

Cardiovascular and Respiratory Systems

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1 Introduction

The cardiovascular and respiratory systems are closely related due to their interdependent functions, working together to ensure the body's oxygenation and circulation. The respiratory system facilitates the exchange of oxygen and carbon dioxide in the lungs, while the cardiovascular system carries oxygen-rich blood from the lungs to various organs and tissues. The oxygenated blood is then delivered to the cells, where it participates in cellular respiration, generating energy and carbon dioxide, which is then transported back to the lungs by the cardiovascular system for elimination. In this handout, we'll discuss both systems separately, but remember that they work together as all other systems do to support human life.

2 Cardiovascular System

2.1 Circulatory Systems Across Species

In some species with simple body plans, a circulatory system is not necessary as diffusion allows for the efficient exchange of gases. These organisms, such as cnidarians (e.g., jellyfish and corals) and flatworms (e.g., planarians), have lower metabolic rates and smaller sizes that create shorter traveling distances for gases and nutrients, which can then diffuse directly through their thin body walls.

- Many of these species have a central **gastrovascular cavity** filled with fluid and surrounded by a thin wall. This aids in gas exchange as well as digestive function.

However, as organisms become larger and more complex, the distances over which diffusion would need to occur become too great for it to be an effective method of transportation. Hence, a **circulatory system**—composed of a heart, interconnected vessels, and circulatory fluid—is necessary.

- In an **open circulatory system**, the circulatory fluid, called **hemolymph**, is also the interstitial fluid that fills the spaces between body cells. It is pumped by the heart from circulatory vessels into the sinuses surrounding the organs.
- In a **closed circulatory system**, the circulatory fluid called **blood** is only found in the vessels and is distinct from the interstitial fluid.

In vertebrates, the heart and blood vessels are usually referred to as the cardiovascular system.

- Rays, sharks, and bony fish have a **single circulatory system**, in which blood flows through the heart once in each complete circuit of the body.
- Amphibians, reptiles, birds, and mammals generally have a **double circulatory system**, in which the heart has two separate pumping chambers: one for pumping oxygen-poor blood to the lungs or gills (i.e., the pulmonary circuit) and the other for pumping oxygen-rich blood to the rest of the body (i.e., the systemic circuit).

From this point on, this section of the handout will focus primarily on the human cardiovascular system.

2.2 Circulation

The human heart is divided into two halves with each containing its own **atrium** (i.e., upper chamber) and **ventricle** (i.e., lower chamber).

- **Pulmonary circulation** begins in the right ventricle, connects to pulmonary capillaries in the lungs, and is then terminated in the left atrium.
- **Systemic circulation** begins in the left ventricle, connects to all peripheral organs and tissues, and is finally terminated in the right atrium.

Arteries carry blood away from the heart, and **veins** carry blood toward the heart.

- Arteries leaving the heart branch into **arterioles**.
- Arterioles branch into billions of **capillaries**, which form networks called **capillary beds**.
- Capillaries unite to form **venules**.
- Venules unite to form **veins** on the way back to the heart.

In systemic circulation, the large artery leaving the left ventricle is the **aorta**, and the large veins emptying into the right atrium are the **superior vena cava** and **inferior vena cava**.

In pulmonary circulation, the large artery leaving the right ventricle is the **pulmonary trunk** (leading to the pulmonary arteries), and the veins entering the left atrium are the four pulmonary veins.

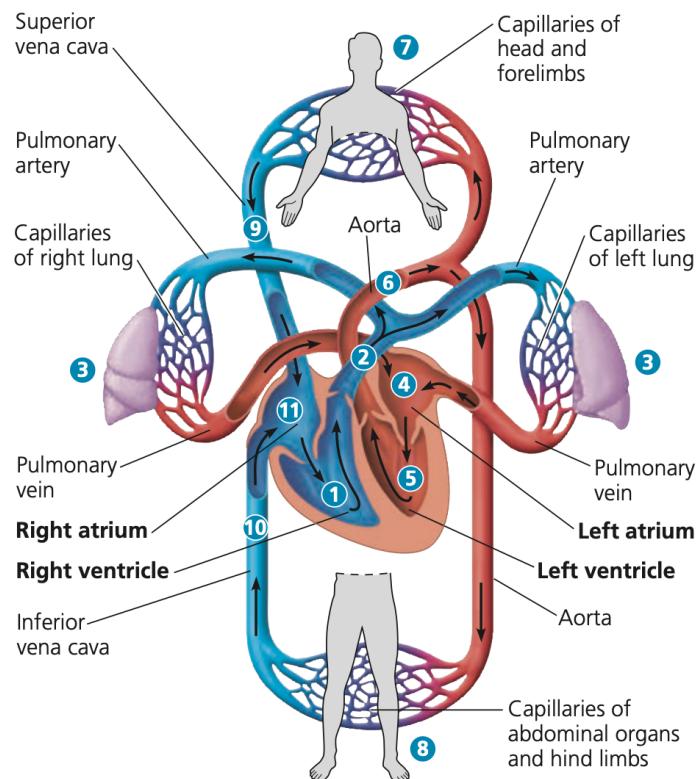


Figure 1: Overview of mammalian circulation. Red represents oxygenated blood being transported to the organs while blue represents deoxygenated blood heading back to the heart.
(Source: Campbell's Biology 11th Edition)

2.3 The Heart

2.3.1 Heart Anatomy

- The heart is surrounded by a double-layered membrane called the **pericardium**. The outer layer is fibrous, while the inner layer is serous.
- The heart wall consists of three layers: the **epicardium** (i.e., outer layer), the **myocardium** (i.e., middle layer composed of cardiac muscle), and the **endocardium** (i.e., inner layer that lines the chambers and valves).
- The **coronary sulcus** and **interventricular sulci** are grooves on the surface of the heart that separate the chambers. The **coronary sulcus** separates the atria from the ventricles, while the **anterior** and **posterior interventricular sulci** divide the ventricles.
- The heart is divided into left and right sides by a muscular wall called the **septum**. The **interatrial septum** separates the atria, and the **interventricular septum** separates the ventricles.
- The heart has four valves that ensure blood flows in one direction.
 - The **atrioventricular (AV) valves** are located between the atria and ventricles.
 - The **right AV valve** is called the **tricuspid valve** and has three flaps.
 - The **left AV valve** is called the **bicuspid or mitral valve** and has two flaps.
 - The **semilunar valves** are located at the exits of the ventricles.
 - The **pulmonary semilunar valve** regulates the entrance to the pulmonary artery.
 - The **aortic semilunar valve** regulates the entrance to the aorta.

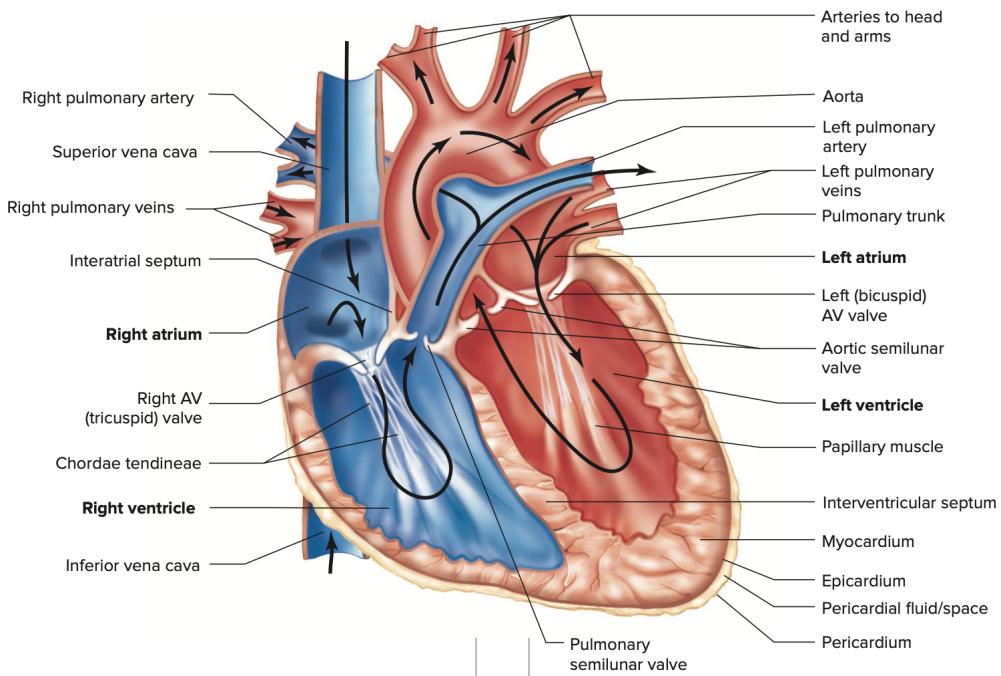


Figure 2: Diagrammatic section of the heart. The arrows indicate the direction of blood flow. (Source: Vander's Human Physiology)

- The heart has a specialized conduction system that coordinates the electrical signals to regulate the heartbeat. It includes the sinoatrial (SA) node, atrioventricular (AV) node, bundle of His, and Purkinje fibers.

