Cardiovascular system is one of the eleven systems of the human organism that plays a critical role in maintaining its homeostasis. The vital role of the CV system makes life impossible without its proper functioning. The CV system is responsible for the following:
1. supplying the tissue and cells of the organism with the needed oxygen and nutrients, without which the organism will not be able to survive.
2. Getting rid of carbon dioxide by circulating it from the peripheral tissues toward the lung, where it will be eliminated, and getting rid of other waste products of the metabolism by circulating them toward the renal system.
3. Participating in protection of the body and wound healing by circulating white blood cells, immune antibodies and other immune modulators.
4. Regulation of body temperature, fluid-electrolytes balance, and acid-base balance.
5. Transporting of hormones, cytokines, drugs, and other chemical substances.

Important note: Heart is just a pump. It has nothing to do with emotions or critical thinking.

Cardiovascular system is composed of three major components that form the circulation:
1- The heart: as a pumping organ of the circulatory system which pumps blood in the arteries and receives it back by the veins.
2- Blood vessels: as containers, through which the circulation of blood takes place.
3- The blood: as a transport medium of the circulation.

During the following chapter we will view the structural and functional properties of those components and the role of each that enables our organism to survive.

1- Cardiac Physiology:

Physiologic anatomy of the heart
Heart is a hollow muscular organ that is located in the middle mediastinum between the two bony structures of the sternum and the vertebral column.

Clinical Physiology:
- Location of heart is a very important one for applying the cardiopulmonary resuscitation (CPR), as it is found between the rigid vertebral column and the flexible sternum. When the sternum is suppressed by applying pressure on the sternum the heart will be emptied, as it will be filled back with blood when the pressure on sternum stops.
- Location of the heart in the middle mediastinum offers a chance for alternative echocardiography (visualizing cardiac structure using the ultrasound waves) by inserting a transducer of ultrasound inside the esophagus. The procedure is known as transesophageal echocardiography.

The heart has a shape of clenched fest that weighs about 300 grams (with mild variation between male and female).

Heart has an apex that is anteriorly, inferiorly, and leftward oriented, and a base, that is posteriorly, superiorly and rightward oriented.

Clinical Physiology: Knowing the orientation of cardiac apex and base is important for applying good physical exam. Apex of the heart can be easily detected by palpitation during the physical
Auscultation of heart can be properly applied when we know the exact location of the apex and base of the heart. Placing the stethoscope on the apex of the heart (fifth intercostal space) enables us to auscultate the mitral valve the best, while placing it on the right second intercostal space near the sterna margin enables us to auscultate the aortic valve. Placing the stethoscope in second left intercostal space enables us to auscultate the pulmonary valve.

In addition to its apex and base the heart has three surfaces: anterior, posterior and left surfaces.

The wall of the heart: The cardiac wall is composed of three layers:

1. **Endocardium**: The innermost layer, which lines the heart chambers and is in direct contact with the blood. It is composed of endothelial cells that are similar to those that line the blood vessels, which assure a smooth surface that is necessary for laminar blood flow, which prevents blood clotting.

   **Clinical Physiology**

   Endocarditis is the inflammation of the endocardium. It is resistant to antibiotic treatment and difficult to cure. Endocarditis usually involves heart valves and chordae tendineae too. Vegetations usually develop as a consequence and increase the risk of clot formation.

2. **Myocardium**: The middle layer of the cardiac wall. It is the thickest among the three layers, which is composed of two types of cardiac muscles:

   a. contractile muscle cells (form about 98-99% of the cardiac muscle).
   b. non-contractile muscle cells (form about 1-2 % of the cardiac muscles and are the cells that form excitatory-conductive system of the heart).

   The cardiac muscle cells are similar to the skeletal muscles in being striated, but similar to the smooth muscles in being involuntary and connected to each other’s by gap junctions that facilitate conduction of electrical potential from one cell to the others. Desmosomes adhere cardiac muscle cells to each others. Cardiac muscle fibers are arranged in a latticework system (fibers divide and then reconnect to each other’s).

3. **Epicardium**: is the outermost and protective layer of the heart. It is composed of connective tissue and forms the inner layer of the serous pericardium (see below).

