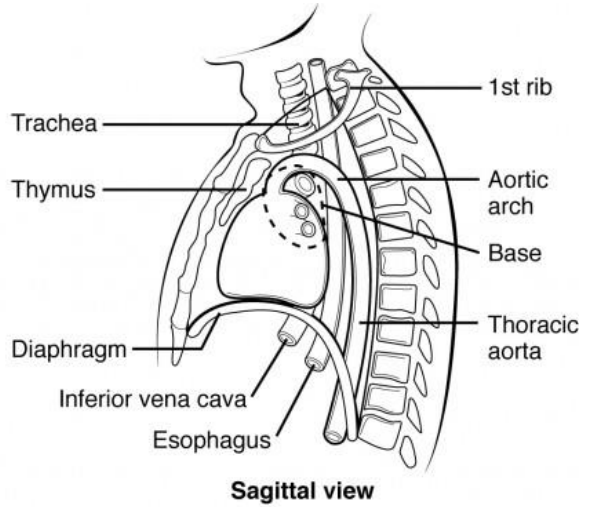
- The heart pumps blood through a closed system of blood vessels.
- For a rate of contraction of 75 contractions/minute.
- Heart would contract approximately 108,000 times in one day.
- 39 million times in one year.
- Nearly 3 billion times during a 75-year lifespan.
- Each pumping chambers ejects approximately 70 mL blood/contraction in a resting condition.
- 5.25 liters of blood/minute.
- 14,000 liters/day and 10,000,000 liters / year.

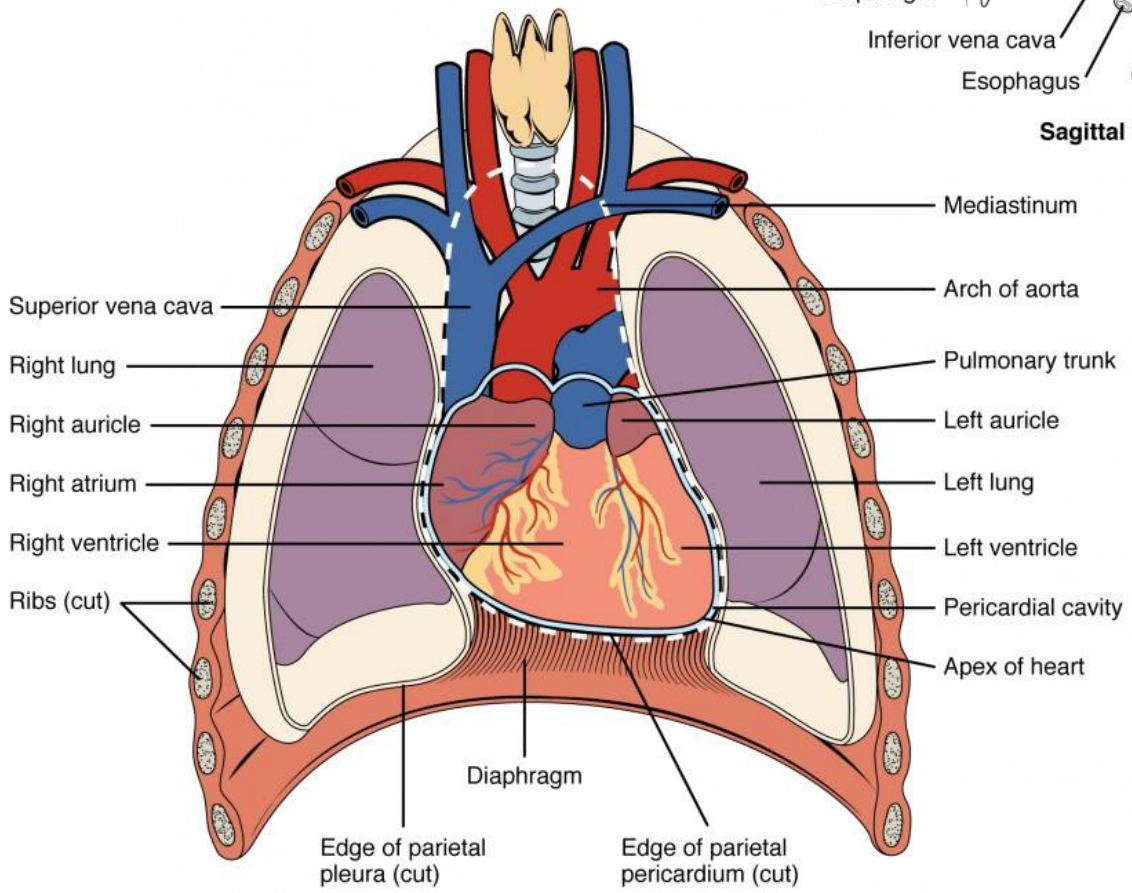
Location of the Heart

The human heart is located medially between the lungs within the thoracic cavity (mediastinum).

The heart is separated from the other mediastinal structures by the pericardium, or pericardial sac in the **pericardial cavity**.

The dorsal side lies near the bodies of the vertebrae.
The anterior side sits deep to the sternum and costal cartilages.



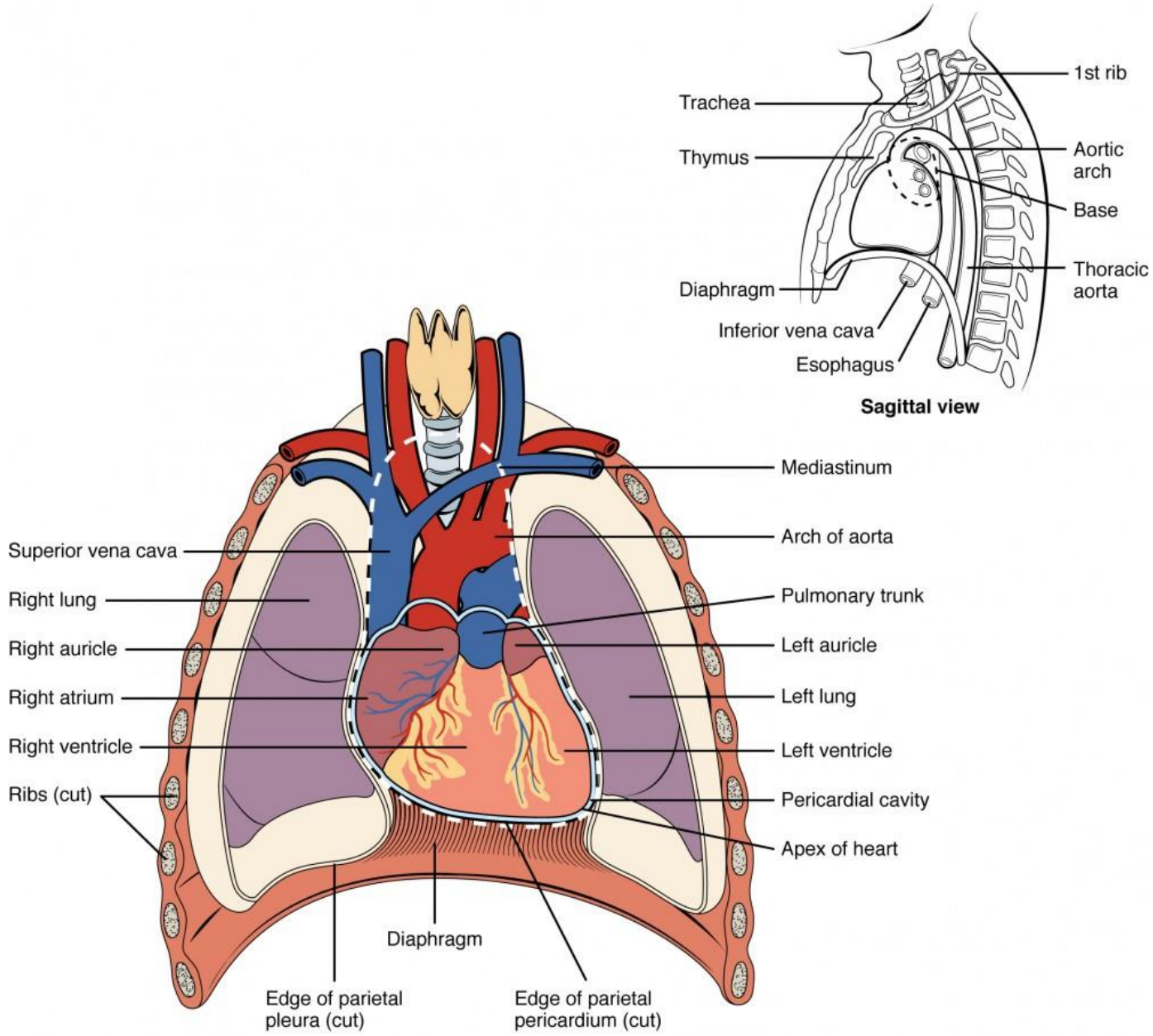


Location of the Heart

The large vessels, (superior and inferior venae cavae, the aorta and pulmonary trunk, are attached to the superior surface called the base.

The apex, lies just to the left of the sternum between the junction of the fourth and fifth ribs.
The right side of the heart is deflected anteriorly.
The left side is deflected posteriorly.

The slight deviation of the apex to the left is reflected in a depression in the medial surface of the inferior lobe of the left lung, called the **cardiac notch**.



Shape and Size of the Heart:

Shaped similar to a pinecone: broad at the base while tapering at the apex.

- Approximately the size of one fist:
- 12 cm in length
- 8 cm wide
- 6 cm in thickness.
- The weight of a female heart is approximately 250–300 grams.
- The weight of a male heart is approximately 300–350 grams.

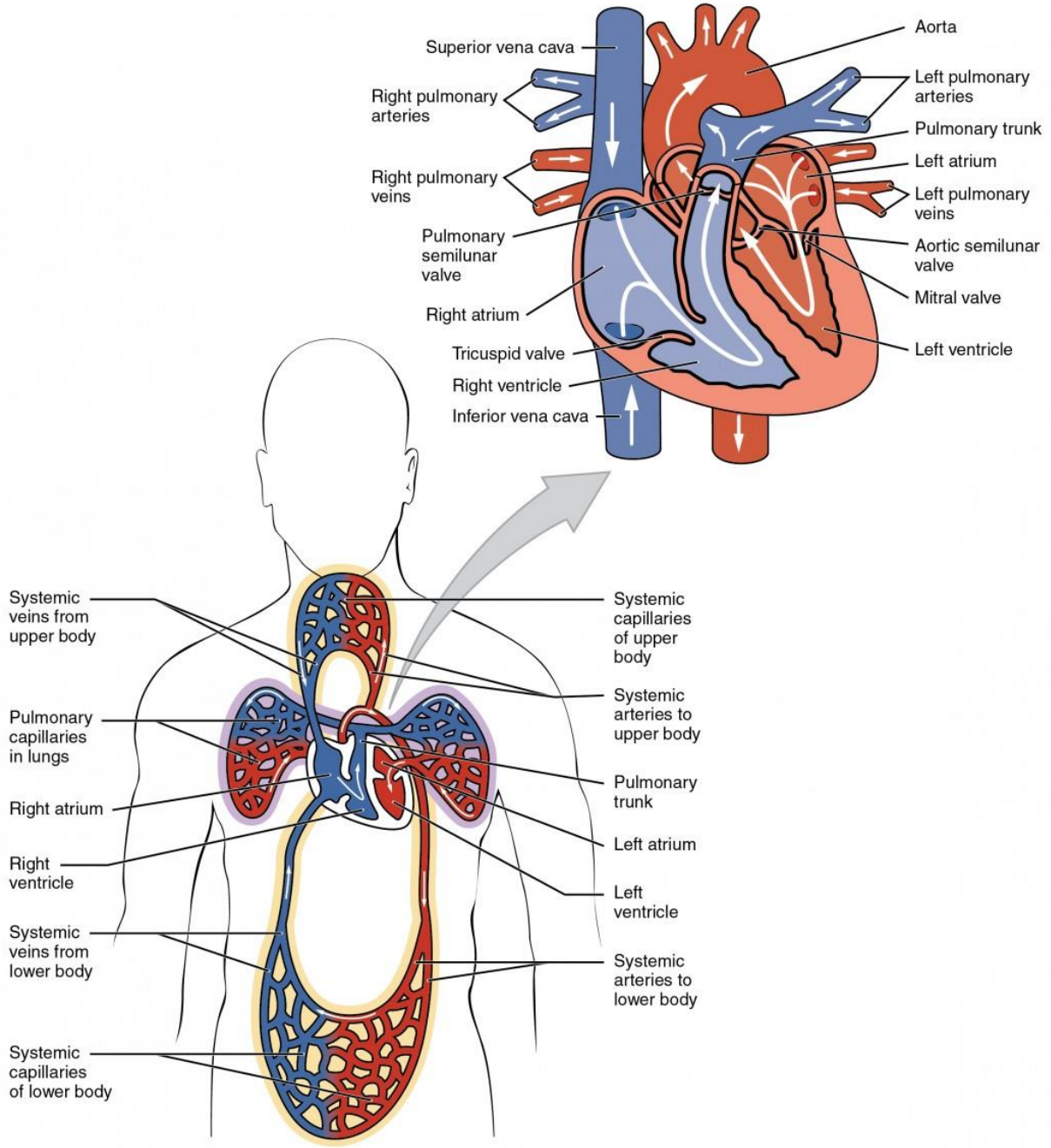
The heart of a well-trained athlete, especially one specializing in aerobic sports, can be considerably larger than this. Cardiac muscle responds to exercise in a manner similar to that of skeletal muscle.

Chambers and Circulation through the Heart:

The human heart consists of four chambers:
Left **atrium** and left **ventricle**.
Right **atrium** and right **ventricle.**

The upper chambers, the right and left atria are receiving chamber and contracts to push blood into the lower chambers right and left ventricles.

The ventricles serve as the primary pumping chambers of the heart, propelling blood to the lungs or to the rest of the body.



