Circulatory system:

Consists of: heart which serves as a pump.
Blood vessels serve as passageway.
Blood serves as media of transport.

HEART:

It is a dual pump (functions as two separate pumps) which ejects blood into vessels.

It is composed of four chambers. The upper chambers are known as left and right atria. These chambers are receiving blood that returned to the heart through main veins and transfer this blood to the lower chambers known as left and right ventricles, which pump blood into main arteries (pulmonary and aortic arteries).

The left and right sides of the heart are separated by septum which prevents mixing blood from the two sides. This is an important function because the two sides have blood with different oxygenation (the left side has well oxygenated blood while the right side has O2-poor blood).

The deoxygenated (poorly oxygenated) blood returns to the heart from the body tissue (the site where O2 has been extracted and CO2 added) through 2 large veins known as superior and inferior venae cavae. The blood from these veins enters the right atrium. From the right atrium blood flows into the right ventricle which pumps the deoxygenated blood into pulmonary circulation through pulmonary artery. The blood that becomes oxygenated in pulmonary circulation returns to the left atrium through 4 pulmonary veins. Then the blood flows into the left ventricle, which pumps the oxygenated blood into systemic circulation through aorta.

Heart valves and circulation:

The flow of blood as we have seen is from veins to atria to ventricles to arteries. This unidirectional flow is provided by the presence of valves (2 between heart chambers + 2 arterial valves) along the way of
blood. These valves open and close passively, according to the pressure difference between the two compartments that are separated.

* The two valves that are located between heart chambers are known as right and left atrioventricular (AV) valves. These valves allow blood to flow from atria to ventricles and prevent the back flowing from ventricles to atria. The right AV valve is known as tricuspid valve (consists of three cusps), and the left AV valve is known as bicuspid valve (consists of two cusps). An alternative name for the left AV valve is mitral valve.

From the edges of valve cusps, small fibrous cords (known as chordae tendineae) extend to attach small nipple shape (known as papillary muscle) that protrude from the inner surface of the ventricular wall. These structures prevent the valves from opening in the opposite direction and keeping them closed during ventricular contraction when high pressure inside ventricles is developed.

* the other two valves are known as aortic and pulmonary valves. These valves also are known as semilunar valves (consist of three cusps that resemble a half moon shape).

The pulmonary valve is located at the junction between the pulmonary artery and right ventricle while aortic valve is located at the junction between aorta and left ventricle. These valves open upon increasing pressure above arterial pressure during ventricular contraction (systole), and close when pressure inside ventricle falls below arterial pressure during ventricular relaxation (diastole).

**STRUCTURE OF THE HEART WALL:**

Heart wall consists of three layers:

- **Endocardium:** a thin layer of endothelium that line the entire heart cavities.

- **Myocardium:** the middle layer. Composed of heart muscle fibers. These fibers have spiral arrangement around the circumference of the heart. The muscle fibers are interconnected to form branching fibers by a specialized structure known as intercalated discs. The intercalated discs provide two types of junction between cells; gap junction consists of connexons that provide electrical communication between contractile cells allowing action potential spreading from one cell to adjacent cell, allowing contraction of ventricular muscle as one unit (functional syncytium) and adhering junctions consists of desmosomes which provide mechanical holding of cardiac muscle cell together.
It is important to note that the contractile atrial muscle cells have no gap junction with ventricular muscle cells, so the activity of atrial muscle cells is separated totally from that of ventricular cells. The transmission of an action potential from atria to ventricles is provided by specialized conductive tissue.

- Pericardium: a double layers of membranous structure. The outer is attached to the connective tissue in the chest cavity and anchors the heart in a proper position within the chest. The inner layer adheres to the heart surface. This layer is known as epicardium. Between the two layers there is a small thin space known as pericardial cavity, in which a thin layer of secreted fluid is found (pericardial fluid).

ELECTRICAL ACTIVITY OF THE HEART & CONDUCTION OF EXCITATION:

Contraction of the heart muscle requires generation of an action potential. This action potential is generated by itself and rhythmically by specialized cells in the heart. This gives the heart a property known as autorhythmicity. After self and rhythmic generation of impulse (action potential), it will be conducted through specialized conductive tissue and resulted in an action potential on the contractile muscle cells, which induce rhythmic contractions of the heart muscle.