**Pericardium:**
The heart is surrounded by a fluid-fill sac, which is known as pericardium. Pericardium is composed of two layers (doubled layer membrane), between which a fluid-fill pericardial cavity exist.

The outer layer is called fibrous pericardium, while the inner layer is called serous pericardium; the later is subdivided into parietal pericardium and visceral pericardium. The visceral pericardium is the previously mentioned outermost layer of heart (epicardium). Pericardial cavity is filled by a clear straw-colored fluid, which volume is about 15-50 ml. It has rich protein and LDH contents. The fluid decreases friction between the pericardial layers as it allows the membrane to glide over each others during the cardiac cycle. Pericardial sac plays an important role in protection of heart from external hazards and infections, as it fixes the heart and limits its motion. It also prevents excessive dilation of the heart.

Clinical physiology:
When there is excessive fluid in the pericardial cavity as a result of pericardial effusion, a cardiac tamponade will develop. Cardiac tamponade means compression of the heart within the pericardial sac, which will prevent the relaxation of the heart (heart will not be able to fully expand), and thus the circulating blood volume will be decreased (obstructive shock). This is a life threatening situation which has to be urgently cured by pericardiocentesis.

Chambers of the heart: Heart has four chambers: two atria and two ventricles. The two right and left atria are separated from the two ventricles by the fibrous skeleton that almost electrically isolates the atriae from ventricles, the thing that makes the AV node the sole electrical link between the atriae and the ventricles.

The fibrous skeleton involves the right (tricuspid) and left (bicuspid) valves. Right and left atriae are separated from each other by the interatrial septum.

The two ventricles are separated by the interventricular septum. Interventricular septum is a muscular one in its lower thick part and fibrous in its upper thin part.

The right atrium receives blood from the two venae cavae, while the left atrium receives blood from the pulmonary veins.

The two atriae hold the blood returning from the veins and empty it only in a given right moment into the ventricles. Ventricles pump the blood into the arteries. The wall of the left ventricle is thicker than that of the right ventricle. Left ventricle pumps oxygenated blood into the aorta and the right ventricles pumps deoxygenated blood in the pulmonary artery.
Heart valves:
There are four valves in the heart: Two atrioventricular valves and two semi-lunar valves:

1. Atrioventricular (AV) valves: These valves are found between the atria and ventricles. Depending on the number of the leaflets, the right atrioventricular valve is also called tricuspid valve (has three leaflets), while the left one is called bicuspid valve (has two leaflets). The shape of the bicuspid valve is similar to the mitre of bishop, so it is also called the mitral valve. The leaflets of the valves are attached to a fibrous ring, called fibrous annulus, while the tips of the leaflets are attached to threads (composed of collagen fibers), known as chordae tendineae, which from their side are attached to papillary muscles in the ventricles. These valves prevent backward flow of blood from ventricles during the systole.

2. Semi-lunar valves: These valves are located on the base of the arteries (aorta and pulmonary artery). They prevent the backward flow of blood from the arteries into ventricles. The structure of the semilunar valves is quite different from that of the AV valves, as they have crescent-shaped cusps that do not have chordae tendineae, instead these cusps are like pockets which are filled of blood when it returns to the ventricles from the lumen of arteries during the diastole, so they get closed and prevent the backward flow of blood.
Clinical Physiology:
Valves are target of many pathological processes that cause what is known collectively as valvular diseases of the heart. The causes are variable. Congenital malformation, infections, metabolic diseases and others may affect the valves and decrease their functional performance. Valvular diseases are usually expressed as valvular stenosis or deficiency. Stenosis impairs normal filling of cardiac chambers (AV valve stenosis) or impair emptying (semilunar stenosis). Valvular insufficiency causes backflow of blood, which interferes with normal proceeding of the cardiac cycle.