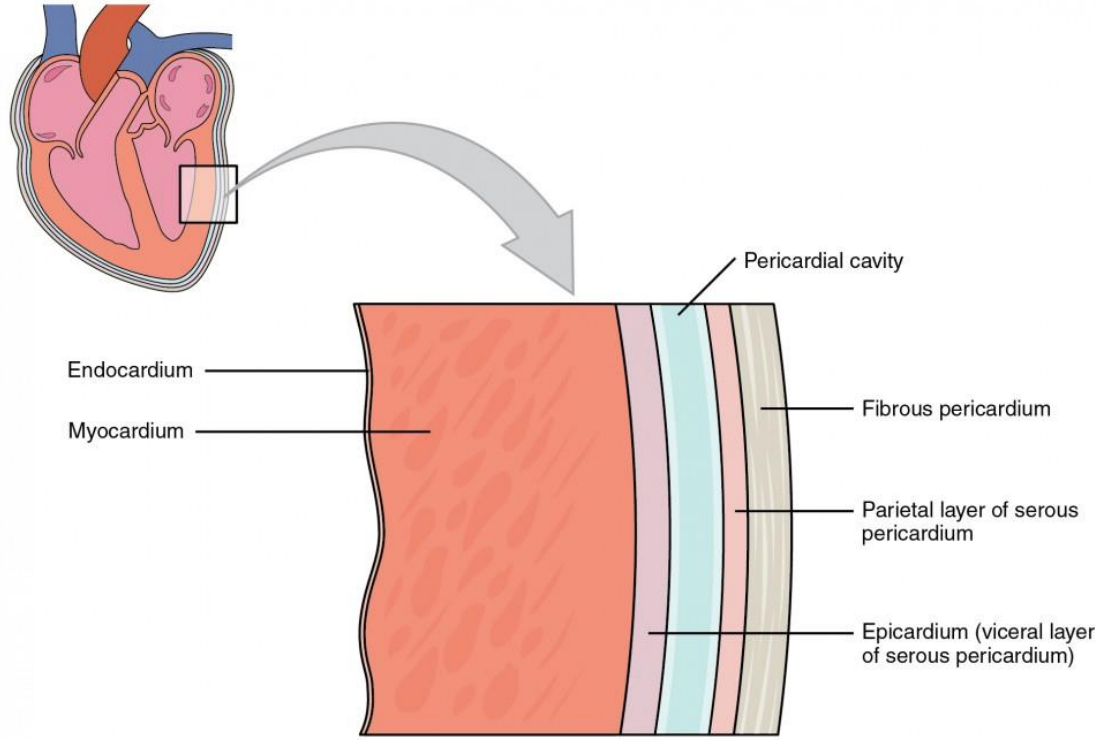
The right ventricle pumps deoxygenated blood into the **pulmonary trunk that** bifurcates into the left and right **pulmonary arteries**.

Highly oxygenated blood returns from lung by **pulmonary veins** to the **left atrium** which pumps the blood into the left ventricle.

Left ventricle pumps oxygenated blood into the aorta and the systemic circuit. Blood returns to right atrium by **superior** and **inferior venea cavea**, which pumps blood into the right ventricle.

Membranes, Surface Features, and Layers
Membranes

Pericardium
surrounds the heart, defines the pericardial cavity **(pericardial sac).**
surrounds the "roots" of the major vessels.

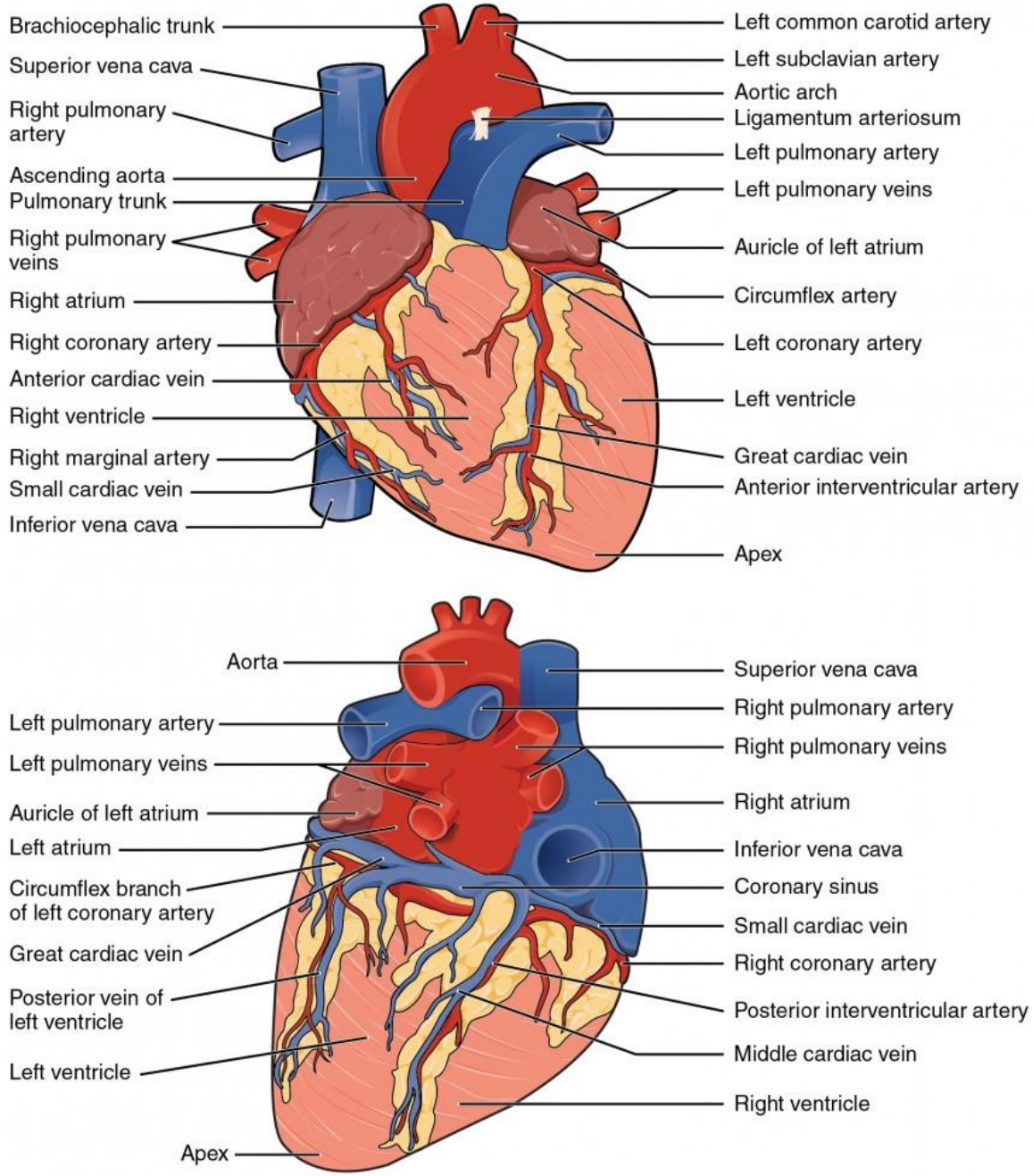


The sturdy outer fibrous pericardium tough, dense connective tissue.
The inner serous pericardium.
The parietal pericardium is fused to the fibrous pericardium
The inner visceral pericardium (**epicardium**is) fused to the heart.
The pericardial cavity, filled with lubricating serous fluid, lies between the epicardium and the pericardium.
The mesothelium secretes the lubricating serous fluid that fills the pericardial cavity and reduces friction as the heart contracts.

Auricle: superficial extension of the atria near the superior surface on each side.

Auricles are relatively thin-walled structures that can fill with blood and empty into the atria. You may also hear them referred to as atrial appendages.

Also prominent **Sulcus** series of fat-filled grooves along the superior surfaces of the heart. Major coronary blood vessels are located in these sulci.



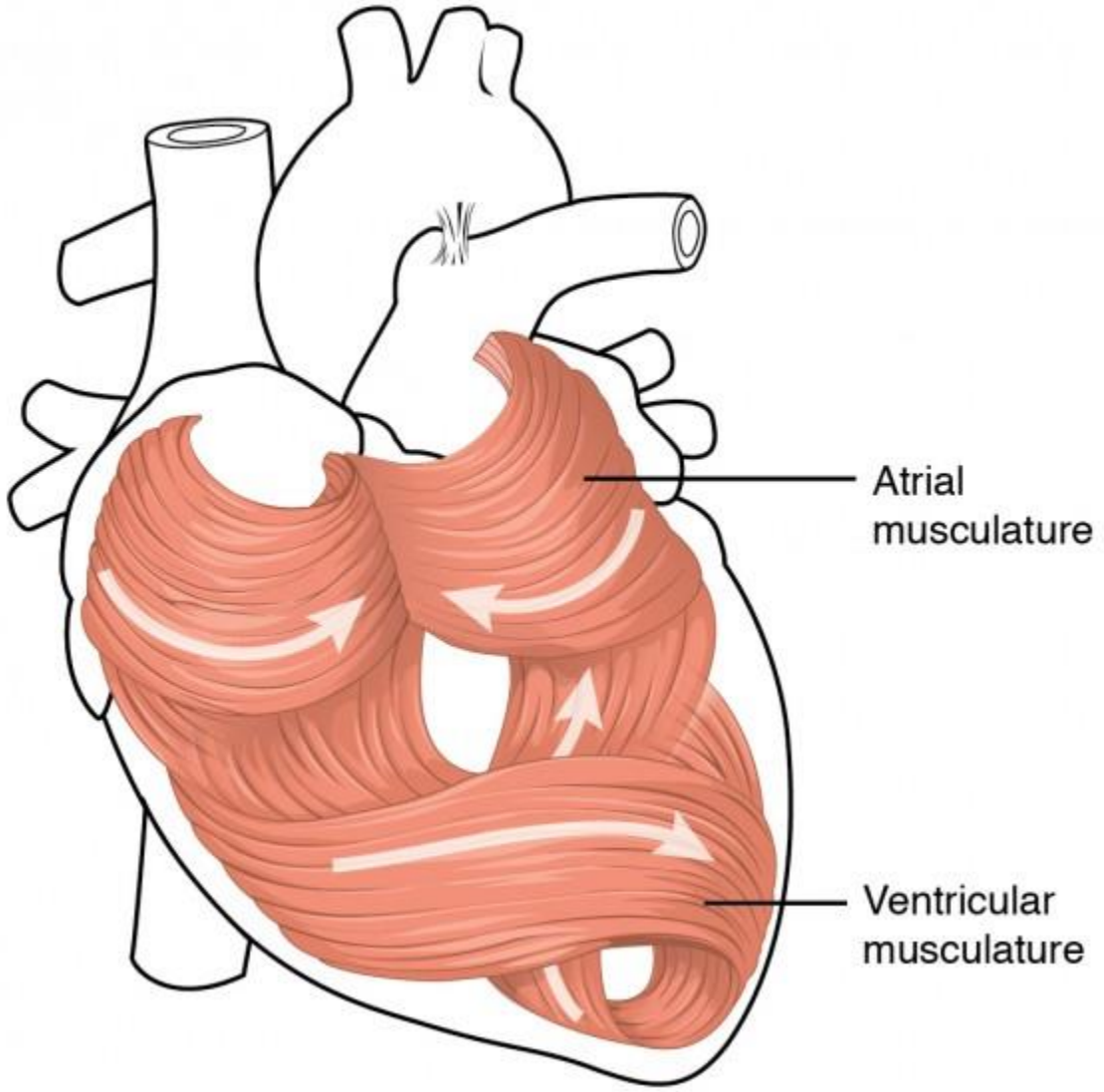
The wall of the heart:

Made of 3 layers of unequal thickness.

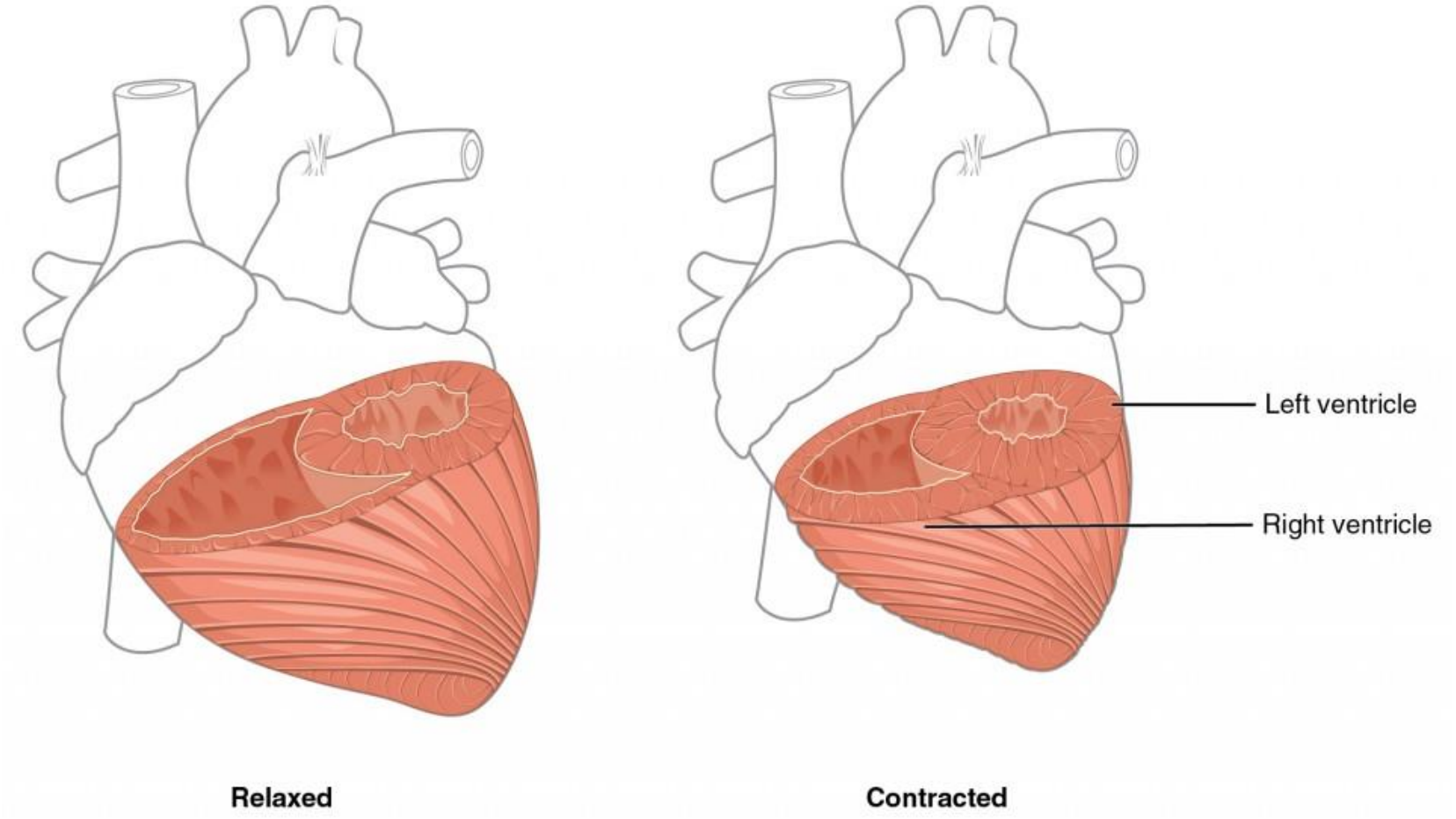
1. Epicardium is also the innermost layer of the pericardium

2. Myocardium made of cardiac muscle.
   Built upon a framework of collagenous fibers, plus the blood vessels and nerve fibers. The muscle pattern is elegant and complex, swirl and spiral around the chambers of the heart.