These auto-rhythmic cells have certain properties which make them specialized in the generation of an action potential by themselves. They do not have a resting potential. Instead, they display a pacemaker activity. Their membrane depolarizes slowly between action potentials until threshold is reached, then the action potential is developed.

The slow depolarization (pacemaker activity) appears by inactivation of K+ channels, which result in a decrease in the outward K+ current and constant inward leakage of Na+ current. This induces slow depolarization of the membrane. This event is followed by activation of voltage Ca++ channels known as Transient Ca++ (T-type). This activation is taking place at (-50mv). More depolarization (at -40 to -30mv) another type of voltage Ca++ channels are activated known as Longer-lasting Ca++ cannels (L type). The activation of L-type channels will induce an action potential. At the end of action potential the cycle is repeated again. This will result in a rhythmic appearance of action potentials.
The cardiac cells that have the autorhythmic property are found in the following location:

- **Sinoatrial (SA) node**: located in the right atrial wall, near the opening of the superior vena cava. These cells generate 70-80 action potentials/minute.

- **Atrioventricular (AV) node**: located at the base the right atrium, just above the junction of the atria and ventricle. These cells generate 40-60 impulses/min.

- **Bundle of Hiss**: (atrioventricular bundle): originates at AV node, enters the interventricular septum, then divides into left and right bundle branches.

- **Purkinje fibers**: small fibers that extend from bundle branches. Both bundles and Purkinje fibers can generate 20-40 impulses/min.

Normally, the SA node, which exhibits the highest rate of autorhythmicity (70-80/minutes), drives all the heart at this rhythm and is known as the **pacemaker of the heart**.

**SPREAD OF CARDIAC EXCITATION:**

The spread of excitation to atria and ventricles is very well coordinated and the followings are met to ensure efficient pumping of the heart:

* **The atrial excitation and contraction should be complete before ventricular excitation and contraction.** This will result in a complete filling of ventricles before ventricular contraction.

* **contraction of heart chambers as a single unit is important to accomplish the efficient pumping.** For that, all atrial muscle when stimulated contract simultaneously (at the same time). This is ensured by rapid transmission of an action potential between the muscle cells through the gap junctions.

* As a result of these coordination, both atria contract simultaneously before the contraction of ventricles. And both ventricles also are excited and contract simultaneously after the contraction of atria is completed.
+ **Atrial excitation:**

The action potential that originates in SA node spreads throughout both atria primarily from cell to cell by gap junction.

In addition to that the impulse can spread from the SA node to left and right atrial muscle by:

- **Interatrial pathway:** which extends from the SA node within the right atrium to the left atrium. Which results in a rapid spread of impulse from the right atrium where the impulse is generated at the SA node to the left atrium. This will ensure simultaneous excitation of both atria.

- **Internodal pathways:** extend from SA to AV nodes. These pathways direct the spread of an action potential from SA node to ventricles through the AV node.

+ **Transmission between the atria and ventricles:**

The conduction of impulse through the AV node is relatively slow, which results in a delay of about 0.1 s in impulse spreading from atria to ventricles (AV delay). This slowness of conduction has an advantage by giving more time for complete ventricular filling.

+ **Ventricular excitation:** after the AV delay, the impulse travels rapidly down the bundle of Hiss to the ventricular muscle cells via Purkinje network fibers. These fibers coordinate the spread of ventricular excitation and by that, ensure that ventricles contract as a unit.

**PROPERTIES OF CARDIAC MUSCLE CELLS:**

- **Action potential in cardiac muscle cells:**

   Action potential in contractile muscle cells that develops after the impulse has reached the contractile cells differs from the action potential generated in autorhythmic cells.

   During rest, the membrane remains at resting potential of about (−90mv). Stimulation of cardiac muscle cells by an impulse generated initially at SA node will induce rapid activation of Na+
channels, that results in a massive influx of Na+ and reversing the potential to about +30mv.

The sudden change in the potential will induce activation of slow Ca++ channels and inactivation of K+ channels. This will result in influx of positively charged Ca++ into the cell and decreased K+ permeability. Thereby, this will maintain the reversed potential (positive inside) for longer time forming the *plateau phase* of an action potential.

The plateau phase is followed by a rapid fall in an action potential toward the resting potential. This appears due to activation of K+ channels (which promotes rapid outward diffusion of K+) and inactivation of Ca++ channels which prevent inward movement of positive Ca++. These events make inside the cell more negative than the outside and restores the resting potential.