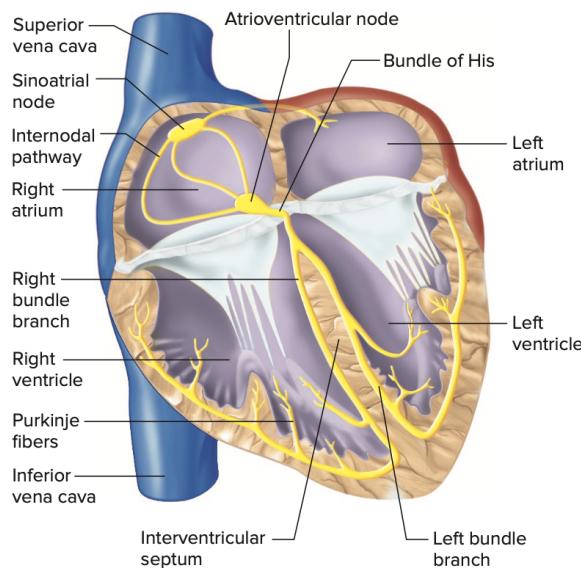


Figure 3: Conducting system of the heart (shown in yellow).
(Source: Vander's Human Physiology)

2.3.2 Heartbeat Coordination through Electrical Conduction

The coordination of cardiac muscle contraction in the heart (atria first, then ventricles) is mediated by the **sinoatrial (SA) node**—a group of conducting cells in the right atrium also known as the pacemaker. The initial depolarization / excitation (i.e., action potential) in the SA node eventually results in the excitation of all cardiac cells, as gap junctions allow action potentials to spread. Therefore, the periodic depolarization of the SA node and subsequent contraction determines the pace of the heart.

The generation of electrical impulses in the SA node involves the interplay of different ion channels that allow for controlled changes in the cell's membrane potential.

- Cells in the SA node have a resting membrane potential, which means they have an electrical charge difference across their cell membranes.
- After the previous heartbeat, the cell membrane is polarized with a negative charge inside and a positive charge outside. This is caused by a steady efflux of K^+ out of the cell.
- The SA node gradually depolarizes in what is called the pacemaker potential through the following ion channel mechanisms:
 - K^+ channels gradually close.
 - Since the SA node is polarized and has a negative membrane potential, voltage-gated **F-type Na^+ Channels (HNC channels)** open and conduct an inward Na^+ current.
 - T-type Ca^{2+} channels** (i.e., transient) briefly open to aid depolarization with an inward Ca^{2+} current.

- Once the threshold is reached, **L-type Ca^{2+} channels** open to allow for an action potential. These Ca^{2+} currents depolarize the membrane slowly and explain the slow movement of potential through nodal cells.
- Finally, the previously opened channels close, and K^+ channels open. The membrane is repolarized and the negative membrane potential again activates the pacemaker mechanisms. The cycle repeats.

Following the generation of an action potential in the SA node, it travels through a conduction system that coordinates muscle contraction.

- The action potential generated by the **SA node** in the right atrium first spreads to the left atrium through gap junctions between cells. Conduction is rapid enough that the right and left atria contract at essentially the same time.
- From the atria, the **atrioventricular (AV) node** allows for the propagation of action potentials towards the ventricles through internodal pathways. This propagation is relatively slow and allows the atria to complete contraction before the ventricles depolarize.
- The action potential propagates down the interventricular septum, which is located between the left and right ventricles, through conducting fibers called the **bundle of His** or **atrioventricular bundle**.
- The bundle of His divides into **Purkinje fibers** that further propagate action potentials up into the ventricles.

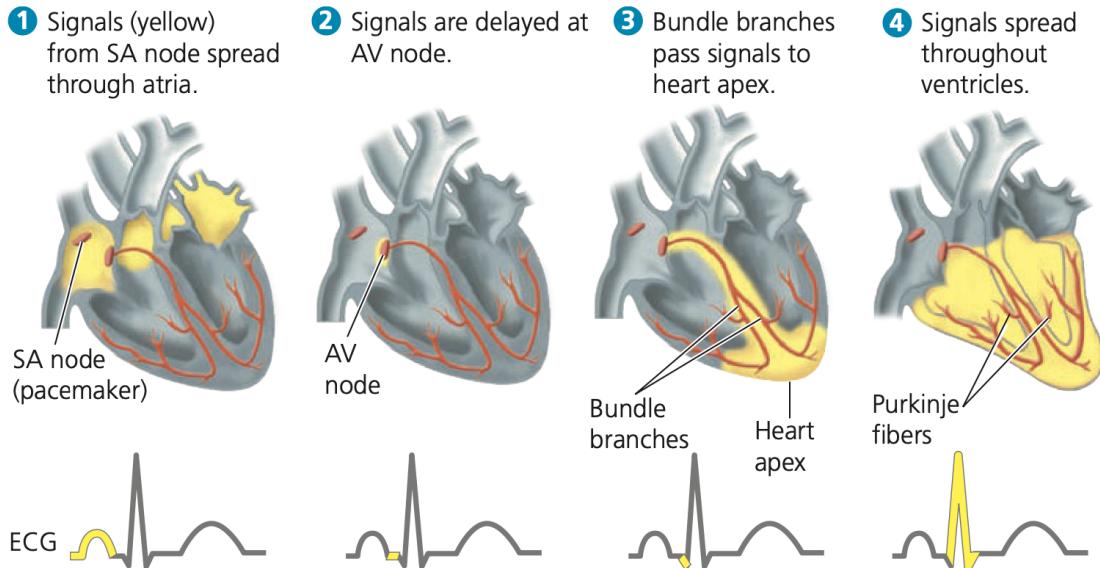


Figure 4: Electrical signals follow a set path through the heart in establishing the heart rhythm. The images display the propagation of action potentials by the SA node, AV node, bundle of His, and Purkinje fibers (from left to right). The corresponding ECG waves will be discussed in the following subsection. (Source: Campbell's Biology 11th Edition)

The cardiac electrical conduction system leads to muscle contraction through **cross-bridge cycling**. It involves the interaction between the proteins actin and myosin within the myocardial

(i.e., cardiac muscle) cells, leading to the shortening (i.e., contraction) of the muscle fibers. Initiation occurs when the depolarization of myocardial cells releases calcium ions from the sarcoplasmic reticulum into the cytoplasm.

- In the resting state, myosin heads are bound to adenosine triphosphate (ATP), and actin sites are covered by tropomyosin, blocking the interaction between actin and myosin.
- Cross-bridge cycling begins when calcium ions (Ca^{2+}) are released into the cytoplasm of the cardiac muscle cell.
- Calcium binds to troponin, a protein complex associated with the thin filament (i.e., actin filament) of the sarcomere (i.e., the basic contractile unit of a muscle cell). This binding causes a conformational change that shifts tropomyosin away from its blocking position on the actin filament.
- Myosin heads now bind to the exposed myosin-binding sites on the actin filament. The myosin heads form cross-bridges with the actin filament.
- Upon binding, the myosin heads undergo a conformational change, pivoting and pulling the actin filament toward the center of the sarcomere. This movement is referred to as the power stroke and results in the contraction of the muscle fiber.
- ATP is hydrolyzed again to release myosin from actin in the detachment stage, allowing the cross-bridge to break.
- The myosin head resets its position for another cycle by binding to a new ATP molecule. As long as calcium ions remain present, the cross-bridge cycling process will continue and lead to repeated muscle contractions.