3. Endocardium is joined to the myocardium with a thin layer of connective tissue. A simple squamous epithelium which is continuous with the endothelial lining of the blood vessels (**Endothelium).**



Right and left ventricles pump the same amount of blood per contraction.
The muscle of the left ventricle is much thicker and better developed to overcome the high resistance required to pump blood into the long systemic circuit. The left ventricle must generate a great amount of pressure.



Internal Structure of the Heart: Septa and valves.

Each contraction cycle flow blood in the tow network of circulation:

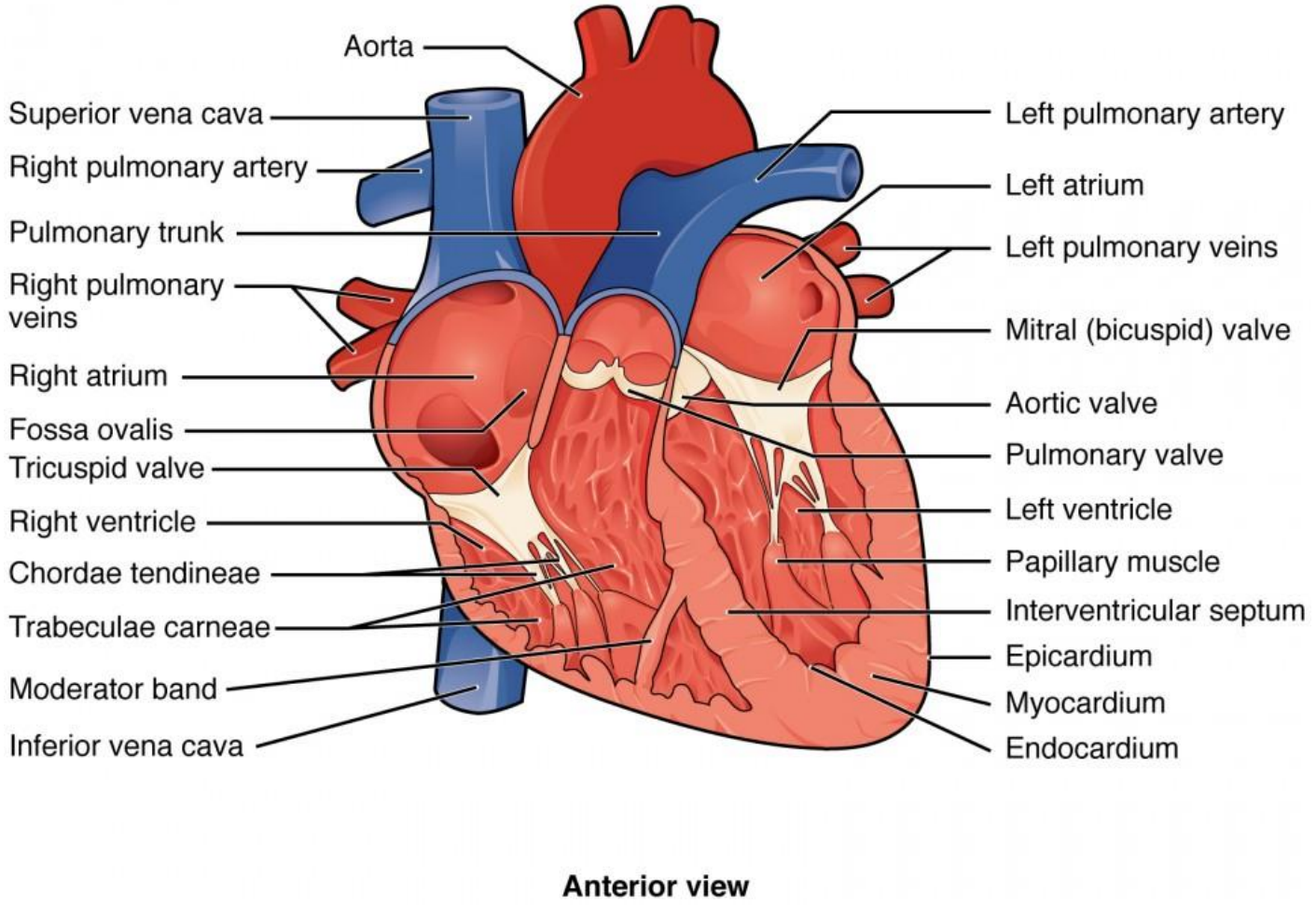
Pairs of chambers that pump blood.

Septa of the Heart: Physical extensions of the myocardium lined with endocardium to divide the heart in four different chambers.

Interventricular septum: between ventricle.

Interatrial septum is located between the two atria with it **fossa ovalis (**remnant of **foramen oval)**. In fetal heart, the foramen oval allowed blood to pass directly from the right to left atrium to bypass the pulmonary circuit.

Within seconds after birth the **septum primum** that previously acted as a valve closes the foramen oval to establishes the typical cardiac circulation pattern.



Atrioventricular Septum:

Marked by four openings allowing blood to move from:

The atria into the ventricles.

The ventricle into the pulmonary trunk.

The ventricle into the aorta.

Atrioventricular valves: between the atria and ventricles.

Semilunar valves: Between ventricle and the pulmonary trunk.
Between ventricle and aorta.

Since these openings and valves structurally weaken the atrioventricular septum, the remaining tissue is heavily reinforced with dense connective tissue called the **cardiac skeleton.**

Four rings that surround:

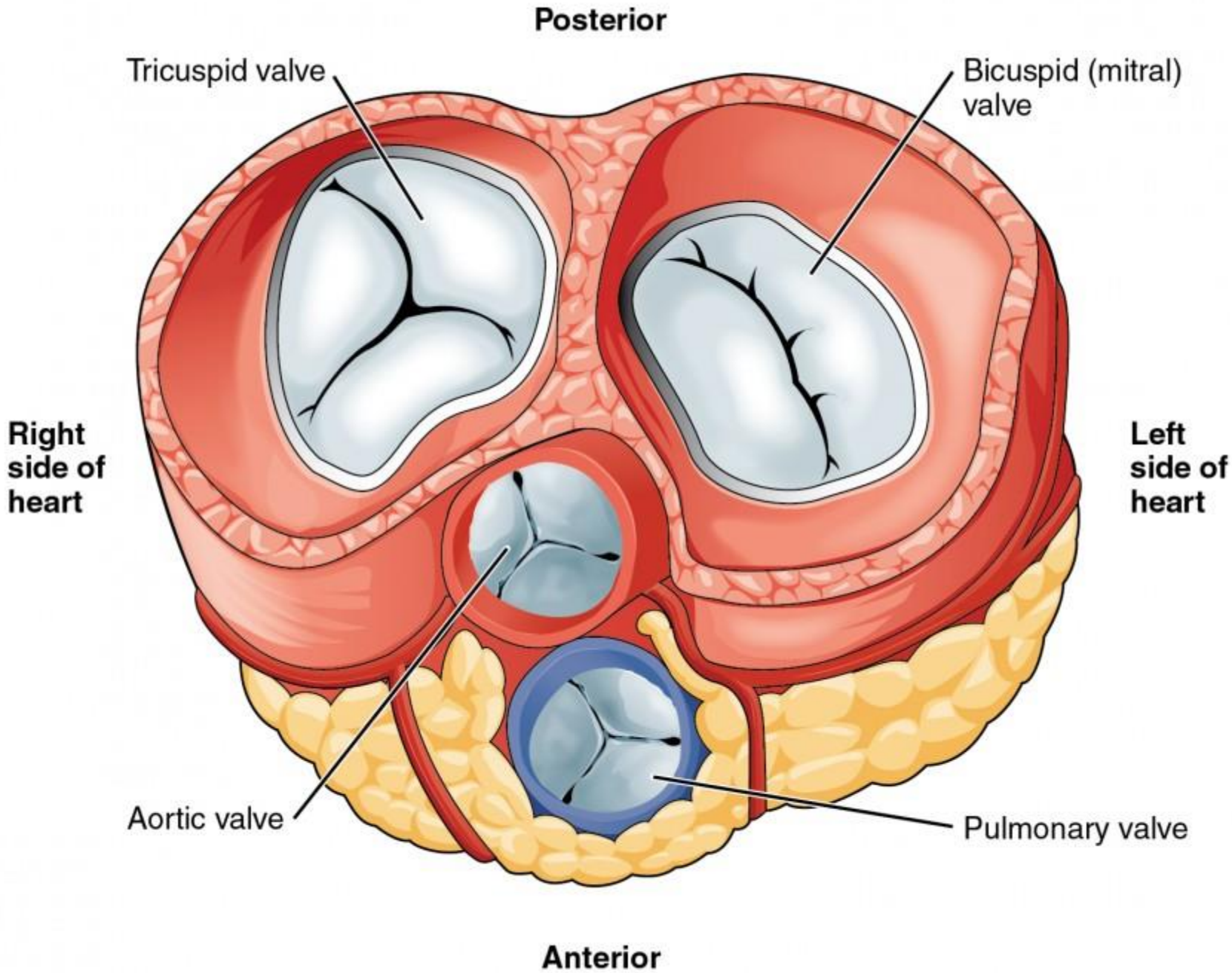
1. The openings between the atria and ventricles.
2. The openings to the pulmonary trunk and to the aorta.
3. Serve as the point of attachment for the heart valves.
4. The cardiac skeleton also provides an important boundary in the heart electrical conduction system.

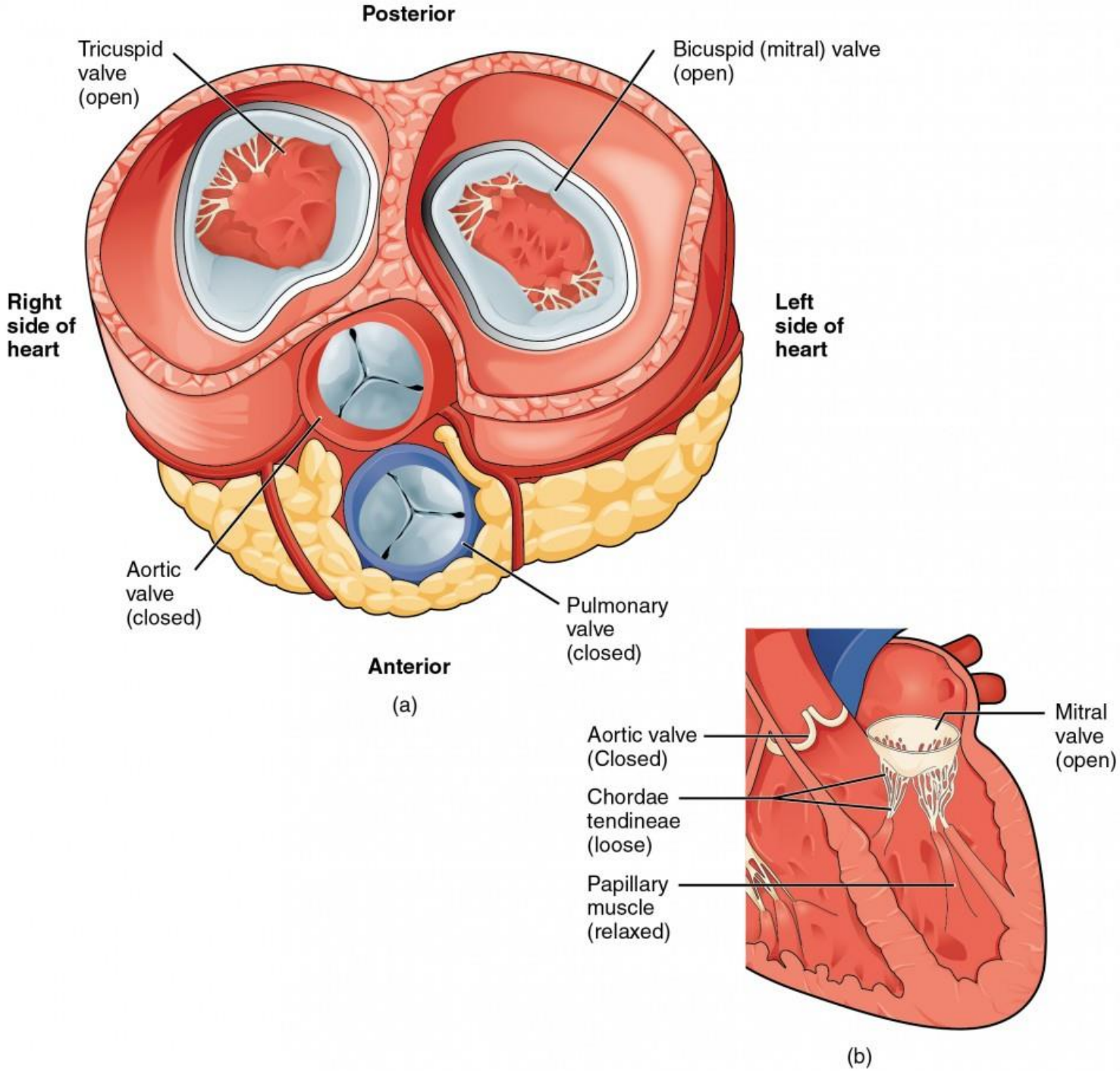
Right Atrium:
Receiving chamber for blood returning from the systemic circulation.
The two major systemic veins, the superior and inferior venae cavae.
The large coronary vein (**coronary sinus).**