- **Excitation contraction coupling:**

  The action potential generated at the membrane travels down along the T tubules, which causes activation of dihydropyridine receptors. These receptors serve also as Ca++ channels. The Ca++ influx through these receptors causes more release of Ca++ from the sarcoplasmic reticulum into the sarcoplasm (Ca++ entry triggers release of Ca++ from sarcoplasmic reticulum). Ca++ also enters the cytosol through the membrane during action potential. This also triggers release of Ca++ from the sarcoplasmic reticulum.

  Like skeletal muscle, the increase in Ca++ concentration will activate troponin-tropomyosin complex, then cross bridges cycling and contraction can take place.

  The relaxation of cardiac muscle results by decreasing Ca++ concentration in cytosol. This will take place by the activity of:
  - Ca++ pump at plasma membrane.
  - Ca++ pump at sarcoplasmic reticulum.
  - Na+-Ca++ exchange at the plasma membrane (secondary active countertransport)

!!! *The tetanus in cardiac muscle is prevented by the long refractory period of the action potential.*
ELECTROCARDIOGRAM (ECG or EKG):

Due to electrical activities (depolarization, repolarization and polarization during rest) that are taking place in the heart, there will be a flow of current generated through body fluids. This current can be recorded by placing electrodes on the body surface around the heart. The recorded current represents comparison in voltage detected at two different points on the body surface and reflects the electrical activity of atrial and ventricular muscles at the time of recording.

For the purpose of standard comparison, the routine ECG recording consists of 12 electrodes system (known as leads):

- 3 bipolar limb leads (I, II, III).
- 3 unipolar limb leads (aVL, aVR, aVF).
- 6 unipolar chest leads.

The same are used for all recordings to give common basis for comparison and for recognizing deviations from normal.

Components of ECG recording and correlation to specific cardiac events:

Normal ECG show 3 distinct wave forms:
- **P wave**: reflects depolarization of atria.
- **QRS complex**: reflects depolarization of ventricles.
- **T wave**: reflects repolarization of ventricles.

Between these waves there are three times when no current is flowing and ECG remains at the baseline. These are represented by:

- **P-R segment**: the period of time after the end of P wave and the beginning of Q if present or R wave of the QRS complex. This represents AV nodal delay.
- **S-T segment**: the period of time after S wave and the beginning of T wave. Coincides with ventricular contraction and emptying. Represents the period in which ventricles are depolarized and before repolarization is taking place (cardiac cells are undergoing the plateau phase of action potential).
- **T-P segment**: the period after T wave and the beginning of P wave of the next cycle. The heart muscle is completely at rest.
Use of ECG in diagnosis of:

* Rate abnormalities:
  
  From the ECG you can calculate the cardiac cycle. by knowing the speed of chart and distance between 2 successive and similar waves you can calculate the time of cardiac cycle.
  
  The heart rate is defined as number of cycles per 60 seconds (minute). By dividing 60/time of cardiac cycle you will get heart. The increase in heart rate over 100 beats/ minute is known as tachycardia, and the decrease below 60/minute is known as bradycardia.

* Rhythm abnormalities:
  
  Rhythm refers to regularity of the ECG waves. Any deviation normal rhythm and sequence is known as arrhythmia. An example: beats originating from an ectopic focus are common deviation of normal rhythm. These are known as extrasystoles. Other rhythm abnormalities can also be detected such as atrial flutter, atrial fibrillation, ventricular fibrillation and heart blocks.

* Cardiac myopathy:
  
  Also ECG abnormalities can be seen when heart muscle is damaged. Usually, heart muscle is unable to extract O2 and nutrients from blood within its chambers. This tissue is supplied through coronary circulation. The inadequate supply to heart muscle is known as myocardial ischemia. The complete blockage of blood vessels supplying that area of the heart is known as acute myocardial infarction. This may result in death of cardiac muscle cells (necrosis). In this case abnormal QRS wave form can be seen when portion of the heart become necrotic.
MECHANICAL EVENTS OF THE CARDIAC CYCLE:

Atria and ventricles go through separate cycles of contraction and relaxation (both ventricles contract and relax together) known as systole (for contraction) and diastole (for relaxation). Contraction appears due to stimulation of heart muscle cells during action potential, which results in Ca++ influx and also release of Ca++ from sarcoplasmic reticulum. Relaxation appears following repolarization of the heart muscle cells. We will discuss the events through which left ventricle undergoes which are identical with the events that appear in the right ventricle.