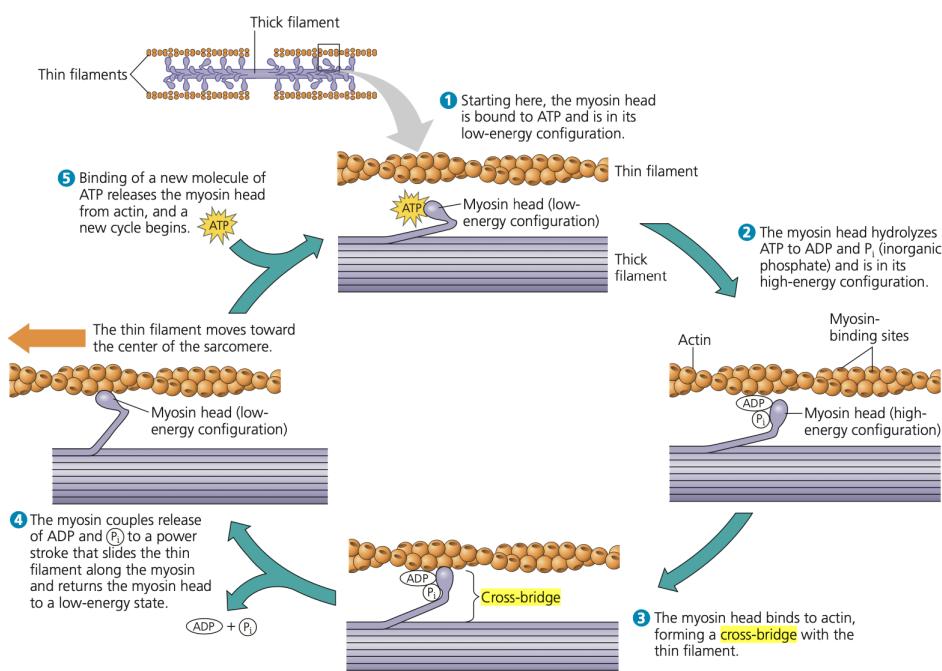


Figure 5: Myosin-actin interactions underlying muscle fiber contraction. (Source: Campbell's Biology 11th Edition)

The action potentials in cardiac cells are very long compared to contraction. This leads to long refractory periods and prevents the buildup of multiple electrical signals.

2.3.3 Electrocardiograms (ECGs or EKGs)

Action potentials in the heart generate currents that can be measured by **electrocardiograms (ECGs or EKGs)** when they reach the skin via body fluids. ECGs have multiple deflections that each represent a certain event. Depolarization toward an electrode is a spike up in the ECG. Thus, the output may be upside down depending on the leads used.

- The **P wave** represents **atrial depolarization**, electrical activity that occurs when the atria contract to pump blood into the ventricles.
- About 0.15 seconds later, the **QRS complex** represents **ventricular depolarization**, the electrical activity that occurs when ventricles contract to pump blood into the aorta and pulmonary trunk.
 - Ventricular depolarization has multiple deflections because the paths taken by the wave of depolarization through the thick ventricular walls differ from instant to instant.
 - It is still called the QRS complex even if the Q wave or the S wave is not present.
 - Atrial repolarization is usually not observed on ECGs because ventricular depolarization (i.e., the QRS complex) happens at the same time.
- The **ST segment** corresponds to **L-type Ca^{2+} channels** increasing action potential time.
- The **T wave** represents **ventricular repolarization**, the electrical recovery of the ventricle following contraction.
- The **U wave** is only sometimes present as a small wave immediately following the T wave. It represents the final phase of ventricular repolarization.

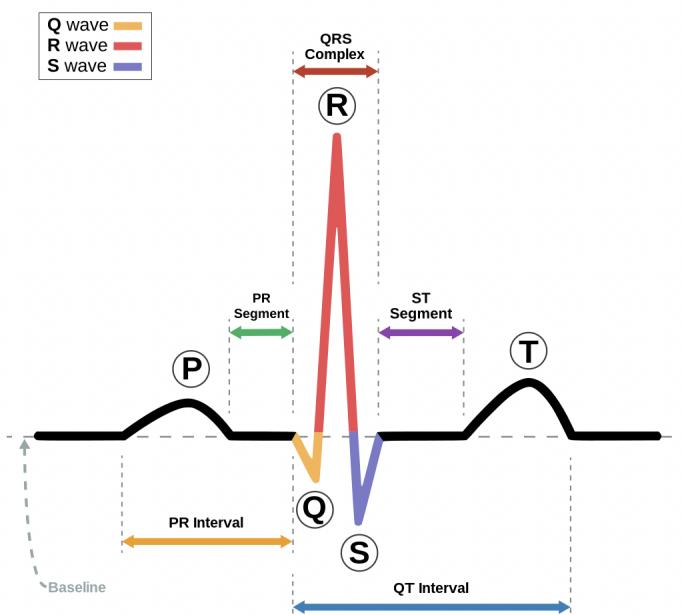


Figure 6: Labeled diagram of the ECG. (Source: Wikipedia)

2.3.4 The Cardiac Cycle

The process of depolarization described in the previous subsection triggers a recurring sequence of heart contraction and relaxation. When the heart contracts, it pumps blood out and when it relaxes, its chambers fill with blood. One complete contraction and relaxation is called a **cardiac cycle**. The contraction phase of the cycle is called **systole**, and the relaxation phase is called **diastole**.

Before we go over the phases of the cardiac cycle, here are some basic principles:

- Contraction increases the pressure in a chamber while relaxation decreases the pressure.
- Blood flows from higher to lower pressure.
- Valves open/close according to pressure gradients.
 - AV valves open when atrial pressures are higher than ventricular pressures and close when the pressure gradient reverses.
 - Semilunar valves open when ventricular pressures are higher than aortic and pulmonary artery pressures and close when the pressure gradient reverses.

The major stages of activity in the cardiac cycle are described below. Please note that the phase numbers are not definite and are just a way to refer to and organize the stages in this handout.

Phase 1: Atrial Contraction (Diastole)

- The firing of the SA node stimulates the atria to depolarize.
- The contraction of the atria (i.e., upper chambers of the heart) forces blood from the atria into the ventricles (i.e., lower chambers). Atrial contraction doesn't account for much of ventricular filling because of prior passive blood flow through the open AV valves in phase 5.
- As atrial contraction completes, atrial pressure falls and the pressure gradient across the AV valves reverses. Since the pressure is higher in the ventricles than in the atria, the AV valves close.

Phase 2: Isometric Ventricular Contraction (Systole)

- The ventricles contract, but all valves in the heart are closed and no blood is ejected. Thus, ventricular volume remains the same.

Phase 3: Ventricular Ejection (Systole)

- The pressure in the ventricles exceeds the pressure in the aorta and pulmonary trunk leading to the pulmonary arteries, causing the semilunar valves to open.
- Blood is pumped into the pulmonary trunk and aorta, which then leads to the lungs and rest of the body, respectively.
- The volume of blood ejected is called the **stroke volume**.
- The pressure gradient reverses, and the semilunar valves close.

Phase 4: Isometric Ventricular Relaxation (Diastole)

- Since all the valves are closed, ventricular pressure drops, while the volume remains unchanged.

Phase 5: Ventricular Filling (Diastole)

- When ventricular pressures drop below atrial pressures, the AV valves open and allow for passive blood flow from the atria into the ventricles.
- Repeat back to phase 1 to finish the filling of the ventricles.