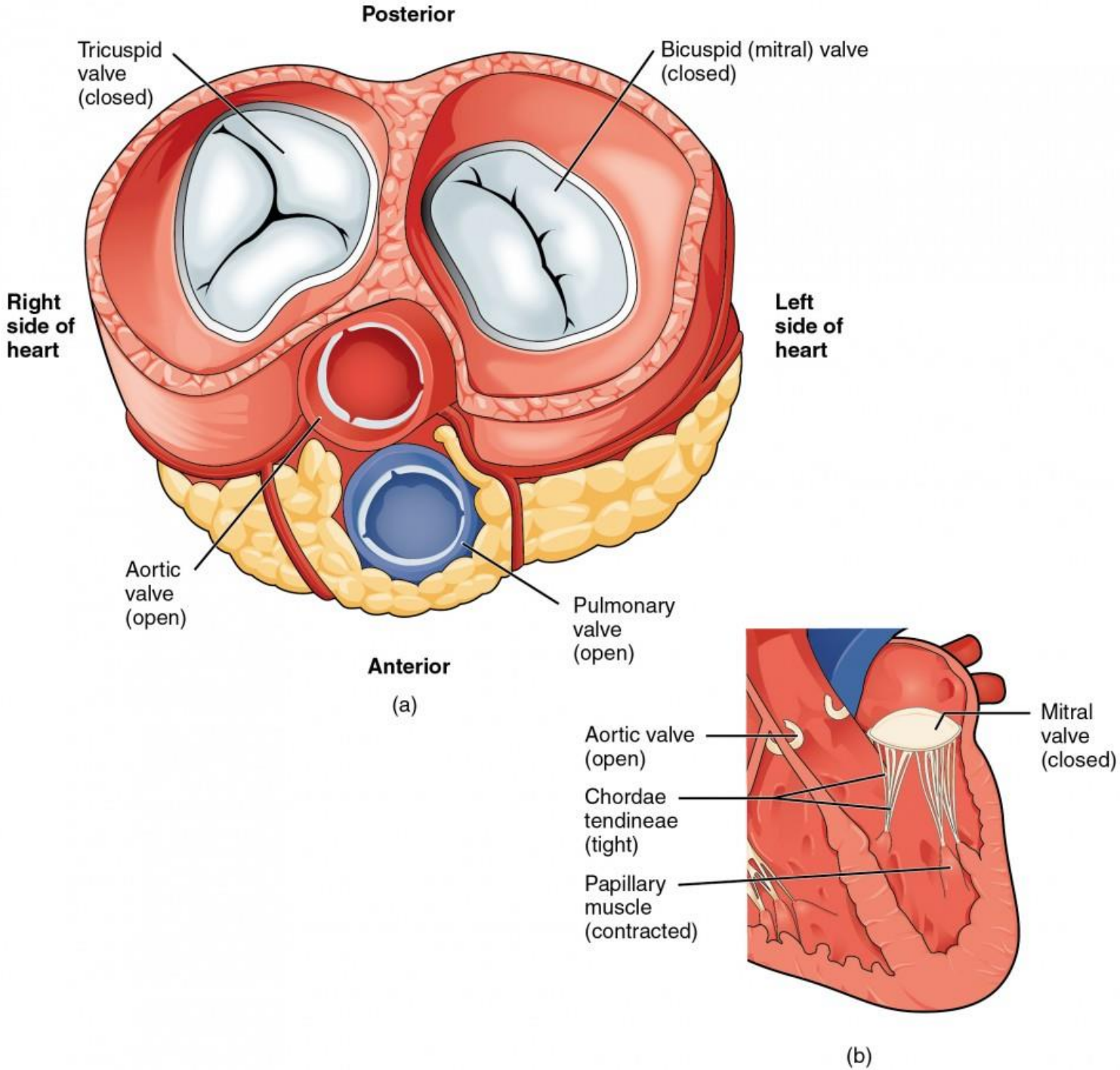
Left atrium:
Receive blood from the fours pulmonary veins on a nearly continuous basis, preventing venous flow from stopping while the ventricles are contracting
Most ventricular filling occurs while the atria are relaxed. Atria contract to actively pump blood into the ventricles just prior to ventricular contraction.

Right Ventricle
The right ventricle receives blood from the right atrium through the tricuspid valve.
During contraction blood flows into the pulmonary trunk.

Left Ventricle:
The major pumping chamber for the systemic circuit. It ejects blood into the aorta through the aortic semilunar valve.


Posterior
Tricuspid valve
Bicuspid (mitral) valve
Right side of heart
Left side of heart
Aortic valve
Pulmonary valve
Anterior


Posterior
Tricuspid valve (open)
Bicuspid (mitral) valve (open)
Right side of heart
Left side of heart
Aortic valve (closed)
Pulmonary valve (closed)
Anterior
(a)
Aortic valve (Closed)
Chordae tendineae (loose)
Papillary muscle (relaxed)
Mitral valve (open)
(b)


Posterior
Tricuspid valve (closed)
Bicuspid (mitral) valve (closed)
Right side of heart
Left side of heart
Aortic valve (open)
Pulmonary valve (open)
Anterior
(a)
Aortic valve (open)
Chordae tendineae (tight)
Papillary muscle (contracted)
Mitral valve (closed)
(b)

Coronary Circulation:

Dedicated, complex, and extensive network of vessel to the heart.

Coronary circulation is not continuous; rather, it cycles, reaching a peak when the heart muscle is relaxed and nearly ceasing while it is contracting.

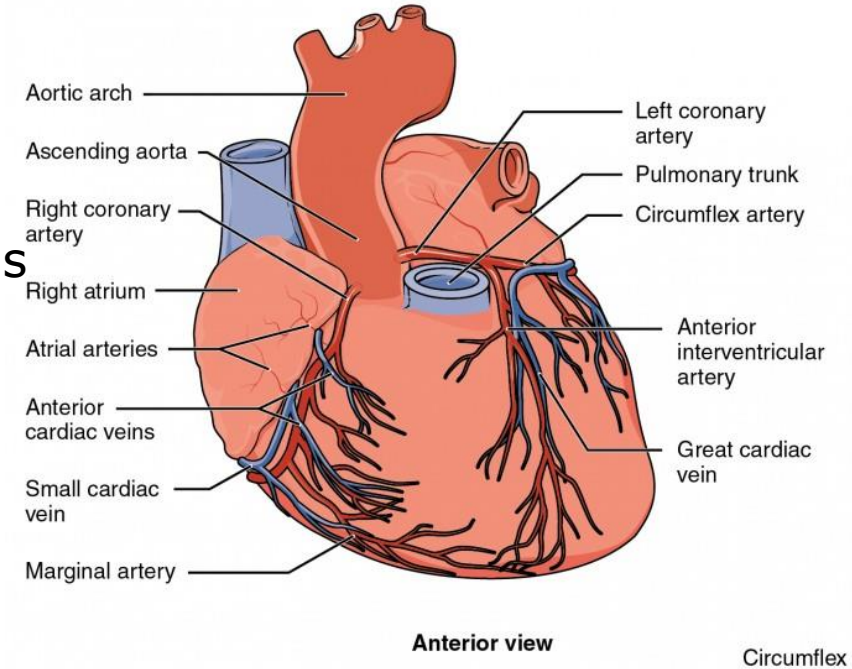
Coronary Arteries

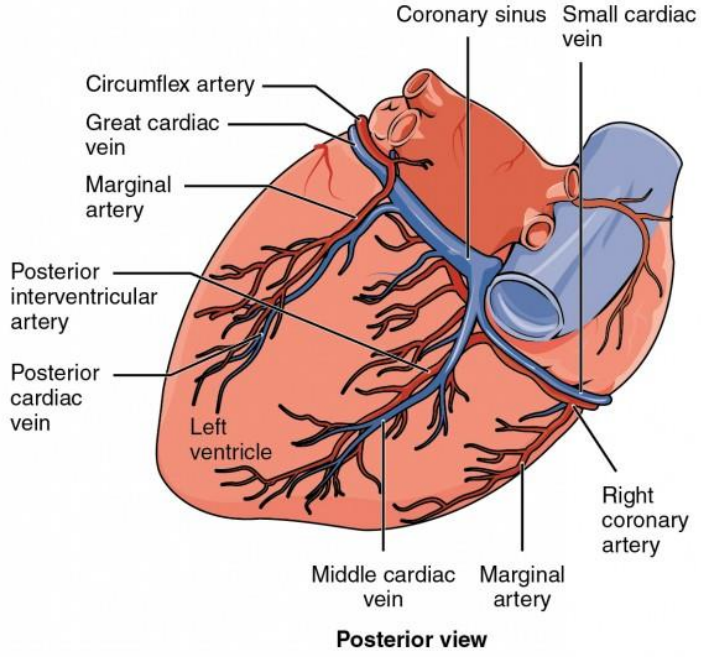
Supply blood to the myocardium and other components of the heart. Emerge from the first portion of the aorta. Coronary vessel branches that remain on the surface of the artery and follow the sulci are called **epicardial coronary arteries**.

The left coronary artery distributes blood to the left side of the heart, the left atrium and ventricle, and the interventricular septum. The **circumflex artery** arises from the left coronary artery and follows the coronary sulcus to the left. Eventually, it will fuse with the small branches of the right coronary artery.

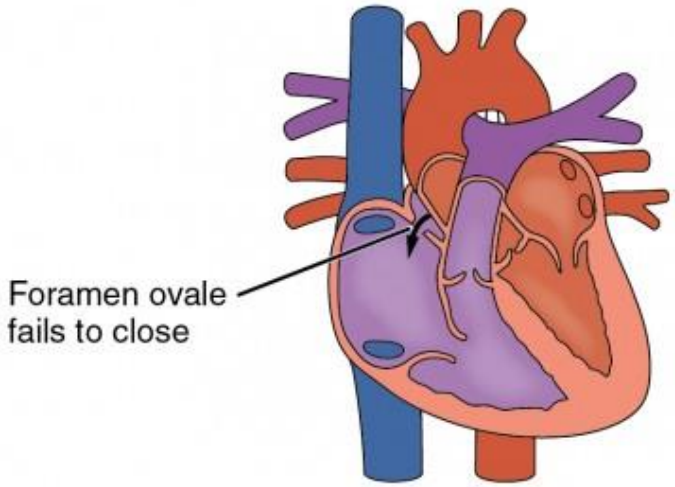
Coronary Veins:

Drain the heart and generally parallel the large surface arteries.