Properties of cardiac muscle
Cardiac muscle is a striated muscle like the skeletal muscle, but it is different from the skeletal muscle in being involuntary and syncytiial.
Syncytium means that cardiac muscle cells are able to excite and contract together due to the presence of gap junctions between adjacent cardiac cells. As we mentioned earlier, the cardiac muscles are of two categories: contractile and noncontractile muscles.
Cardiac muscle has four properties, due to which the heart is able to fulfill its function as a pumping organ. Studying and understanding these properties is essential for students to understand the cardiac physiology as a whole.
1. Rhythmicity (Chronotropism): means the ability of heart to beat regularly (due to repetitive and stable depolarization and repolarization). Rhythmicity of heart is of a myogenic in origin, because cardiac muscles are automatically excited muscles and does not depend on the nervous stimulus to initiate excitation and
then contraction. The role of nerves is limited to the regulation of the heart rate and not to initiate the beat. There are many evidences that approve the myogenic and not neurogenic origin of the rhythmicity of cardiac muscle. For example:

- Transplanted heart continues to beat regularly without any nerve supply after cutting of nerves of the transplanted heart.
- Embryologically the heart starts to beat before reaching any nerves to them. This is specially observed in chicken embryo.
- Some drugs that paralyze the nerves (such as cocaine) do not stop the heart in given doses.

Spontaneous rhythmicity of the cardiac muscle due to the existence of excitatory-conductive system, which is composed of self-excitation non-contractile cardiac muscle cells. The SA node of the mentioned system excites in a rate, that is the most rapid among the other components of the system (110 beats/minute), which makes it the controller or (the pacemaker) of the cardiac rhythm of the entire heart.

Mechanism, responsible for self-excitation in the SA node and the excitatory conductive system is due to the following properties of the cell membrane of these cells:

1. Non-gated sodium channels, that allows influx of sodium down its concentration gradient (funny current).
2. Decreased permeability to potassium
3. Existence of slow and fast calcium channels.

These properties enable the cations (sodium through the none-gated sodium voltage channels, calcium through calcium slow channels) to enter the cell and depolarize the cell membrane without need for external stimulus.

The resting membrane potential of non-contractile cardiac cell is -55 -60 millivolts (less than that of excitable nerve cells -70). The threshold is also less negative than that of nerve cells (-40 millivolts, compared to -55 mV of nerve cell membrane).

The decreased permeability to potassium from its side decreases the efflux of potassium during the repolarization phase of the pacemaker potential. All of these factors give the pacemaker potential its characteristic shape (see the figure bellow)

![Diagram](image.png)

Repeating of the pacemaker potential between the action potentials of contractile muscle cells is the cause of spontaneous rhythmicity of cardiac muscle cells.

**Factors, affecting the rhythmicity of the cardiac muscle:**

I. Factors that increase the rate (positive chronotropic factors):

1. sympathetic stimulation: as its neurotransmitter norepinephrine increases the membrane permeability to sodium and calcium.
2. moderate warming: moderate warming increases temperature by 10 beats for each 1 Fahrenheit degree increase in body temperature, this is due to decrease in permeability to potassium ions in pacemaker membrane by moderate increase in temperature.
3. Catecholaminic drugs have positive chronotropic effect as they have similar mechanism of action.
4. Thyroid hormones: have positive chronotropic effect, due to the fact that these drugs increase the sensitivity of adrenergic receptors to adrenaline and noradrenalin.
5. Mild hypoxia, as it causes partial depolarization of cardiac muscle cell membrane.
6. mild alkalemia: mild alkalemia decreases the negativity of the resting potential.

II. Factors that decrease rhythmicity (negative chronotropic):
1. Vagal stimulation: the basal level of vagal stimulation inhibits the sinus rhythm and decreases it from 110-75 beats/minute. This effect is due to increase in permeability of the cardiac muscle cell to potassium, which causes rapid potassium efflux, leading to increase in the negativity inside the cardiac cells (hyperpolarization).
2. Moderate cooling
3. Severe warming: due to cardiac damage, as a result of intercellular protein denaturation. Excessive cooling on the other hand decreases metabolism and stops rhythmicity.
4. Cholinergic drugs (such as methacholine, pilocarpine..etc) have negative chronotropic effect.
5. Digitalis: these drugs causes hyperpolarization of the cell membrane. This effect is similar to that of vagal stimulation.
6. Acidemia. This is due to denaturation of cell membrane proteins
7. Typhoid or diphtheria toxins.

2. Excitability (Bathmotropism): Excitability means the ability of cardiac muscle to respond to signals. Here we are talking about contractile muscle cells that are excited by the excitatory conductive system and generate an action potential.