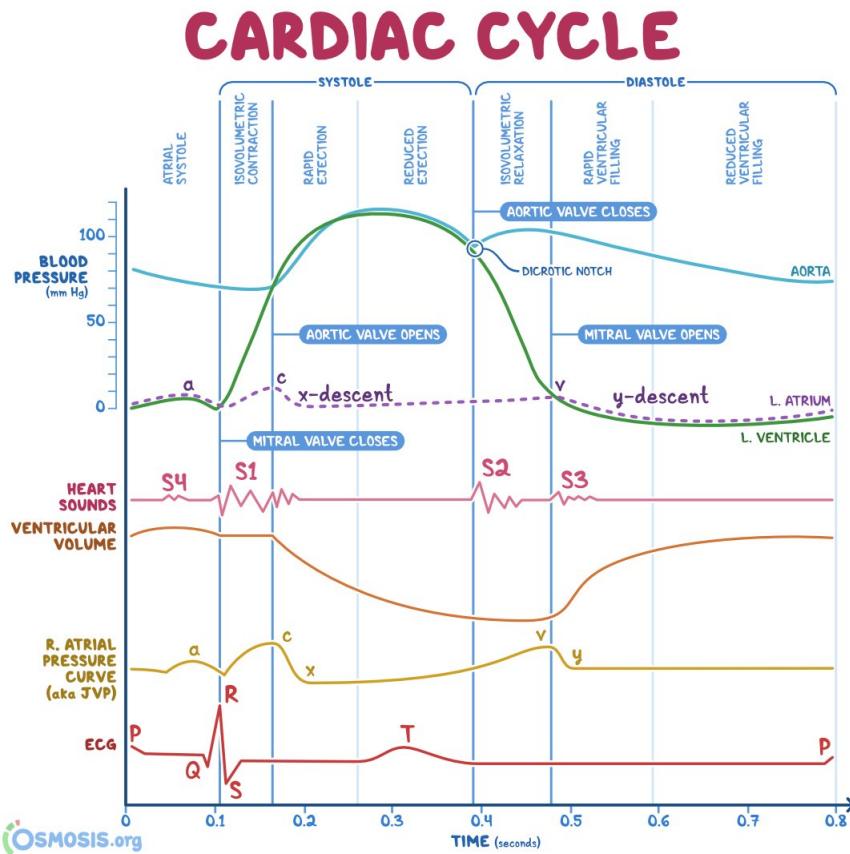


Figure 7: Summary of events in the left atrium, left ventricle, and aorta during the cardiac cycle. (Source: Osmosis.org)

2.3.5 Heart Sounds

Two heart sounds result from the closing of the two sets of heart valves during the cardiac cycle. They can be heard through a stethoscope placed on the chest wall.

- The first sound (S1) is a soft lub caused by the closure of the AV valves (between phases 1 and 2). It marks the start of systole.
- The second sound (S2) is a louder dub caused by the closure of the pulmonary and aortic valves (between phases 3 and 4). It marks the start of diastole.

Example 2.1 (USABO Open Exam 2009) Which of the following statements about the cardiac cycle is correct?

- (A) At no time during the cardiac cycle are the mitral and aortic valves both open.
- (B) The pressure in the left atrium exceeds that of the left ventricle throughout the ventricular ejection period.
- (C) Most filling of the ventricle in diastole in a resting individual occurs with atrial contraction.
- (D) The second heart sound is most closely associated with the closure of the left atrioventricular (i.e., mitral) valve.
- (E) The first heart sound is the result of turbulence associated with ventricular filling.

Solution: The mitral valve refers to the left AV valve, which opens with the right AV valve but never with the semilunar valves (i.e., aortic and pulmonary valves). Therefore, the **answer is A**. If both the AV valves and the semilunar valves were open at the same time, blood would flow uncontrollably between the arteries, atria, and ventricles. B is incorrect because there is no blood in the left atrium during ventricular ejection. C is incorrect because most of the ventricular filling is done passively before atrial contraction occurs. D is incorrect because the first heart sound, not the second, is associated with the closure of the AV valves. For the same reason, E is also incorrect.

2.4 The Vascular System

2.4.1 Anatomy of Blood Vessels

Recall that the vascular system has many types of blood vessels. These include arteries, arterioles, metarterioles, capillaries, venules, and veins.

- All blood vessels have an inner single-celled layer of endothelial cells (i.e., endothelium). Beyond that, there are many differences.
- **Arteries** and **veins** have three main layers: the **tunica intima** (i.e., inner layer with endothelium and elastic lamina), the **tunica media** (i.e., middle layer with smooth muscle, elastic tissue, and collagen), and the **tunica externa** (i.e., outer layer with mostly collagen).
 - **Arteries** have a thicker tunica media with many layers of smooth muscle and elastic fibers. This allows them to withstand the pressure generated by the heart's pumping action and helps maintain blood pressure.
 - **Veins** have a thinner tunica media and a larger lumen than arteries. Their walls are more collapsible and expandable, aiding in the storage of blood and the maintenance of venous return. Veins also have **valves** to prevent the backflow of blood. Arteries don't need valves, since the pressure from the heart is so strong that blood can only flow in one direction.

- **Arterioles** are smaller vessels that lead from arteries to capillaries. They have a relatively thin wall of epithelium and smooth muscle. Arterioles play a crucial role in regulating blood flow and blood pressure by changing their diameter in response to various stimuli.
- **Capillaries** consist of a single layer of endothelial cells and a **basal lamina**, which allows for the efficient exchange of gases, nutrients, and waste products between the blood and surrounding tissues. Since capillaries lack smooth muscle, blood flow is regulated by **precapillary sphincters** that open or close blood flow to a particular capillary bed.
- **Venules** are small vessels that collect blood from capillaries and lead to veins. They have a structure similar to capillaries but with smooth muscle cells.

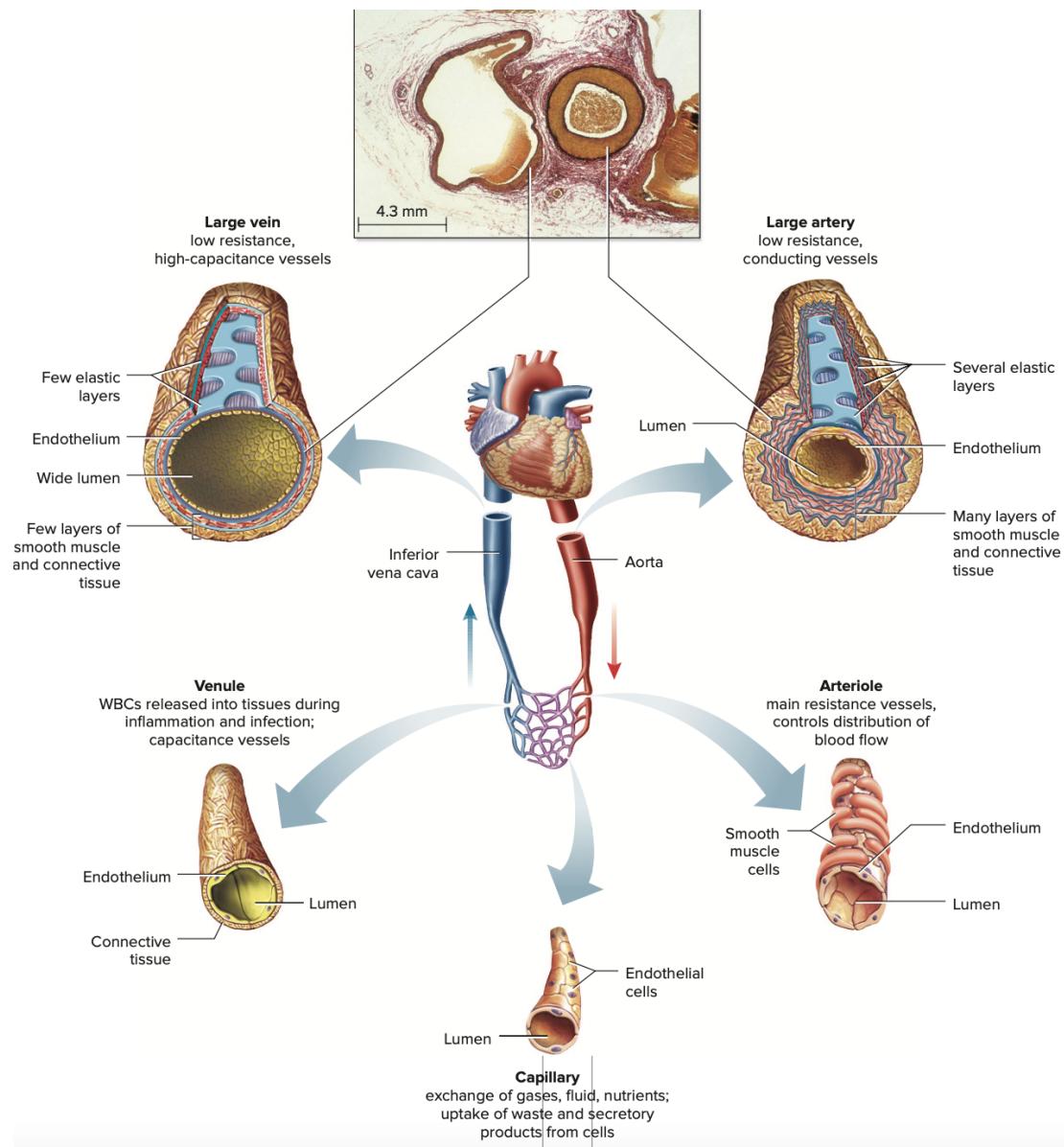


Figure 8: Comparative features of blood vessels. Sizes are not drawn to scale. (Source: Vander's Human Physiology)

2.4.2 Blood Pressure

Arterial blood pressure changes throughout the cardiac cycle.