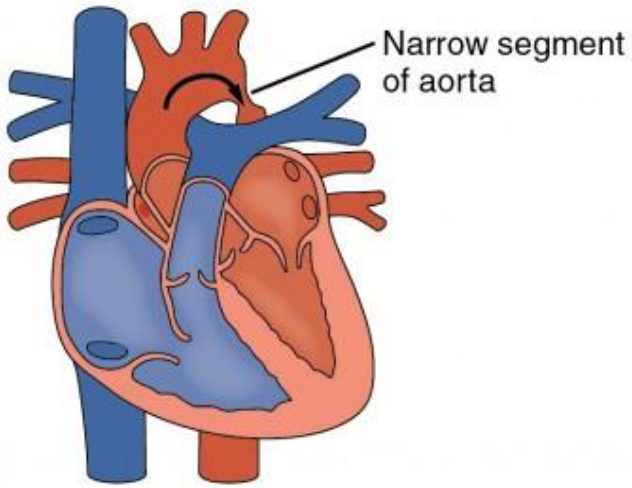




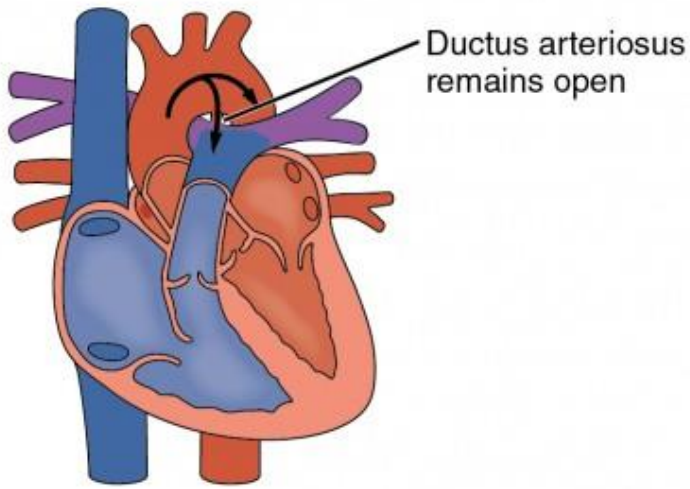
Disorders of the Heart: Heart Defects



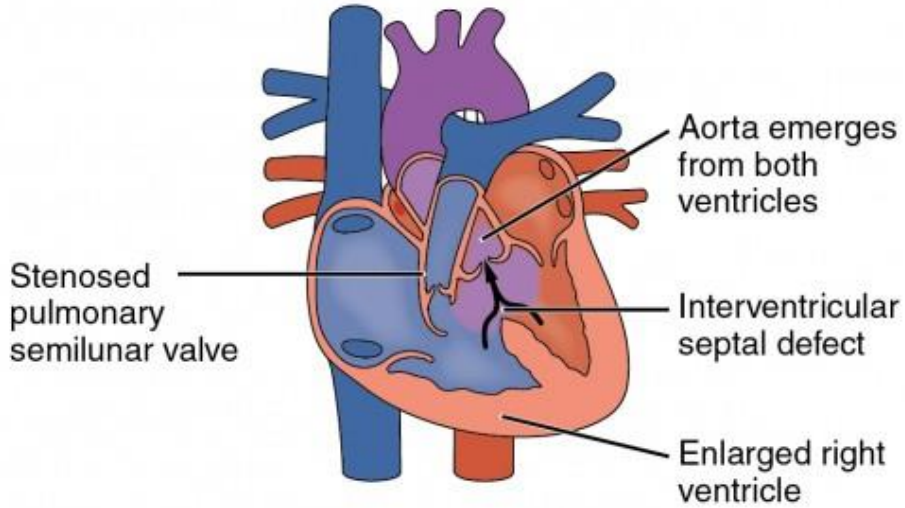
(a) Patent foramen ovale



(b) Coarctation of the aorta



(c) Patent ductus arteriosus



(d) Tetralogy of Fallot

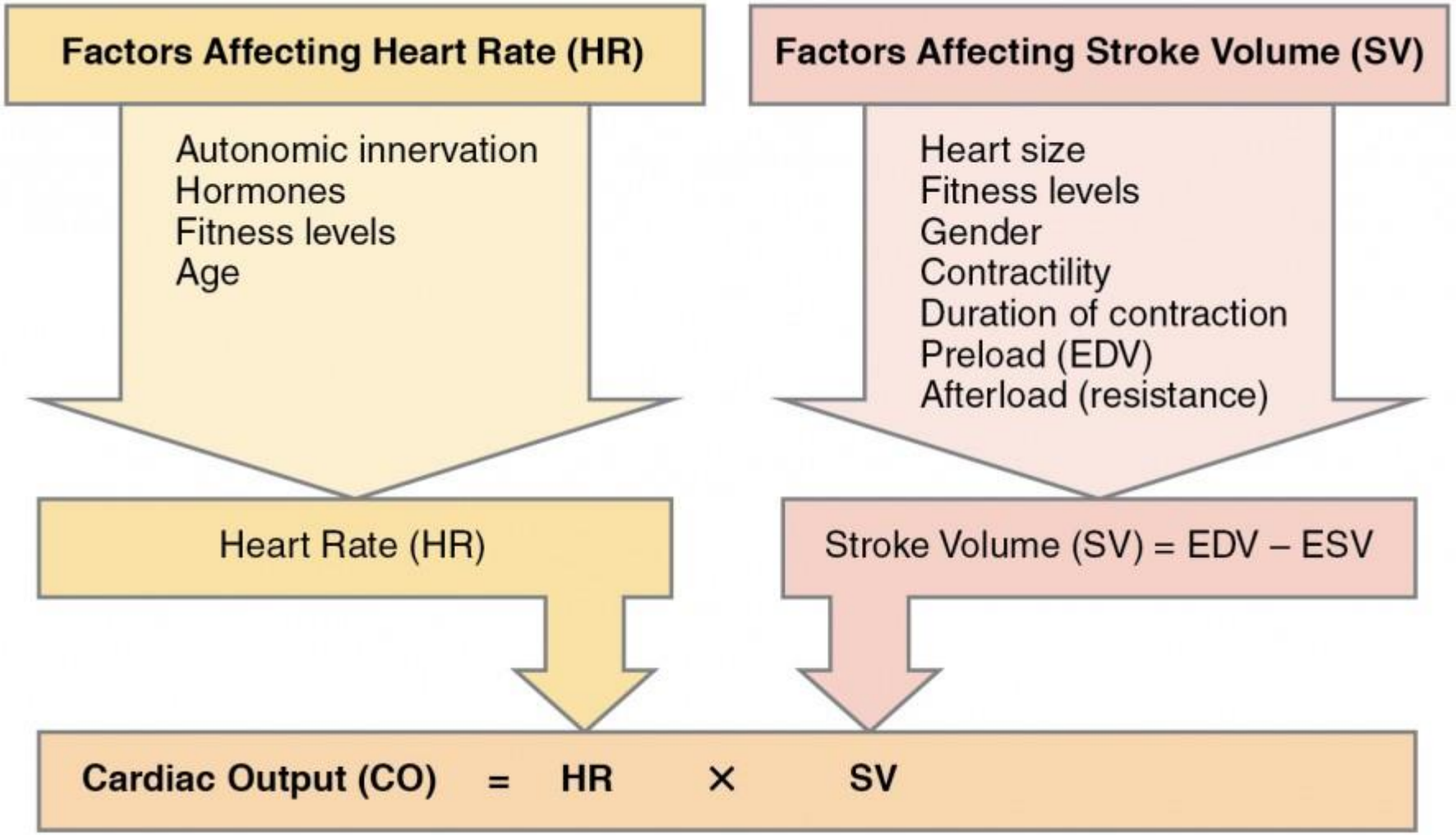
Cardiac Physiology

There is an inherent autorhythmicity in cardiac cells keeping the heart beating.
But heart is regulated by and responds to outside influences as well.
Neural and endocrine controls are vital to the regulation of cardiac function.

Resting Cardiac Output (CO):

- Amount of blood pumped by each ventricle in one minute.
- Stroke volume (SV): amount of blood pumped by each ventricle.
- Heart rate (HR), in contractions per minute (or beats per minute, bpm).
- **CO = HR × SV**

End Diastolic volume (EDV)= filled volume of the ventricle
End Systolic volume (ESV)= residual volume of blood in ventricle after ejection.
SV = EDV – ESV.
SV is about 70 ml for a 70-kg.
Resting HR is about 75 bpm.
CO = 5.25 L/minute for each ventricle separately.
CO is about 18.5L/minute in healthy young exercising. 4–5 fold resting rate.
Cardiac reserve = CO_{max}- $CO_{resting}$



Bradycardia: HR < 60 bpm at rest.
Tachycardia: HR > 100 bpm at rest.

Cardiovascular Centers

Two paired cardiovascular centers of the medulla oblongata.

The cardioaccelerator regions stimulate activity:

Sympathetic stimulation of the cardioaccelerator nerves.

The cardioinhibitory centers decrease heart activity:

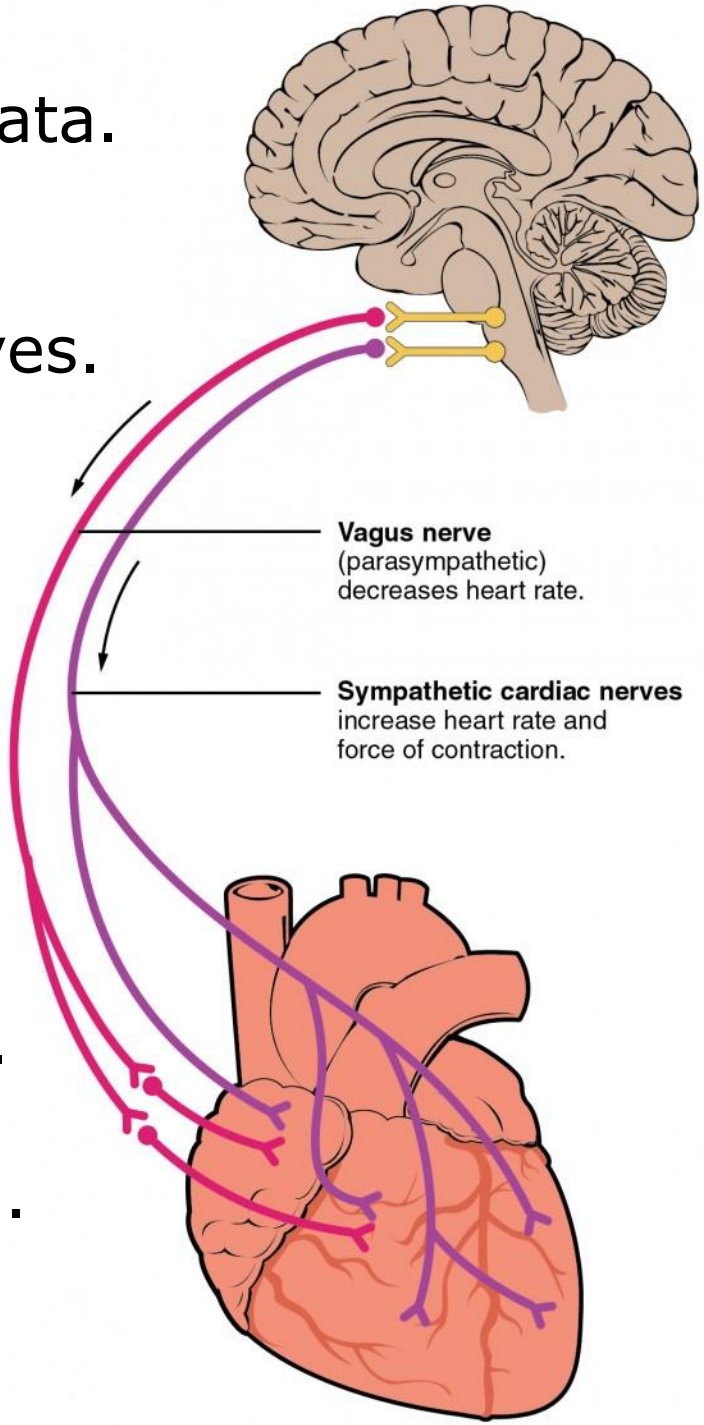
Parasympathetic stimulation

Component of the vagus nerve, cranial nerve X.

During rest, both centers provide slight stimulation to the heart, contributing to **autonomic tone**.

Normally, vagal stimulation predominates (unregulated).

SA node would initiate a sinus rhythm of about 100 bpm.

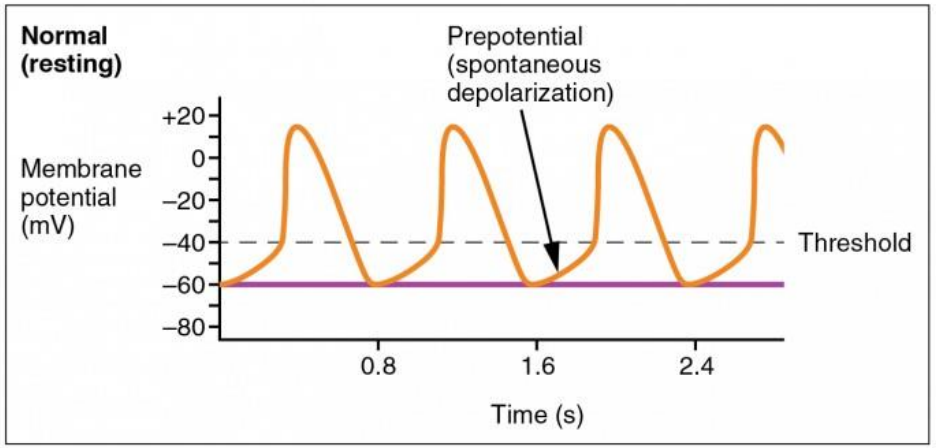


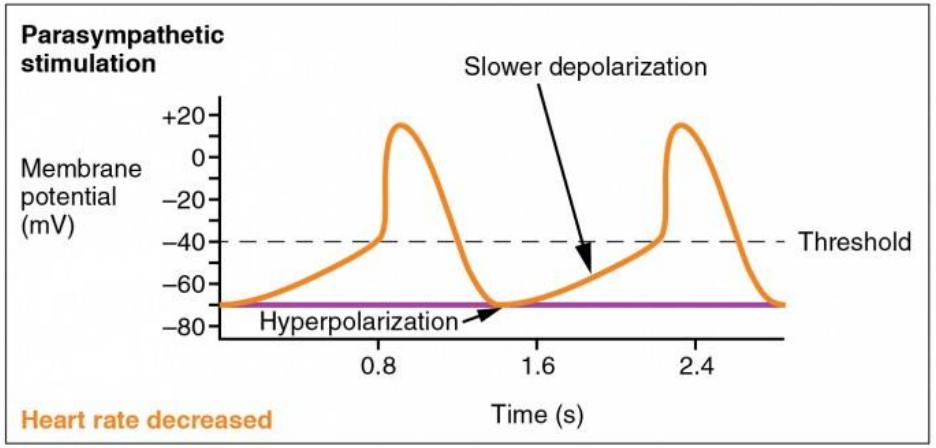
Sympathetic stimulation releases norepinephrine (NE) at the neuromuscular junction of the cardiac nerves.
NE shortens the repolarization period, thus speeding rate of depolarization and contraction to increase HR.

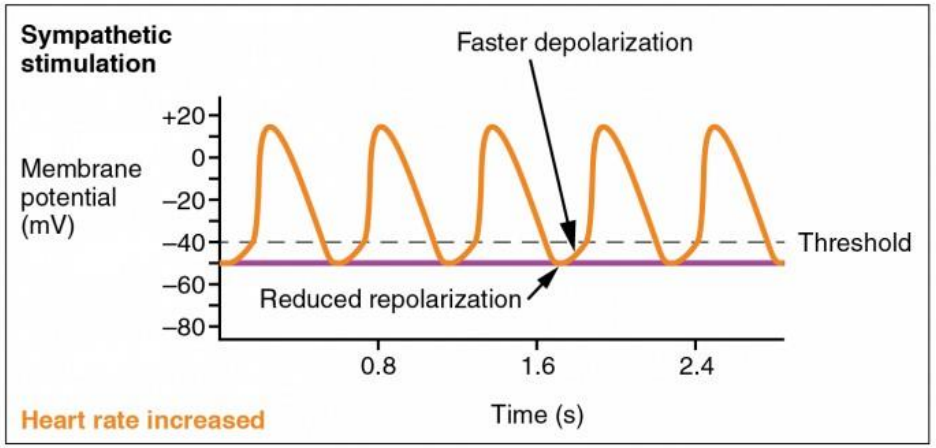
Parasympathetic stimulation releases the neurotransmitter acetylcholine (ACh) at the neuromuscular junction.
ACh slows HR by opening ligand-gated K^+ channels to slow the rate of spontaneous depolarization. By extending repolarization it increases the time before the next spontaneous depolarization occurs.

Without any nervous stimulation, the SA node would establish a sinus rhythm of approximately 100 bpm.
Since HR < 100 bpm it becomes evident that parasympathetic stimulation slows HR.

Decreasing parasympathetic stimulation decreases the release of Ach to increase HR up to approximately 100 bpm.
To increase HR beyond 100 bpm require sympathetic stimulation.







Note that Cardiovascular Center receives information from different places of the body to regulate HR & CO accordingly.