* **In the early ventricular diastole:** atria are still also in diastole (this correspond to T-P segment). At this time blood flows from atria to ventricles. This happens because of the maintained higher pressure in atria due to continuous inflow of blood from venous system. This higher pressure in atria than in ventricles keeps AV valve opened.

As a result, *ventricular volume increases even before atrial contraction takes place.*

* **In the late ventricular diastole:** SA node has fired an impulse. And depolarization will spread throughout atrial muscle (corresponding to P wave). This action potential will bring contraction of atrial muscle and more increase in atrial pressure. This will maintain AV valve opened.

As a result, *additional volume of blood is added to the ventricles by atrial contraction.*

* **At the end of diastole:** filling of the ventricles is complete. The volume of blood in ventricles at this time is about 135ml. This is known as **End Diastolic Volume (EDV),** which represents the maximum amount of blood, the ventricles can contain during cardiac cycle.

At this time, the impulse generated at SA node during diastole has passed through AV node and specialized conduction system
(bundle of Hiss and Purkinje fibers) causing depolarization of ventricles (QRS complex) signaling the onset of ventricular systole.

* **The onset of ventricular systole:** The excitation induced by depolarization will cause contraction of ventricular muscle. The contraction will cause an increase in ventricular pressure above atrial pressure.

  This will cause closure of AV valves.

The contraction continues, the increase in pressure in ventricles continues also. When the ventricular pressure (that caused by contraction) exceeds arterial (aortic and pulmonary) pressure, *this will force aortic and pulmonary valves (semilunar valves) to open.*

Between the closure of AV valves and opening of semilunar valves, no change in ventricular volume will take place as no blood is leaving or entering ventricles. This time of contraction at which no change in ventricular volume will take place is known as **isovolumetric ventricular contraction.** During this period, the pressure in ventricles continues to increase as the volume remains constant.

As a result of increasing pressure in ventricles, *this will force semilunar valves to open and ejection of blood from ventricles into aorta and pulmonary artery (ventricular ejection phase)* causing an increase in pulmonary and aortic pressure and decrease in ventricular volume.

(Note: ventricular systole includes both **isovolumetric ventricular contraction** and **ventricular ejection phase**).

* **At the end of ventricular systole:** ventricular contraction will not end with ejection of all volume of blood found in ventricles at the end diastole. Instead, about 65ml of blood remains in left ventricle after the ejection phase is complete. This is known as **End Systolic Volume (ESV)** which represents the least amount of blood found in ventricle during cardiac cycle. The amount of blood ejected out of each ventricle into aorta or pulmonary artery during ejection phase is about 70ml. This amount is known as **stroke volume.**

At the end of ventricular systole, ventricular muscle repolarize, this will be signified by T wave. And relaxation in ventricular muscle will take place. This will reduce pressure in ventricles below aortic pressure.
As a result, *semilunar valves will close*. The **closure of aortic valve** will produce a small increase in aortic pressure curve known as **dicrotic notch**.

The decrease in ventricular pressure will continue during early diastole until pressure falling below atrial pressure. This will cause opening of AV valves. During the time between closure of aortic valve and opening of AV valve, no blood can leave or enter as ventricles continue to relax (no change in ventricular volume will be). This is known as **isovolumetric ventricular relaxation**.

**Note:**
- Atrial repolarization and ventricular depolarization occur simultaneously (at the same time). So, the electrical events that accompany atrial repolarization are masked by electrical events of ventricular depolarization (QRS complex). After this time, atria become in diastole throughout the duration of ventricular systole. Blood continues to flow from pulmonary veins into left atria. As a result, pressure inside atria increases and blood is accumulated at this site. Once AV valves are opened at the beginning of ventricular diastole, rapid flow of blood from atria to ventricle will cause a rapid increase in ventricular volume. So, in **early ventricular diastole** rapid filling phase of ventricles will take place. Then, ventricular filling is proceeding slowly throughout remaining time of atrial diastole (reduced filling phase). Once atria becomes in systole more ventricular filling will take place (filling caused by atrial contraction). Most of ventricular filling takes place in the **early diastole during rapid filling phase**.