- **Systolic pressure** is the force of the blood being pushed into the aorta by the left ventricles. It occurs when the ventricles contract and pump blood into the arteries. Blood enters faster than it can exit through the veins, so the diameter of the arteries increases to accommodate. This causes the pulse that can be felt by placing your fingers on your wrist or your neck.
- **Diastolic pressure** is the force of blood being pushed by the aortic stretching and rebounding. It occurs during ventricular diastole when the ventricles are relaxed. Some of the pressure in the arteries is relieved and the elastic walls snap back in diameter.
- **Pulse pressure** is the difference between systolic and diastolic pressure.

Blood pressure is regulated by vasodilation and vasoconstriction.

- **Vasodilation** is the widening of blood vessels through the relaxation of smooth muscle in vessel walls. This leads to a decrease in resistance to blood flow, which can result in a decrease in blood pressure.
- **Vasoconstriction** is the narrowing of blood vessels when the smooth muscle in the vessel walls contracts. This increases resistance to blood flow and can lead to an increase in blood pressure.

$$\text{Blood Pressure} = \text{Cardiac Output} \times \text{Total Peripheral Resistance}$$

$$\text{Cardiac Output} = \text{Heart Rate} \times \text{Stroke Volume}$$

$$\text{Stroke Volume} = \text{End Diastolic Volume} - \text{End Systolic Volume}$$

Stroke volume is affected by the following:

- The **Frank-Starling Law**, which states that stroke volume increases as ventricular volume (i.e., end-diastolic volume) increases.
- Contractility, which is dependent on the sympathetic nervous system.
- Afterload, the resistance the heart has to overcome to push blood from the ventricle into the arteries, an increase in which causes a decrease in stroke volume.

Example 2.2 (USABO Open Exam 2018) Which of the following is most accurate regarding the anatomy and physiology of the vertebrate vascular system?

- (A) The thin walls of veins are an adaptation that allows the tissues of the vein itself to obtain, via diffusion, sufficient oxygen from oxygen-poor venous blood. Otherwise, the tissue of thick-walled vessels carrying deoxygenated blood would experience inadequate oxygenation and die.
- (B) Arteries and veins contain valves to prevent backflow of blood.
- (C) Elastic fibers made of the protein elastin in the tunica media allow arteries to accommodate fluctuating blood pressures. They are almost absent in the tunica media of veins.

(D) The larger arteries have a thick layer of smooth muscle, the motion of which helps propel blood forward.

(E) Vascular endothelial growth factor (VEGF) is a signaling protein that stimulates branching and growth of capillaries. The gene encoding VEGF is often lost or inhibited in solid tissue cancers.

Solution: Elastic fibers, primarily composed of elastin, provide elasticity to the arterial walls by allowing them to expand and recoil in response to changes in blood pressure caused by the heart's pumping action. Veins, on the other hand, have thinner walls and are less dependent on elastic fibers for their function. Therefore, the **answer is C**. A is incorrect because the thin walls of veins are not primarily designed for the vein tissues themselves to obtain oxygen. Oxygen exchange between tissues and blood occurs primarily in capillaries. B is incorrect because valves are present in veins but not arteries. D is incorrect because, while larger arteries do have a thick layer of smooth muscle, the primary function of this smooth muscle layer is to help regulate blood pressure. It does not directly propel blood forward; the heart's pumping action does that. E is incorrect because VEGF overexpression, not inhibition, is associated with cancer since it forms new blood vessels to support tumor growth. This is not covered in this handout, but C being correct should be enough to answer this question.

2.5 Blood

2.5.1 Components of Blood

Blood is composed of **formed elements** suspended in a liquid called plasma. These formed elements include the following:

- **Erythrocytes (red blood cells)** that carry oxygen and carbon dioxide to and from the tissues, respectively.
- **Leukocytes (white blood cells)** that protect the body from infection as major components of the immune system.
- **Thrombocytes (platelets)**, cell fragments that form blood clots.

In addition to the suspended elements, various substances are dissolved in plasma, such as the **plasma proteins**, nutrients, metabolic waste products, hormones, and a variety of mineral electrolytes including Na^+ , K^+ , and Cl^- .

Plasma

Over 90% of plasma is water; the rest is dissolved substances. The plasma proteins constitute most of the plasma solutes and can be classified into **albumins** (osmotic pressure), **globulins** (immune defense), and **fibrinogen** (clotting factor).

Serum is plasma without fibrinogen and other proteins involved in clotting.

Multipotent Hematopoietic Stem Cells

All blood cells differentiate from **multipotent hematopoietic stem cells**. As shown in the diagram below, an undifferentiated cell first branches into a bone marrow lymphocyte precursor cell, which becomes a lymphocyte, or a committed stem cell, which yields everything else. Note that lymphocytes are only one type of leukocytes (white blood cells); the other types come from committed stem cells.

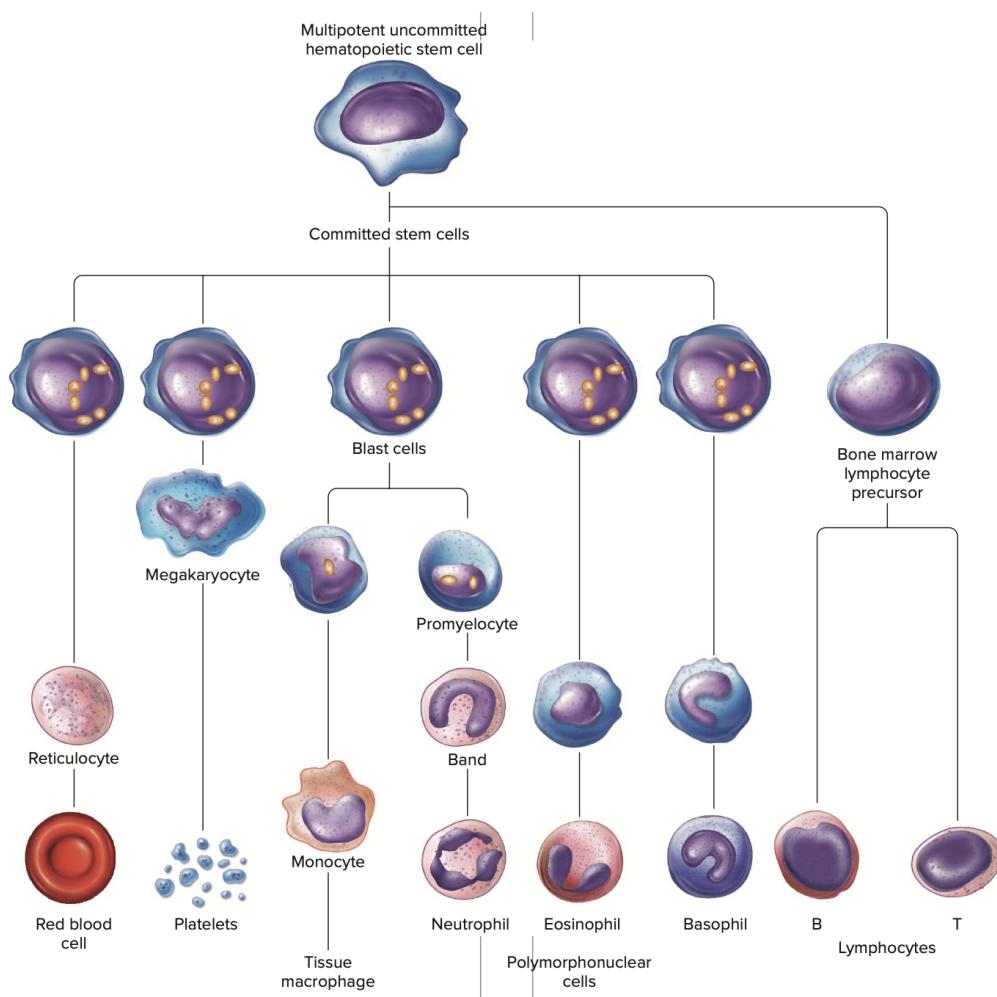


Figure 9: Differentiation paths of multipotent hematopoietic stem cells.
(Source: Vander's Human Physiology)

Erythrocytes (Red Blood Cells)

- Erythrocytes are able to transport gases because they contain large amounts of **hemoglobin**, a protein that binds to oxygen and carbon dioxide. We'll talk a LOT more about hemoglobin and its properties in the respiratory section.
- Erythrocytes are small in size and are slightly curved so that the center of each cell is thinner than the outside rim. This gives them a high surface area-to-volume ratio, which allows for rapid diffusion of gases.