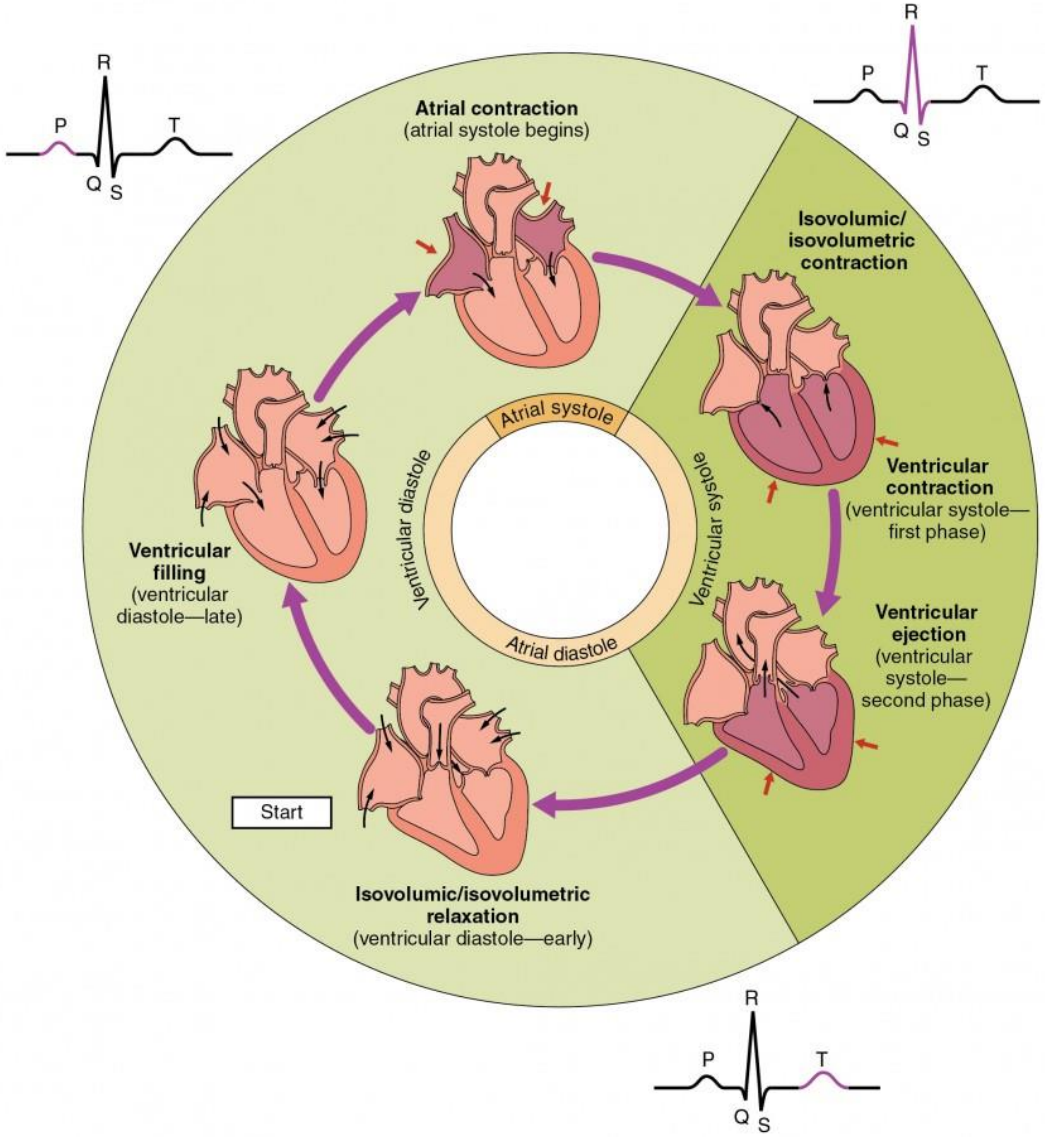
Cardiac Cycle:
Time period from start of Atria contraction and ends with ventricular relaxation.

Systole: period of contraction of the heart while pumping blood into circulation.

Diastole: period of relaxation allowing the chambers to refill with blood.

Both the atria and ventricles undergo systole and diastole.

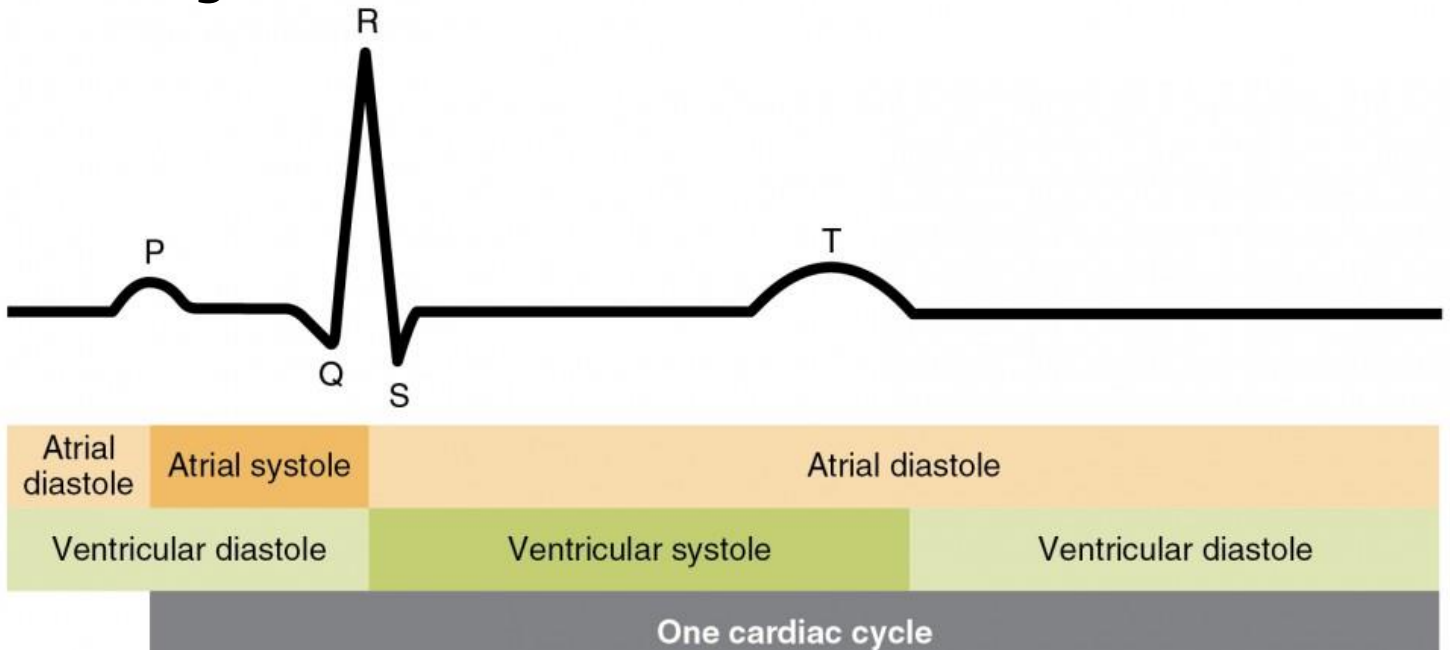
Pressures and Flow
Blood move from area of high to low pressure.
During atria diastole, blood flows in from veins.
Increase in atrial pressure move passively blood in ventricles. Atrial systole pump blood into ventricles.
Ventricular systole pump blood into pulmonary trunk and into the aorta.



At the beginning both the atria and ventricles are in diastole.
Blood is flowing into the atria.
The two atrioventricular valves (tricuspid and mitral valves) are open.
Blood flows from atria into the ventricles (about 70–80 percent of ventricular filling).
The two artery semilunar valves are closed preventing backflow of blood.

Atrial Systole and Diastole

Contraction of the atria follows depolarization (P wave). Atrial muscles contract from the superior portion toward the atrioventricular septum to pump blood into ventricles through the open atrioventricular (tricuspid, and mitral) valves. Atrial systole (100 ms) complete the filling of the ventricles and atrial muscle returns to diastole.



Ventricular Systole total of 270 ms.
Follows the depolarization of the ventricles (QRS).
At the end of atrial systole ventricles contain approximately 130 mL (**end diastolic**

Volume (EDV) or **preload)**.
As ventricle contract, the pressure rises, but not yet high enough to open pulmonary and aortic valves.
However, blood pressure quickly rises above that of the atria (in diastole), blood tries to flow back toward the atria, closing the tricuspid and mitral valves (**isovolumic contraction phase)**.

In the second phase of ventricular systole, the **ventricular ejection phase**, the contraction of the ventricular muscle has raised the pressure above the pressures in the pulmonary trunk and the aorta. Blood is pumped from the heart, pushing open the pulmonary and aortic semilunar valves.
Although pressure generated by left ventricle > pressure generated by right ventricle, both ventricles pump the same volume of blood (stroke volume).

Ventricular Diastole 430 ms.
Follows repolarization of the ventricles (T wave).
During the early phase of ventricular diastole, as the ventricular muscle relaxes, pressure begins to fall and when below pressure in both the pulmonary trunk and aorta, blood flows back toward the heart closing semilunar valves (**isovolumic ventricular relaxation phase).**

In the late ventricular diastole, as the ventricular muscle relaxes, pressure on the blood within the ventricles drops even further below the pressure in the atria opening the tricuspid and mitral valves.
As pressure drops in ventricles, blood flows from the major veins into the relaxed atria and from there into the ventricles.
Both chambers are in diastole, the atrioventricular valves are open, and the semilunar valves remain closed.
The cardiac cycle is complete.

Cardiac Muscle and Electrical Activity:

Autorhythmicity: Unique property of cardiac muscle cells to initiate electrical potential at a fixed rate spreading from cell to cell to trigger the contraction.

Myocardial contractile cells representing 99 % atrial and ventricular cells.

- Conduct impulses for contractions that pump blood through the body.

Myocardial conducting cells representing 1% of the cells.

- Form the conduction system of the heart.
- Except for Purkinje cells, they are much smaller than the contractile cell
- Have few of the myofibrils needed for contraction.
- Function similar to neurons, although they are specialized muscle cells.
- Initiate and propagate the action potential that travels throughout the heart and triggers the contractions that propel the blood.

Structure of Cardiac Muscle

Cardiomyocytes have striations, alternating pattern A bands and light I bands (arrangement of the sarcomeres).

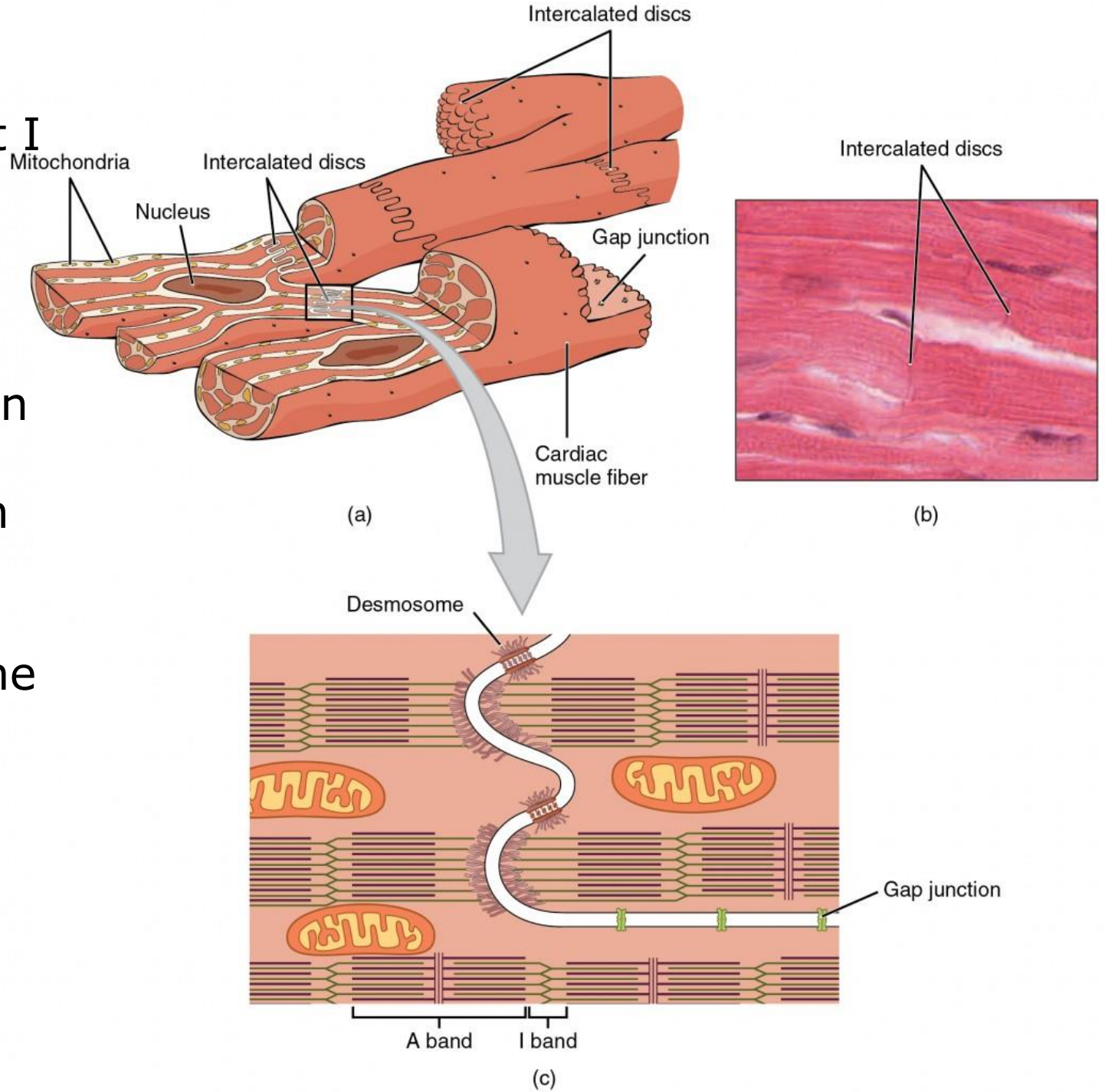
Cardiac muscle cells branch freely.

Intercalated disc forms the junction between two adjoining cells which support the synchronized contraction of the muscle.

Large numbers of gap junctions that allow the passage of ions between the cells for synchronize the contraction.