Cardiac action potential is similar to action potential in nerve and skeletal muscle tissue, with one difference, which is the presence of plateau phase. Plateau phase is unique for cardiac muscle cells.
The resting membrane potential for cardiac muscle is about -80 mV.
When the cardiac muscle is stimulated an action potential is generated. The action potential in cardiac muscle is composed of four phases, which are:
1. Depolarization phase (Phase 0):
   A result of opening of sodium channels, which increase the permeability to sodium, which will lead to a rapid sodium influx into the cardiac muscle cell.
2. Repolarization: Repolarization in cardiac muscle is slow and triphasic:
   a. Phase 1 (early partial repolarization): A small fast repolarization, results from potassium efflux and chloride influx.
   b. Phase 2 (Plateau): After the early partial depolarization, the membrane remains depolarized, exhibiting a plateau, which is a unique phase for the cardiac muscle cell. Plateau is due to opening of slow calcium-sodium channels, delay in closure of sodium channels, and to decreased potassium efflux.
   c. Phase 3 (Rapid repolarization): opening of potassium channels and rapid efflux of potassium.
   d. Phase 4 (Returning to resting level) in other words: The phase of complete repolarization. This is due to the work of sodium-potassium pump.
Absolute refractory period:
Coincides with phase 0, phase 1, and phase 2. During this period, excitability of the heart is totally abolished. This prevents tetanization of the cardiac muscle and enables the heart to contract and relax to be filled by blood.

Relative refractory period:
Coincides with the rapid repolarization and allows the excitability to be gradually recovered.

Clinical Physiology: Extrasystole is a pathological situation, due to abnormal impulses, arising from ectopic focus. It is expressed as an abnormal systole that occur during the early diastole. Extrasystole is due to a rising of excitability above the normal, which usually occurs after the end of the relative refractory period (read about staircase phenomenon of Treppe).

Ventricular Extrasystole

3. Conductivity: Means ability of cardiac muscle to propagate electrical impulses through the entire heart (from one part of the heart to another) by the excitatory-conductive system of the heart. Excitatory conductive system of the heart involves:
1. Sinoatrial node (SA node): Here the initial impulses start and then conducted to the atria through the anterior inter-atrial pathway (to the left atrium), to the atrial muscle mass through the gap junction, and to the Atrioventricular node (AV node) through anterior, middle, and posterior inter-nodal pathways. The average conductive velocity in the atria is 1 m/s.

2- AV node: The electrical impulses cannot be conducted directly from the atria to the ventricles, because of the fibrous skeleton, which is an electrical isolator, located between the atria and ventricles. So the only conductive way is the AV node. But there is a delay in the conduction occurs in the AV node.

This delay is due to:
- The smaller size of the nodal fiber.
- The less negative resting membrane potential
- Fewer gap junctions.

There are three sites for delay:
- in the transitional fibers, that connect inter-nodal pathways with the AV node (0.03).
- AV node itself (0.09 s).
- In the penetrating portion of Bundle of Hiss (0.04 s).

This delay actually allows atria to empty blood in ventricles during the cardiac cycle before the beginning of ventricular contraction, as it prevents the ventricles from the pathological high atrial rhythm.

The average velocity of conduction in the AV node is 0.02-0.05 m/s

3- Bundle of Hiss: A continuous with the AV node that passes to the ventricles through the inter-ventricular septum. It is subdivided into: Right and left bundle. The left bundle is also subdivided into two branches: anterior and posterior branches.

4- Purkinje’s fibers: large fibers with velocity of conduction 1.5-4 m/s.

the high velocity of these fibers is due to the abundant gap junctions, and to their nature as very large fibers as well.

The conduction from AV node is a one-way conduction. This prevents the re-entry of cardiac impulses from the ventricles to the atria.

Lastly: The conduction through the ventricular fibers has a velocity of 0.3-0.5 m/s.

4. Contractility: Means ability of cardiac muscle to convert electrical energy of action potential into mechanical energy (work).

Excitation contraction relationship: Contraction of cardiac muscle starts after depolarization and continues for about 250 ms, reaching its maximum at the end of the plateau.