- Erythrocytes are produced in the **red bone marrow**. Erythrocyte precursors are able to produce hemoglobin, but ultimately lose their nuclei and organelles and are unable to do so as erythrocytes.
- Young erythrocytes, called **reticulocytes**, are defined by still having some ribosomes left. Once they leave the bone marrow, they tend to lose their ribosomes and become erythrocytes.
- The product of the breakdown of hemoglobin is called **bilirubin**, which returns iron and other substances to circulation and gives plasma its yellow color.

Leukocytes (White Blood Cells)

Please read the immune system handout to learn more about leukocytes. This handout puts a bigger emphasis on erythrocytes since they are the main players in gas exchange.

Thrombocytes (Platelets)

Platelets are nonnucleated cell fragments that are produced when cytoplasmic portions of **megakaryocytes**—large bone marrow cells—pinch off. Platelets contain numerous granules, small membrane-bound vesicles that can contain clotting factors, growth factors, adhesive factors, and more.

2.5.2 Blood Clotting

Blood clotting is also known as **coagulation** and helps prevent excessive bleeding when a blood vessel is injured.

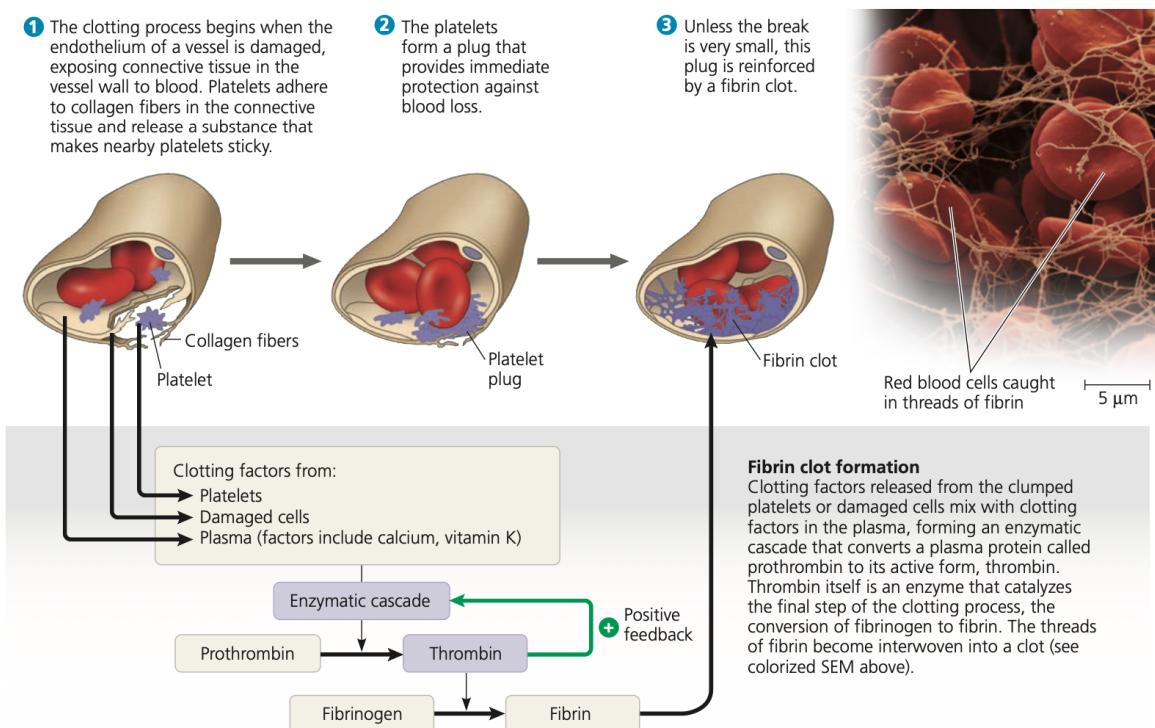


Figure 10: Blood clotting. (Source: Campbell's Biology 11th Edition)

- When a blood vessel is damaged, it undergoes vasoconstriction, where the smooth muscles in the vessel wall contract. This helps reduce blood flow to the site of injury and minimize blood loss.
- Platelets are activated and stick to the exposed collagen in the vessel wall.
- The activated platelets aggregate together at the site of injury, forming a temporary plug that helps stop bleeding.
- The **coagulation cascade** is a series of reactions involving proteins called **clotting factors**. These factors work in a sequential manner, leading to the formation of **thrombin**, an active enzyme, from **prothrombin**, an inactive enzyme. Thrombin then converts **fibrinogen**, a soluble protein into **fibrin**, insoluble fibers.
- Fibrin threads form a mesh around the platelet plug, creating a stable blood clot. Over time, the clot contracts and pulls the wound edges closer together.

2.6 Cardiovascular Diseases

Coronary Artery Disease (CAD)

- **Symptoms:** Chest pain (angina), shortness of breath, fatigue, and sometimes nausea or pain radiating to the arms, neck, or jaw during physical activity.
- **Cause:** CAD occurs when the coronary arteries, which supply oxygen-rich blood to the heart muscle, become narrowed or blocked due to a buildup of plaque (i.e., **atherosclerosis**). This reduces blood flow to the heart, leading to oxygen deprivation and chest pain.

Hypertension (High Blood Pressure)

- **Symptoms:** Often asymptomatic, but can cause headaches, shortness of breath, nosebleeds, and blurry vision in severe cases.
- **Cause:** Hypertension is characterized by consistently elevated blood pressure in the arteries. It can result from factors like genetics, unhealthy diet, lack of exercise, obesity, and stress. Over time, high blood pressure can strain blood vessel walls, increasing the risk of heart disease, stroke, and other complications.

Heart Attack (Myocardial Infarction)

- **Symptoms:** Severe chest pain, shortness of breath, sweating, nausea, and pain radiating to the arms, neck, jaw, or back.
- **Cause:** A heart attack occurs when a coronary artery becomes completely blocked, usually due to a blood clot forming on a plaque-covered artery wall. This leads to a lack of blood supply and oxygen to a portion of the heart muscle, causing damage.

Stroke

- **Symptoms:** Sudden numbness or weakness in the face, arm, or leg, confusion, trouble speaking, severe headache, and difficulty walking or maintaining balance.

- **Cause:** Stroke occurs when blood flow to the brain is disrupted due to a blocked blood vessel (ischemic stroke) or a ruptured blood vessel (hemorrhagic stroke), leading to brain tissue damage.

Aortic Aneurysm

- **Symptoms:** Often asymptomatic until rupture, but can cause chest or back pain, difficulty breathing, and low blood pressure.
- **Cause:** Aortic aneurysm is the abnormal bulging of the aorta due to weakened vessel walls. If the aneurysm ruptures, it can lead to life-threatening internal bleeding.

Anemia

- **Symptoms:** Fatigue, shortness of breath, swelling in legs and ankles, irregular heartbeat, and dizziness.
- **Cause:** Cardiomyopathy refers to diseases that weaken or enlarge the heart muscle. It can be inherited or acquired and can lead to heart failure.

Sickle Cell Disease

- **Symptoms:** Pain episodes (i.e., sickle cell crises), fatigue, anemia-related symptoms, susceptibility to infections, and organ damage due to poor blood flow.
- **Cause:** Sickle cell disease is a genetic disorder characterized by the presence of abnormal hemoglobin known as **hemoglobin S (HbS)**. This leads to the formation of crescent-shaped red blood cells that can cause blockages and reduced oxygen delivery.

Cardiomyopathy

- **Symptoms:** Fatigue, weakness, pale skin, shortness of breath, dizziness, and rapid heartbeat. The severity of symptoms varies based on the type and cause of anemia.
- **Cause:** Anemia is characterized by a decrease in the count of red blood cells or hemoglobin in the blood.

3 Respiratory System

The respiratory system's functions in humans are closely tied to the circulatory system and include transporting oxygen from the environment to the blood and eliminating carbon dioxide. This is **GAS EXCHANGE!**

3.1 Respiratory Systems Across Species

Not all species have lungs and not all species need a circulatory system to aid in gas exchange.