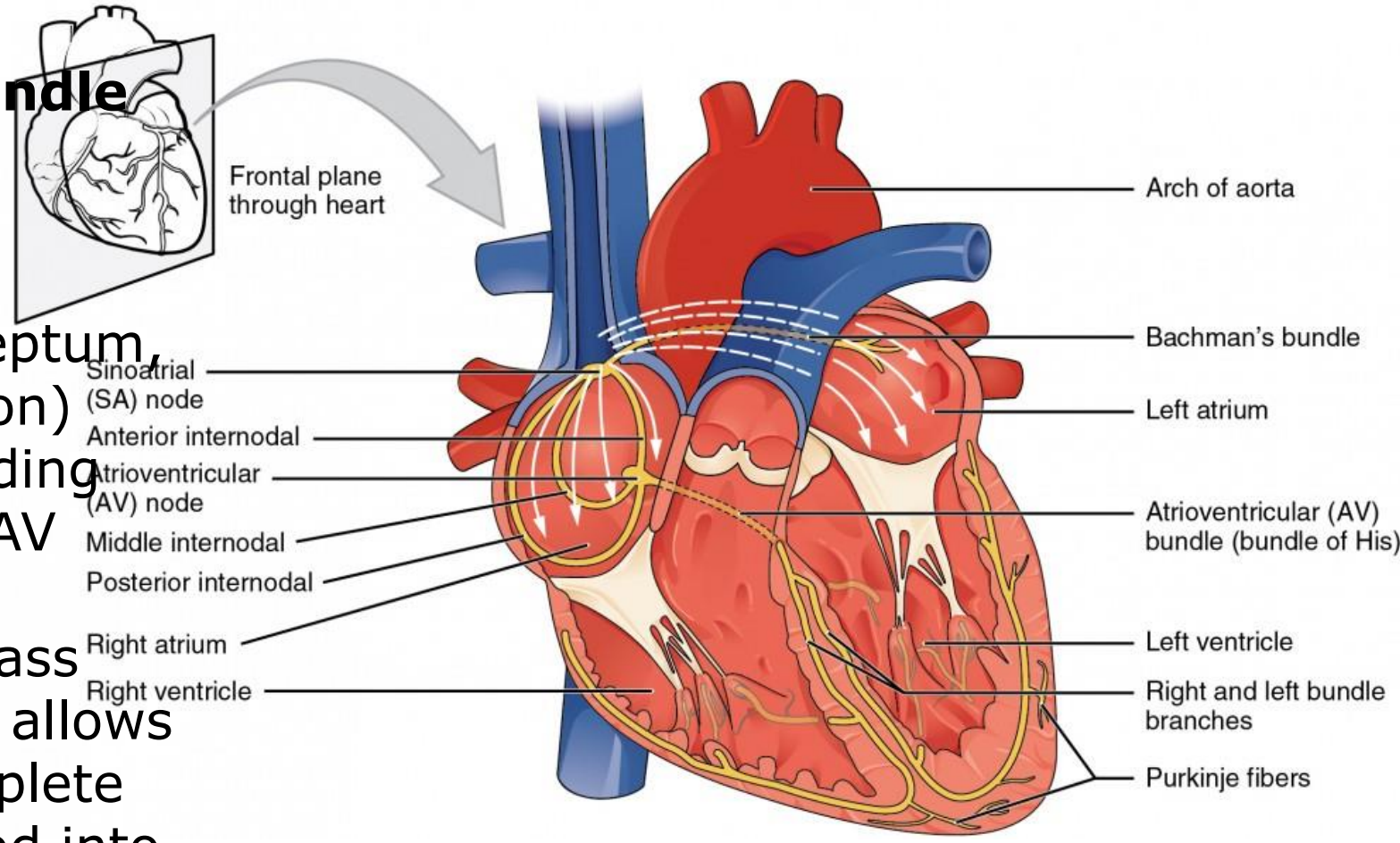
Aerobic metabolism of lipids and carbohydrates.

Myoglobin, lipids, and glycogen are all stored within the cytoplasm.



Cardiac Muscle and Electrical Activity: The cardiac conduction system include: The sinoatrial (SA) node: P**acemaker**. This impulse spreads from the SA node throughout the atria via the **internodal pathways**, to the atrial myocardial contractile cells and the atrioventricular (AV) node.
The impulse takes 50 ms to travel between these two nodes.
In addition, the **Bachmann's bundle** conducts the impulse directly from the right toleft atrium.

As the impulse reaches the AV septum, connective tissue (cardiac skeleton) prevents the impulse from spreading into the ventricles except at the AV node.
It takes the impulse 100 ms to pass through the AV node. This pause allows the atrial cardiomyocytes to complete their contraction that pumps blood into the ventricles.



Purkinje fibers initiate ventricular depolarization

Membrane Potentials and Ion Movement in Cardiac Conductive Cells

Action potentials are different between cardiac conductive cells and cardiac contractive cells.

While Na^+ and K^+ play essential roles, Ca^{2+} is also critical for both types of cells.

Cardiac conductive cells do not have a stable resting potential.

Conductive cells have Na^+ channels that allow a slow Na^+ influx rising membrane potential from an initial −60 mV to –40 mV generating **spontaneous depolarization**.

At this point, Ca^{2+} channels open and Ca^{2+} enters the cell, depolarization rapid to+5 mV. Ca^{2+} channels close.

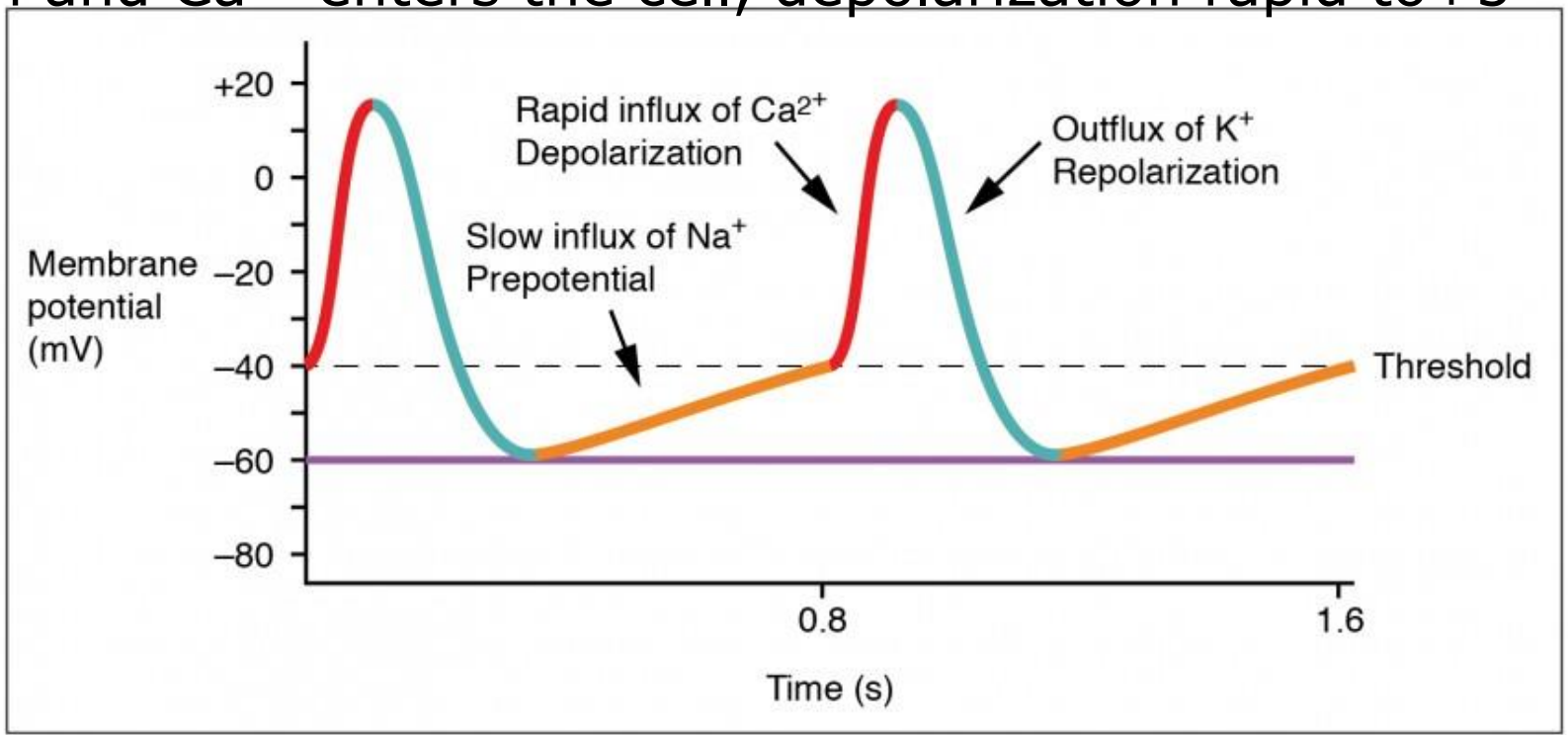
K^+ channels open, outflux of K^+.

Repolarizationto −60 mV.

K^+ channels close and

Na^+ channels open to repeat

The cycle.

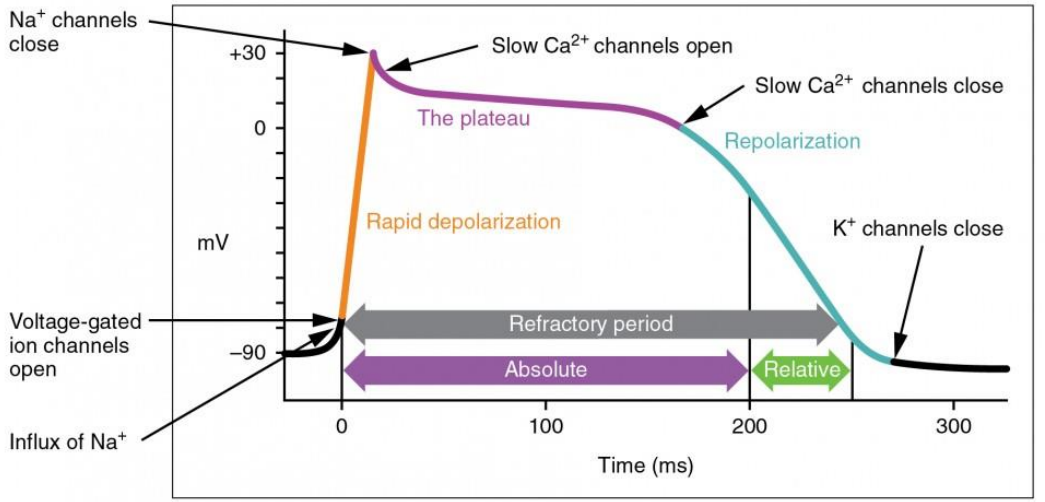


Membrane Potentials and Ion Movement in Cardiac Contractile Cells:

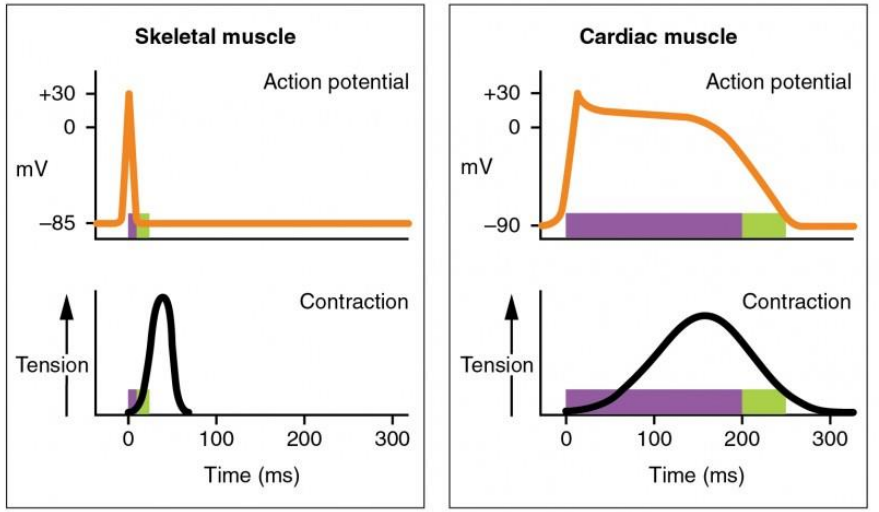
A rapid depolarization is followed by a plateau phase and then repolarization. The plateau phase causes the long refractory periods required for the full contraction of cardiac muscle cells to pump blood effectively before firing for a second time.

Contractile cardiac myocytes normally do not initiate their own electrical potential, although they are capable of doing so, but rather wait for an impulse to reach them.

Contractile cells demonstrate a much more stable resting phase than conductive cells at approximately −80 mV for cells in the atria and −90 mV for cells in the ventricles.



(a)



(b)

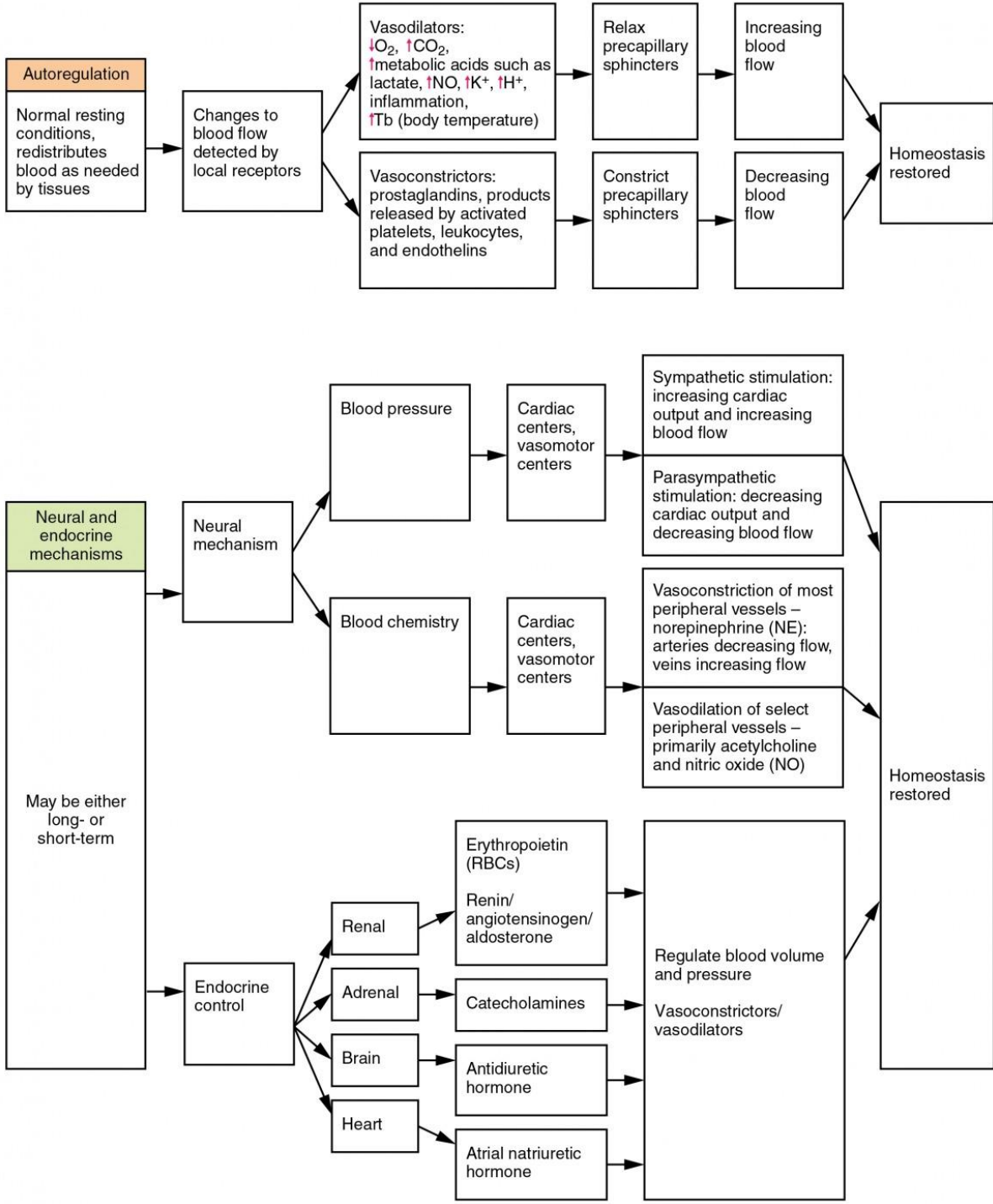
Homeostatic Regulation of the Vascular System

Blood flow must be redirected continually to the more active tissues because there is not enough blood flow to distribute blood equally to all tissues simultaneously.