Excitation of plasma membrane will open calcium channels and thus calcium efflux increase. The increase calcium inside the cardiac muscle cell will stimulate the sarcoplasmic reticulum to release the stored calcium. The increased calcium will then stimulate the myofilaments in the cardiac muscle cell to initiate contraction.
The excitation-contraction coupling of cardiac muscle is similar to that of skeletal muscle, except the lack of motor nerve stimulation. Cardiac muscle is a self-excited muscle, but the principles of contraction are the same. The difference is only in calcium influx, as the cardiac muscle does not need a nerve signal to cause the calcium pumping from the sarcoplasmic reticulum, instead, the extracellular calcium that influx through the t-tubules causes pumping of calcium. So; cardiac muscle contraction depends on both extracellular calcium and the sarcoplasmic calcium. For that, the t-tubule of cardiac muscle cells are with five times larger than that of skeletal muscle cells, but the sarcoplasmic reticulum is less developed.

The steps of contraction of cardiac muscle are:

- The action potential of sarclemma opens voltage-dependent calcium channels.
- Calcium that has been influxed through the membrane of t-tubules will activate ryanodine receptor channels in the membrane of the sarcoplasmic reticulum, this will release the calcium ions.
- Calcium ions then attach to the Troponin and causes changes in shape and position of troponin, which will move the Tropomyosin, which is attached to Troponin, this in turn will uncover the myosin binding site on Actin molecule (G actin).
- Uncovering of myosin binding site will enable the myosin head to connect to actin and swivel, this will pull the actin forward.
- Here we have to notice that many myosin heads (not only a single head) swivel in the same time, pulling the entire thin filament forward.
- ATP molecule bind to the myosin head at the end of swivel, breaking the bond between the actin and myosin and the myosin swivel backward. This would break the ATP into ADP and organic phosphate Pi, which causes the myosin to bind to a new actin molecule and swivel forward again.
- The end result of this series of processes is shortening of the sarcomere.

Relaxation of cardiac muscle cell occurs as follows:

- at the end of plateau phase the calcium influx is cut off.
- calcium is pumped back to the sarcoplasmic reticulum by the calcium ATPase pump and to the ECF by the Na-Ca exchanger.
- When the intracellular calcium is decreased, the contraction stops.

Note: Duration of contraction in atrial cardiac muscle cells is shorter (0.2 s) than that of the ventricular cells (0.3 s).

There are many rules that control the contractility of the cardiac muscles, which are:

1. All or none rule: due to the syncytial nature of the cardiac muscle. There are atrial syncytium and ventricular syncytium. This rule makes the heart an efficient pump.
2. Staircase phenomenon: means gradual increase in muscle contraction following rapidly repeated stimulation.
3. Starling's law of the heart: The greater the initial length of cardiac muscle fiber, the greater the force of contraction. The initial length is determined by the degree of diastolic filling. The pericardium prevents overstretching of heart, and allows optimal increase in diastolic volume. Thankful to this law, the heart is able to pump any amount of blood that it receives. But overstretching of cardiac muscle fibers may cause heart failure.
Cardiac cycle

**Definition:** The mechanical events, occurring in the heart within one beat (from the beginning of a heart beat to the beginning of the next beat).

Cardiac cycle involves five stages. The first two of five are responsible for filling the ventricles. During these two stages, the blood moves from the atria to fill the ventricles. The other three stages are responsible for emptying the ventricles and ejecting blood into the arterial system.

To understand these events of the cardiac cycle let's imagine that we are describing events occurring within one half of the heart only (right or left) because the same events occur simultaneously in the other one.

**Phases of cardiac cycle:**
1. Early diastole (also called the atrial diastole, or complete heart diastole): During this phase:
   - Atria are relaxed
   - Ventricles are relaxed
   - Semilunar valves are closed
   - Atrioventricular valves are open

   During this phase the blood moves passively from the venous system into the ventricles (about 80% of blood fills the ventricles during this phase).

2. Atrial systole: During this phase:
   - Atria are contracting
   - Ventricles are relaxed
   - AV valves are open
   - Semilunar valves are closed
   - Atrial pressure increases. The a wave of atrial pressure appears here.
P wave of ECG starts here

Intraventricular pressure increases due to the rush of blood then decreases due to continuous relaxation of ventricles.