- Most marine animals have **gills**, out-foldings of the body surface that greatly increase the surface area for gas exchange. Water flows over the gills, and oxygen diffuses into the bloodstream, while carbon dioxide diffuses out.

- Fish use a **countercurrent exchange** mechanism to maximize oxygen uptake from water. Water and blood flow through the gill filaments in opposite directions, so when the oxygen-rich water encounters blood with lower oxygen concentration, oxygen diffuses from the water into the blood along the entire length of the gill filament.
- The most common respiratory system in terrestrial animals is the insect **tracheal system**, a network of tiny tubes that deliver oxygen directly to the body cells. Oxygen enters the tracheae through small openings called spiracles on the insect's body. Tracheae then branch into smaller tubes, eventually reaching individual cells for gas exchange.
- Another common respiratory system centers around localized **lungs** that then need a circulatory system, which can be open or closed, to transport gases throughout the body. Some species may use other methods of gas exchange in addition to having lungs.
 - Amphibians rely heavily on gas exchange through their skin, lungs, and mouth lining. If they have lungs, they are relatively small.
 - On the other hand, reptiles and mammals rely almost entirely on their lungs. Turtles are the exception since they also have gas exchange through their mouth and anus in addition to the lungs. Some species, such as birds and crocodiles, also have air sacs that maintain unilateral flow through the lungs.

All species with lungs can be classified as ventilating through positive pressure breathing or negative pressure breathing.

- **Positive pressure breathing** is found in amphibians like frogs and some reptiles. Inhaling involves gulping air into the mouth, inflating the lungs, and then closing the mouth to force air into the lungs. It is not as efficient as negative pressure breathing because it requires more energy.
- **Negative pressure breathing** is found in mammals and birds. The diaphragm contracts and flattens, and the rib cage expands, creating a larger chest volume. The decrease in intrathoracic pressure causes air to flow into the lungs to equalize the pressure.

3.2 Organization of the Respiratory System

This section refers to the human respiratory system. The right and left lungs contain **alveoli** — sites of gas exchange in the blood. **Airways** are tubes that allow air to flow between the alveoli and the external environment.

3.2.1 Airways and Blood Vessels

The **upper airways** include the nose, mouth, pharynx, and larynx.

- Air passes from the nose or mouth into the **pharynx**, which branches into the **esophagus** and **larynx**. Here, food and air separate.
- The **larynx** houses the **vocal cords** — elastic tissue stretched horizontally across its lumen (i.e., cavity). Air passing through the larynx causes the vocal cords to vibrate, producing sounds.

The airways beyond the larynx can be divided into two zones:

- **Conducting zone:** extends from the top of the trachea to the end of the terminal bronchioles. Contains no alveoli/no gas exchange.
 - The larynx opens into a long tube called the **trachea** (i.e., windpipe), which branches into two bronchi that enter their respective lung.
 - The walls of the trachea and bronchi contain rings of cartilage, which give their cylindrical shape and support. The first branches that don't contain cartilage are termed **bronchioles**.
 - The bronchioles are surrounded by smooth muscle, which contracts or relaxes to alter its radius, similar to blood vessels.
- **Respiratory zone:** extends from the respiratory bronchioles down. Contains alveoli and is thus the region of gas exchange with the blood.
 - Alveoli first begin to appear attached to the walls of the **respiratory bronchioles**.
 - The number of alveoli increases in the **alveolar ducts**, and the airways then end in grape-like clusters called **alveolar sacs**, which consist entirely of alveoli.

Within each lung, there are more than 20 generations of branching. The figure below can help visualize the branching of airways described above.

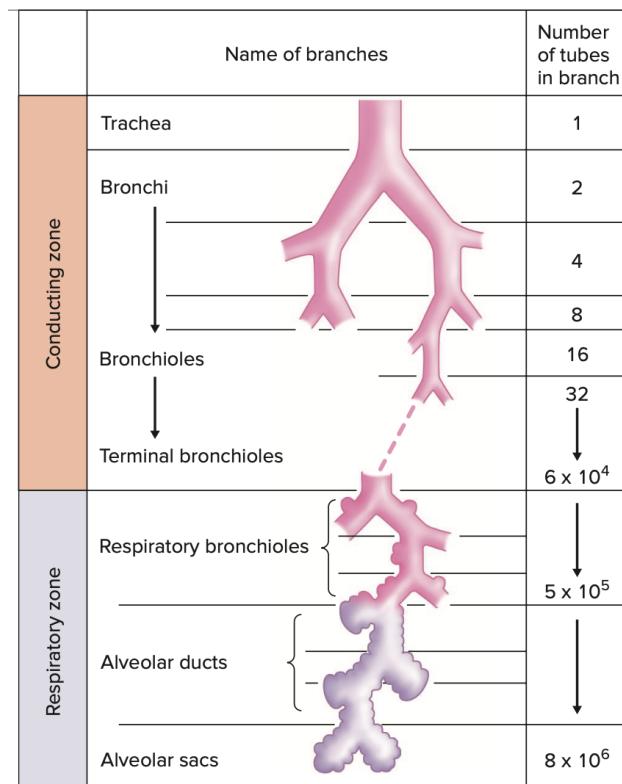


Figure 11: Airway branching. Asymmetries in branching patterns between the right and left bronchial trees are not depicted. The diameters of the airways and alveoli are not drawn to scale.
 (Source: Vander's Human Physiology)

The respiratory defense system prevents debris and pathogens from reaching alveoli.

- The oral and nasal cavities trap airborne particles in nasal hairs and mucus.
- The epithelial surfaces of the airways to the end of the respiratory bronchioles contain a **mucociliary escalator** consisting of cilia that secrete mucus and constantly beat upward toward the pharynx. They trap particulate matter and move it up to the pharynx to be swallowed.
- Bronchioles constrict in response to irritation, preventing particulate matter from entering the alveoli.
- Macrophages engulf and destroy inhaled particles and bacteria that have reached the alveoli.

Pulmonary blood vessels accompany the airways and also undergo branching, eventually ending up as **capillary networks** that supply the alveoli. Pulmonary circulation has a very low resistance to blood flow and therefore a low pressure, which minimizes the accumulation of fluid in the interstitial spaces of the lungs.

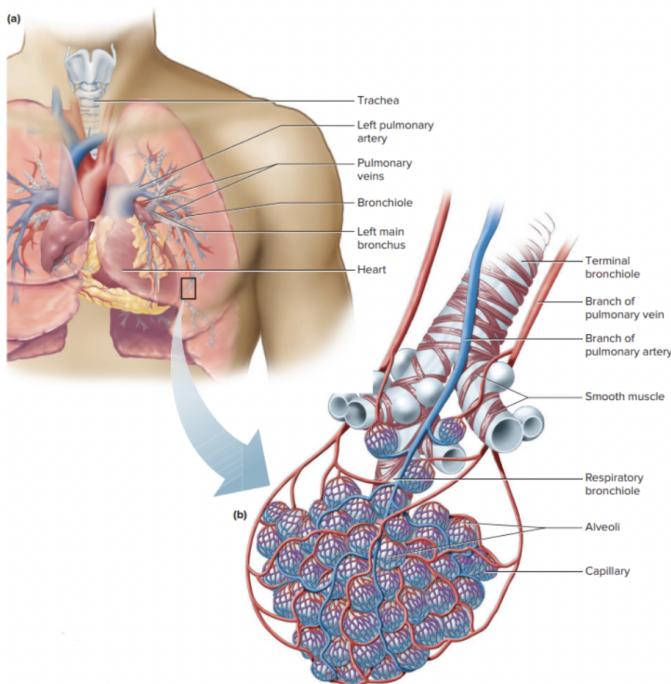


Figure 12: Relationships between blood vessels and airways. Red represents oxygenated blood; blue represents deoxygenated blood. Virtually the entire lung, not just the surface, consists of such clusters of alveoli. (Source: Vander's Human Physiology)

3.2.2 Alveoli

Each “grape” in the cluster of alveoli above is one single alveolus. Typically, a single alveolar wall separates the air into two adjacent alveoli.

- **Type I alveolar cells** are flat epithelial cells that create a continuous one-cell thick lining to most of the air-facing surfaces of the wall. Their main function is to provide a minimal barrier for the diffusion of gases (i.e., oxygen and carbon dioxide) between the air in the alveoli and the adjacent capillaries. This thinness allows for rapid and efficient gas exchange.