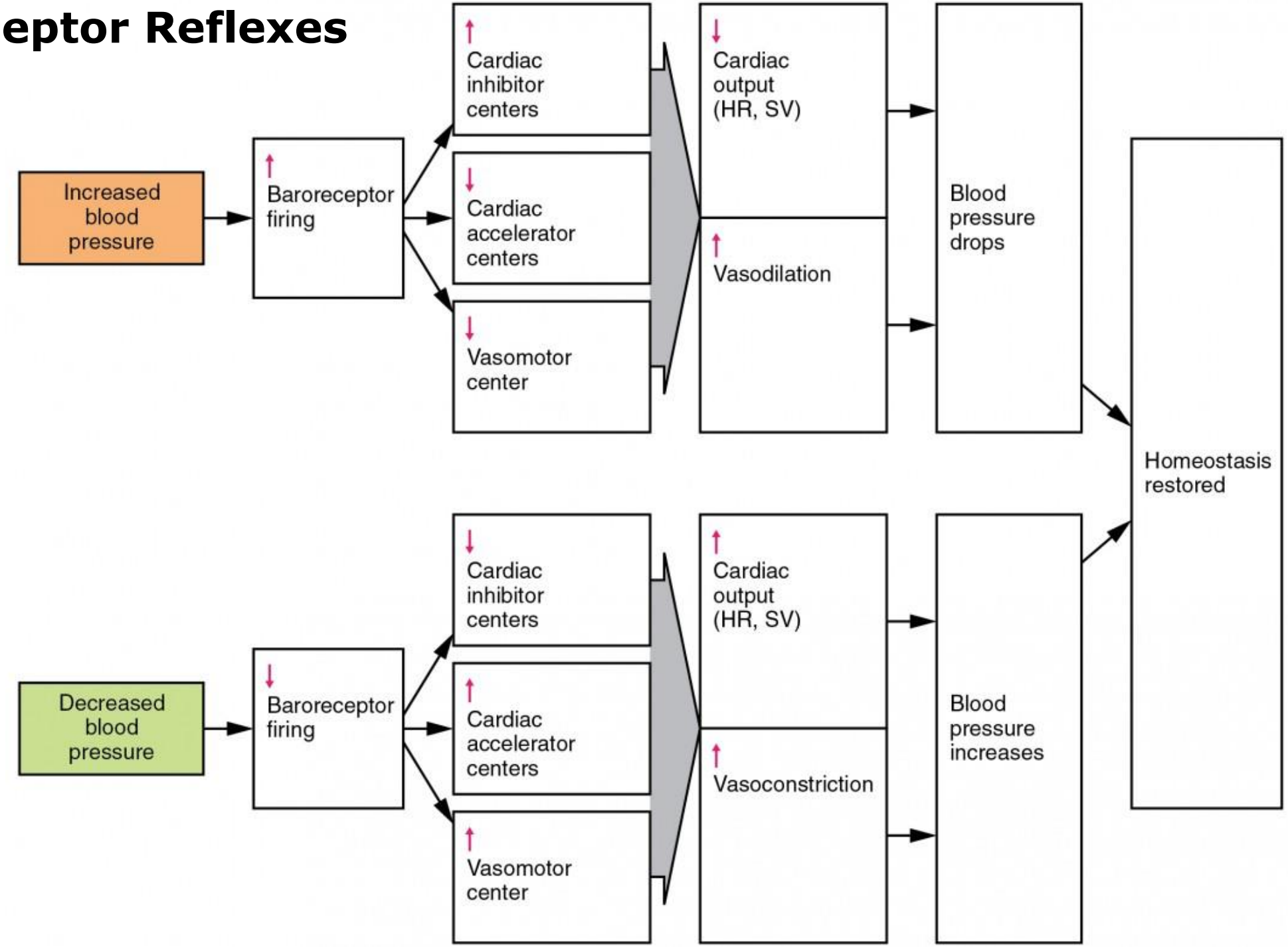
Table 1. Systemic Blood Flow During Rest, Mild Exercise, and Maximal Exercise in a Healthy Young Individual

Organ	Resting (mL/min)	Mild exercise (mL/min)	Maximal exercise (mL/min)
Skeletal muscle	1200	4500	12,500
Heart	250	350	750
Brain	750	750	750
Integument	500	1500	1900
Kidney	1100	900	600
Gastrointestinal	1400	1100	600
Others (i.e., liver, spleen)	600	400	400
Total	5800	9500	17,500

The Cardiovascular Centers in the Brain

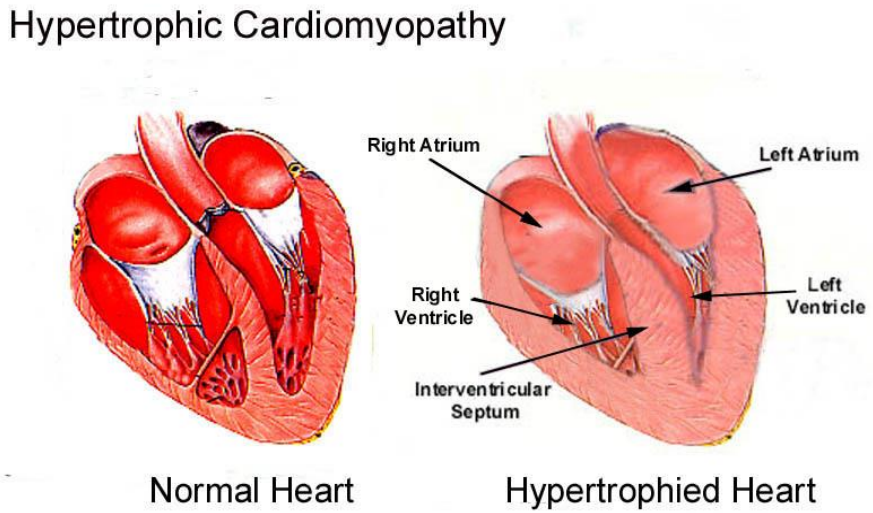


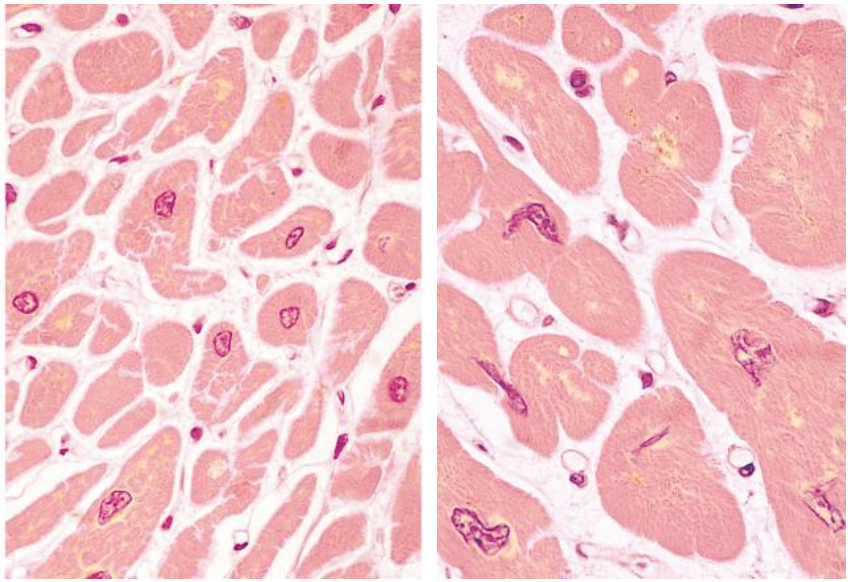
Baroreceptor Reflexes



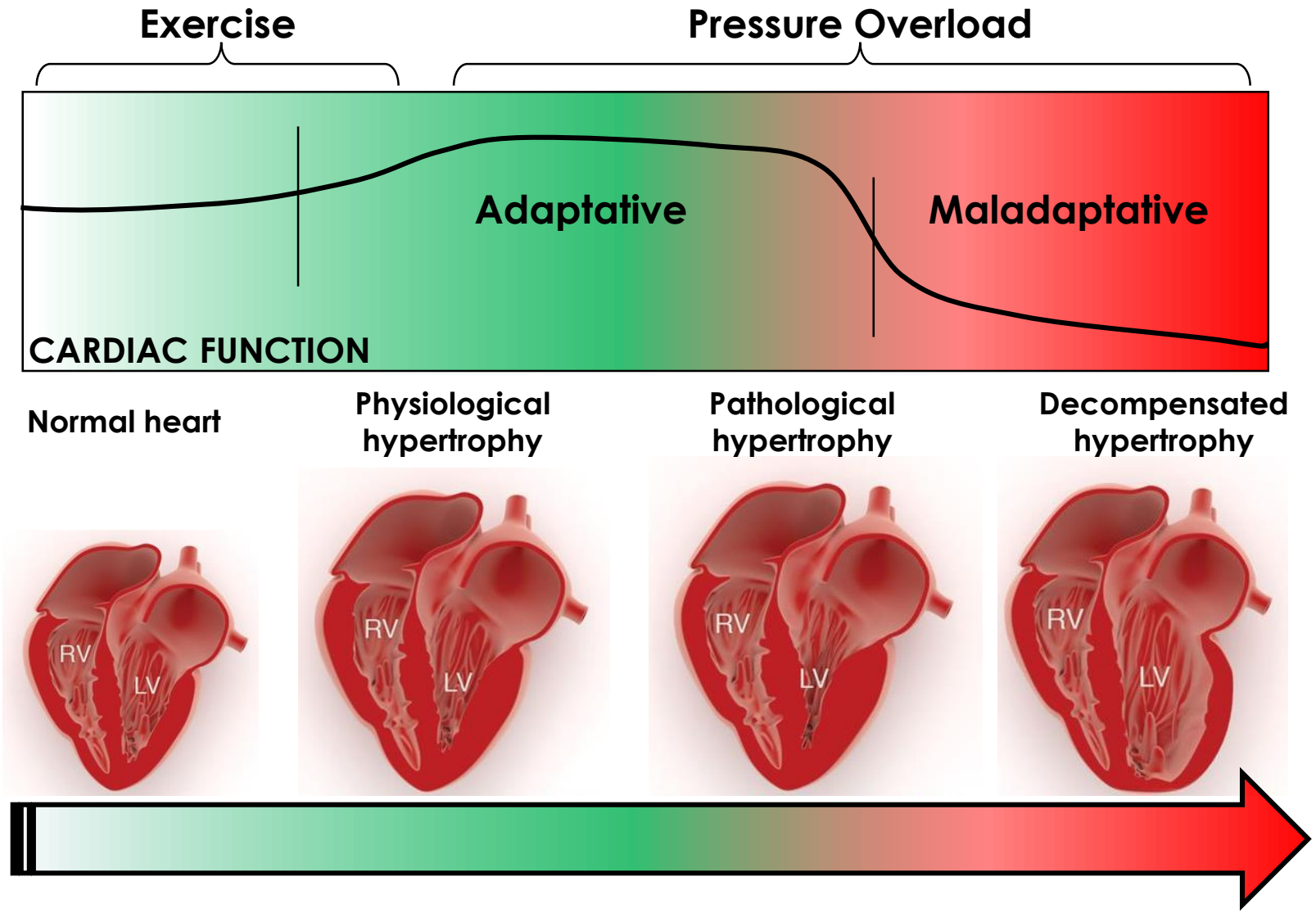
Hypertrophy

- Can be pathologic (hypertrophy of myocardium – hypertension/aortic valve disease





Normal heart Hypertrophic heart


Exercise
Pressure Overload
Adaptative
Maladaptative
CARDIAC FUNCTION
Normal heart
Physiological hypertrophy
Pathological hypertrophy
Decompensated hypertrophy
RV
LV
RV
LV
RV
LV
RV
LV

Pathological cardiac hypertrophy and heart failure are closely linked

- Heart failure occurs when the heart is unable to pump sufficiently to maintain blood flow to meet the body's needs

- It is triggered by various pathological stimuli, including hypertension, heart stroke, ischemia due to coronary heart disease, valve insufficiency or stenosis, myocarditis, congenital defects

- First, myocardial hypertrophy occurs: myocytes growth in size trying to compensate pump function and diminish ventricular wall tension

- Muscle growth is not accompanied by formation of new capillaries, thus O_2 and nutrients supply is insufficient to sustain myocardium function. Muscle mass increases, but cardiomyocyte are disorganized and fibrosis develops

- Thus, hypertrophic heart is weaker than normal heart