**HEART SOUNDS:**

Two major heart sounds are usually heard with stethoscope during cardiac cycle. The first heart sound is low-pitched, soft, and relatively long (is said like lubb), and associates the closure of AV valves. The second heart sound has higher pitch, and is shorter and sharper (is said like dupp), and associates the closure of semilunar valves.

The closure of AV valves appears when pressure inside ventricles rises above the pressure in atria, **the first heart sound that resulted from this closure will signal the onset of ventricular systole**.

The closure of semilunar valves occurs at the onset of ventricular relaxation. So, **the second heart sound signals the onset of ventricular diastole**.
Abnormal function of valves will result in abnormal heart sounds called **heart murmurs**.

**Cardiac output (CO):**

Volume of blood ejected from left ventricle into systemic circulation or from right ventricle into pulmonary circulation in each minute (ml/minute).

\[
\text{CO} \quad = \quad \text{SV (stroke volume)} \times \text{HR (heart rate)}.
\]

\[
\text{ml/min} \quad \times \quad \frac{\text{ml/beat}}{\text{beats/min}}
\]

The volume ejected each minute is closed to the total blood volume (5 liters).

*Any factor that can affect HR or SV will change cardiac output (CO).*

**Regulation of cardiac output:**

**Regulation of stroke volume:**

3 factors are important in the regulation of stroke volume:

1. **preload:**

   Stroke volume depends on end diastolic volume. The more blood enters ventricles during diastole, the more ejection of blood will be during the next systole.

   Usually, the more return of blood (venous return) will cause more ventricular filling. The more filling will result in a greater ejection of blood from ventricles according to **(Frank-Starling law of the heart)**.

   The preload depends on the **duration of ventricular diastole and venous pressure**. The duration of ventricular diastole will affect the time of ventricular filling. A shorter ventricular diastole will decrease ventricular filling and decrease the preload. This will happen when heart rate exceeds 160 beats/minute, which results in a very short filling time.
The venous pressure will affect the return of blood into the right ventricle. More pressure in veins results in a more volume of blood returning into the right ventricle and more forceful contraction during the next systole.

2. Contractility:

The stroke volume depends also on the strength of cardiac muscle contraction (contractility). Any substance that can increase contractility of the heart muscle is having a positive inotropic effect. An example of these: increased Ca++ in the extracellular fluid, increased sympathetic stimulation, digitalis, and epinephrine. Other situations may result on negative inotropic effects such as decreased sympathetic stimulation, increased K+ in the extracellular fluid, and the use of Ca++ channel blockers.

3. Afterload:

Ejection of blood from ventricles requires higher pressure in ventricles than in arteries. The pressure that must be overcome to cause opening of semilunar valves and ejection of blood is called the afterload. Any condition that results in an increase in the afterload will decrease the stroke volume causing more blood to remain in ventricle at the end of diastole.

Regulation of the heart rate:

1. Autonomic regulation of the heart rate:

Signals that regulate heart rate originate in cardiovascular centers located in medulla oblongata. This center receives inputs from proprioceptors (receptors in striated muscles), chemoreceptor (receptors that monitor chemical changes in the blood), and baroreceptors (receptors monitoring pressure changes in blood vessels). Other inputs are received by cardiovascular centers from higher centers in the brain such as cerebral cortex and limbic system.

Cardiovascular center affects the activity of the heart by fibers that can stimulate sympathetic system or parasympathetic system.

Sympathetic system: originates in the thoracic region of the spinal cord. The norepinephrine (released by sympathetic fibers) acts on β1 receptors to:
1. Increase the rate of depolarization of SA and AV node. This will result in increased pacemaker firing and a higher heart rate. (Positive Chronotropic Effect)

2. Increase contractility of heart muscle by enhancing Ca++ entry through voltage gated slow Ca++ channels. (Positive Inotropic Effect).

**Parasympathetic system:** fibers via vagus nerve that release Ach, which act on M receptors to:

1. Slow the rate of depolarization of SA and AV nodes. This will decrease pacemaker firing and heart rate. (Negative Chronotropic effect).

**2. Chemical regulation of heart rate:**

**Hormones:**
- Epinephrine released by adrenal gland to act in the same way as norepinephrine.
- Thyroid hormones also can increase heart rate. (These hormones increase expression of β (beta) adrenergic receptors)

**Ions:**
Relative concentration of K+, Na+ and Ca++ affect heart rate and cardiac contractility.

**3. Other factors can affect heart rate:**
age, fever, and hypothermia.