- **Type II alveolar cells** are thicker, specialized cells interspersed between the type I cells. They produce **pulmonary surfactant**, a mixture of lipids and proteins that coats the inner surface of the alveoli. Its crucial role is to reduce the surface tension of the fluid lining the alveoli. By lowering surface tension, surfactant prevents the alveoli from collapsing during exhalation, making it easier for the lungs to expand during inhalation.
- Some alveoli have pores in their walls to allow airflow between them.
- The walls contain capillaries and a very small interstitial space, which consists of interstitial fluid and a loose meshwork of connective tissue. In many places, this space is absent, and the basement membrane and capillary walls fuse.
- As a result, the blood within an alveolar wall capillary is separated from the air within the alveolus by an extremely thin barrier.

3.2.3 Thoracic Wall

- The lungs are situated in the **thorax**, the compartment of the body between the neck and abdomen.
 - The thorax is bounded at the neck by muscles and connective tissue and completely separated from the abdomen by the **diaphragm**, a large dome-shaped sheet of skeletal muscle.
 - The wall of the thorax is formed by the spinal column, ribs, sternum, and several groups of muscles that run between the ribs (i.e., intercostals).
 - The thoracic wall also contains connective tissue with elastic properties.
- Each lung is surrounded by a completely closed sac called the **pleural sac**, consisting of a thin sheet of cells called **pleura**. The sacs of both lungs are separate.
- **Visceral pleura:** pleural surface that is coating the lung; firmly attached to the lung by connective tissue.
- **Parietal pleura:** attached to and lines the interior thoracic wall and diaphragm.
- These layers of pleura are not attached to each other but are separated by the pleural cavity, which contains a thin layer of intrapleural fluid.

3.3 Lung Ventilation

Breathing ventilates the lungs. **Inpiration** is the movement of air from the external environment into the alveoli during breathing and **expiration** is the opposite. One inspiration and one expiration is a **respiratory cycle**.

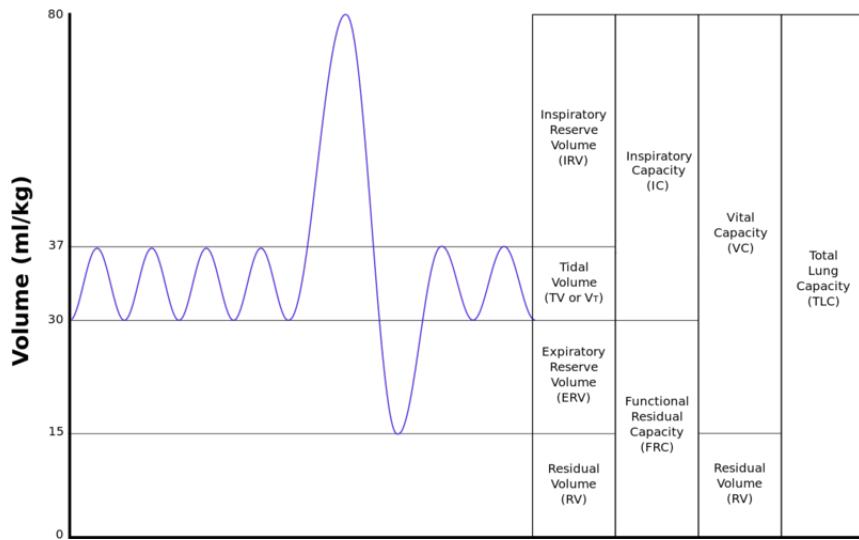


Figure 13: Lung volumes and capacities. (Source: Wikipedia)

Tidal volume is the volume of air inhaled and exhaled with each breath. The tidal volume during maximal inhalation and exhalation is the **vital capacity**. The air that remains in the lungs after exhalation is called the **residual volume**.

3.4 Homeostatic Control of Breathing

The brainstem, specifically the medulla oblongata and pons, contain neural networks called the respiratory centers.

- Central chemoreceptors located in the medulla sense changes in the pH of cerebrospinal fluid due to changes in blood carbon dioxide (CO_2) levels.
- Peripheral chemoreceptors, primarily located in the carotid bodies and aortic bodies, detect changes in arterial blood oxygen (O_2) and carbon dioxide levels.
- Increased CO_2 levels in the blood lead to a decrease in blood pH. Chemoreceptors send signals to the medulla that trigger an increase in breathing rate to eliminate excess CO_2 and restore pH balance.
- This is a negative feedback loop: as CO_2 levels rise, the respiratory centers stimulate increased breathing; as CO_2 levels decrease, the stimulation decreases, and breathing slows down.

3.5 Gas Exchange

Partial pressure is the pressure exerted by a particular gas in a mixture of gases. A gas will always net diffuse from a region of higher partial pressure to a region of lower partial pressure.

Most circulating oxygen is bound to **respiratory pigments** such as hemoglobin. **Hemoglobin** is made up of four subunits bound together.

- The four polypeptides of hemoglobin are collectively known as **globin**.
- Each globin subunit consists of a **heme** group attached to it.

- Each heme group contains 1 iron atom Fe^{2+} , to which O_2 binds.
- 4 hemes = 4 iron atoms = 4 O_2 per **hemoglobin**
- Can exist as **deoxyhemoglobin** (Hb) or **oxyhemoglobin** (HbO_2).

Below is an overview of gas exchange through the lungs and circulatory system.

Oxygen (O_2)

- Oxygen-poor blood from the body flows through pulmonary arteries into the capillaries surrounding the alveoli.
- In the alveoli, oxygen from inhalation diffuses from the high-concentration alveolar air into the low-concentration blood in the capillaries.
- Oxygen molecules that diffuse into the blood bind to hemoglobin in red blood cells to form oxyhemoglobin.
- Oxyhemoglobin is transported through the circulatory system to tissues, where oxygen is released for cellular respiration.

Carbon Dioxide (CO_2)

- Carbon dioxide produced by cells during metabolism diffuses into the bloodstream.
- Most of the carbon dioxide combines with water to form bicarbonate ions (HCO_3^-) in red blood cells, which are then transported to the lungs.
- Once in the lungs, carbon dioxide diffuses from the high-concentration blood in the capillaries into the low-concentration alveolar air.
- During exhalation, the carbon dioxide-rich air is expelled from the lungs.

3.6 Respiratory Diseases

Chronic Obstructive Pulmonary Disease (COPD)

- **Symptoms:** Persistent cough, difficulty breathing, excessive mucus production, and wheezing.
- **Cause:** COPD includes chronic bronchitis and emphysema. It's mainly caused by smoking or exposure to lung irritants, leading to airway inflammation and damage.

Cystic Fibrosis

- **Symptoms:** Persistent cough with thick mucus, recurrent lung infections, digestive issues, and poor growth.
- **Cause:** Cystic fibrosis is a genetic disorder that causes a buildup of thick mucus in the lungs and other organs, leading to respiratory and digestive problems.

Asthma

- **Symptoms:** Wheezing, coughing, shortness of breath, and chest tightness.
- **Cause:** Asthma is primarily caused by an exaggerated immune response to certain triggers. It is a chronic respiratory condition characterized by inflammation and narrowing of the airways, making breathing difficult.

Pulmonary Edema

- **Symptoms:** Shortness of breath, rapid and labored breathing, coughing with frothy pink or blood-tinged sputum, increased heart rate, and anxiety.
- **Cause:** Pulmonary edema is a condition characterized by the accumulation of fluid in the air sacs (i.e., alveoli) of the lungs. It often occurs when the left side of the heart fails to effectively pump blood. This can lead to increased pressure in the pulmonary veins and capillaries, causing fluid to leak into the alveoli.

Obstructive Sleep Apnea

- **Symptoms:** Loud snoring, gasping for breath during sleep, daytime sleepiness, and difficulty concentrating.
- **Cause:** OSA occurs when the upper airway collapses during sleep, temporarily interrupting breathing. It's often related to obesity and anatomical factors.

4 Conclusion

Fini! I hope this handout was helpful in your USABO endeavors. I wrote it to include more content than Campbell's, but it's definitely not as in-depth as Vander's. Ultimately, the goal of this handout was to provide a good baseline of knowledge for the open exam. If you want to learn more about these systems, I would read the respective chapters of Vander's (or Martini's if you want more anatomy). Good luck with the rest of your studying; you got this!

- Vivian Ye