The remaining 20% of blood is moved to fill the ventricles during this phase, due to atrial contraction.

3. Isovolumetric contraction: During this phase:
   - Atria are relaxed
   - Ventricles are contracting
   - AV valves are closed
   - Semilunar valves are closed
   - First heart sound
   - QRS complex.
   - The c wave of intra atrial pressure appears here, due to the bulging of AV valve into the atrium.

The ventricular fibers start to contract during this phase, and the intraventricular pressure increases. This results in closing the AV valves, but the pressure is not yet enough to open the semilunar valves, so the blood volume remains unchanged, and the muscle fibers length also remain unchanged, so we call this phase as Isovolumetric contraction (iso: the same, volu=volume, metric=length).

4. Ejection phase: Blood is ejected from the ventricles into the aorta and pulmonary artery.
   During this phase:
   - Ventricles are contracting
   - Atria are relaxed
   - AV valves are closed
   - Semilunar valves are open
   - Second heart sound
   - Intraventricular pressure is increased, due to continuous contraction
   - Increased aortic pressure.
   - T wave starts.
   - At the end of this phase the v wave of atrial pressure appears.

5. Isovolumetric relaxation: This phase due to backflow of blood in aorta and pulmonary system after the ventricular contraction is up and the ventricles relax. This backflow closes the semilunar valves.
   During this phase:
   - Ventricles are relaxed
   - Atrial are relaxed
   - Semilunar valves are closed.
   - AV valves are closed.
   - Ventricular pressure fails rapidly
   - Atrial pressure increases due to continuous venous return. The v wave appears here.
   - Aortic pressure: initial sharp decrease due to sudden closure of the semilunar valve (diacrotic notch), followed by secondary rise in pressure, due to elastic recoil of the aorta (diacrotic wave)
   - T wave ends in this phase
Heart sounds

Heart sounds are a result of beating heart and resultant blood flow that could be detected by the stethoscope during auscultation. Auscultation is a part of physical examination that doctors have to practice them perfectly.

Before discussion the origin and nature of the heart sounds we have to distinguish between the heart sounds and hurt murmurs. Heart murmurs are pathologic noises that results from abnormal blood flow in the heart or blood vessels.

Physiologically, blood flow has a laminar pattern, which means that blood flows in form of layers, where the central layer is the most rapid. Laminar blood flow could be turned into turbulent one.

![Laminar Flow vs Turbulent Flow](image)

Turbulent blood flow is a result of stenotic (narrowed) valves or blood vessels, insufficient valves, roughened vessels' wall or endocardium, and many other diseases. The turbulent blood flow causes noisy murmurs inside or outside the heart.

Heart sounds (especially first and second sounds) are mainly a result of closure of the valves of the heart, while the third sound is a result of vibration of ventricular wall and the leaflets of the opened AV valves after rapid inflow of blood from the atria to ventricles. The third heart sound is physiologic in children but pathological in adults.

The four heart sound is a result of the atrial systole and vibration of the AV valves, due to blood rush during atrial systole. It is inaudible neither in adults nor in children. It is just detectable by the phonocardiogram.
Phonocardiogram is a special device, designed to detect sounds with low frequency and amplifying them to be recorded by a special apparatus.

Characteristic of heart sounds:
1. First heart sound (S1, lub): a soft and low pitch sound, caused by closure of AV valves. Usually has two components (M1 (mitral) and T1 (tricuspid). Normally M1 precedes T1.
2. Second heart sound (S2, dub) : sharp and high pitch sound. It is caused by closure of semilunar valves. It also has two components A2 (aortic) and P2 (pulmonary). A2 precedes P2.
3. Third heart sound (S3): low pitched sound.
4. Fourth heart sound (S4) very low pitched sound.
As we notice: the first three sounds are related to ventricular activity, while the fourth heart sound is related to atrial activity.
Closure of valves is not the direct cause for heart sounds, but sharp blocking of blood of backward returning of blood by the closing valve is the direct cause.
Here is how heart sounds appear on phonocardiogram. Some pathological murmurs are also presented:

email me for any questions or any other notes:
aqra1971abdul@gmail.com