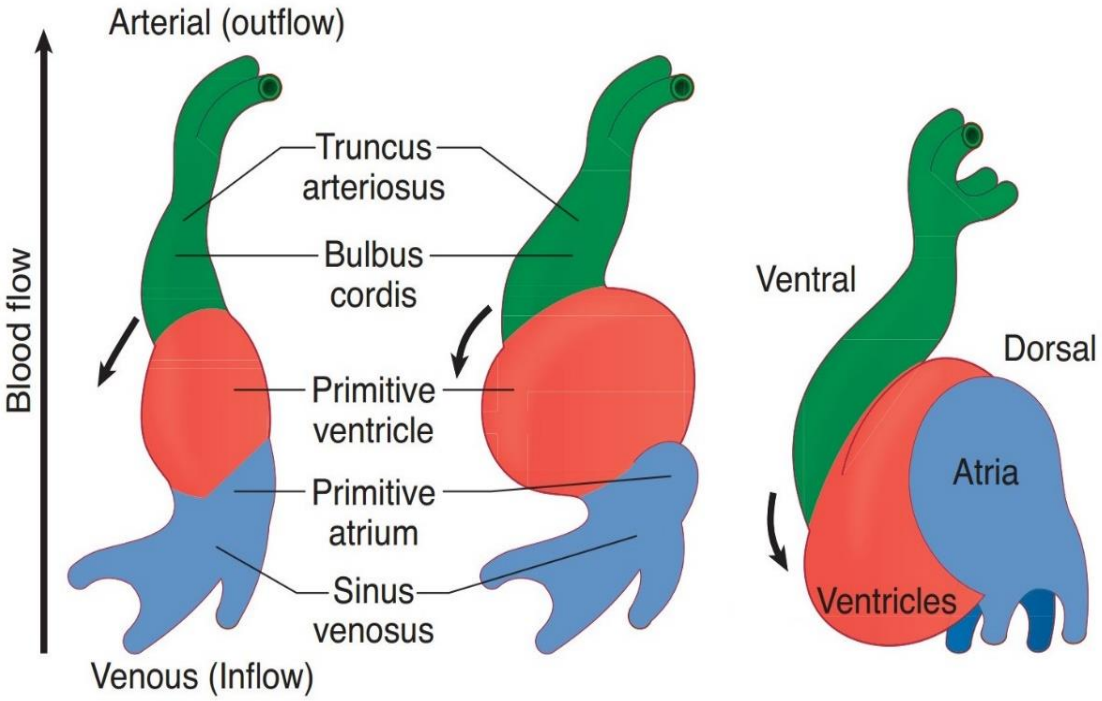
CHAPTER 1

Embryology

Development of the Heart

- First functional organ in vertebrate embryos; beats spontaneously by week 4 of development.
- Heart development begins with the formation of two endocardial tubes which merge to form the tubular heart, also called the primitive heart tube.
- The primitive heart tube forms 4 dilatations and a cranial outflow tract (truncus arteriosus).



Septation of the chambers

- The heart tube undergoes major septation events to divide it into a right and left heart.
- The atrial, ventricular, and truncal septations occur concurrently.

Septation of the Atria

- Complete septation of the atria does not occur until birth.
- During fetal circulation, it is critical that there is continuous right to left shunting (foramen ovale) across the interatrial wall to provide oxygenated blood to the left heart and systemic circulation.
- Atrial septation involves the formation of two foramina and two septa and the foramen ovale.

- The major events and structures of atrial septation include:

A. Septum Primum:

- Septum primum grows downward toward the endocardial cushion from the roof of the primitive atrium.

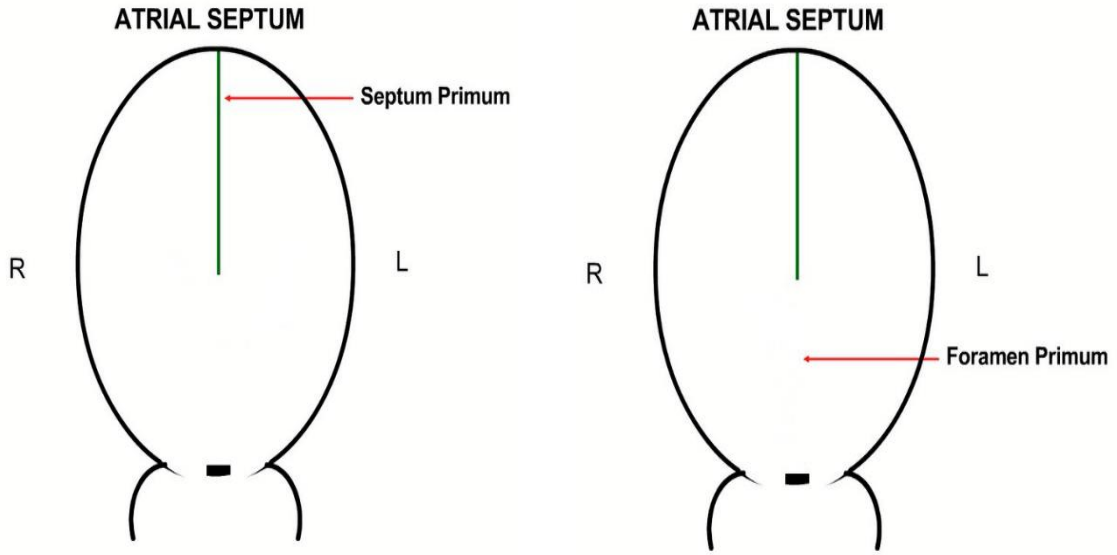
- There is a space between the first septum and the endocardial cushion called the foramen primum.

B. Foramen Primum:

- The foramen primum is closed by the fusion of the septum primum with the endocardial cushion a short time later.

- Neural crest cells migrate into the endocardial cushion.

- The endocardial cushion contributes to the right and left atrioventricular canals, the atrioventricular valves, membranous part of the interventricular septum, and the aorticopulmonary septum.



C. Foramen Secundum:

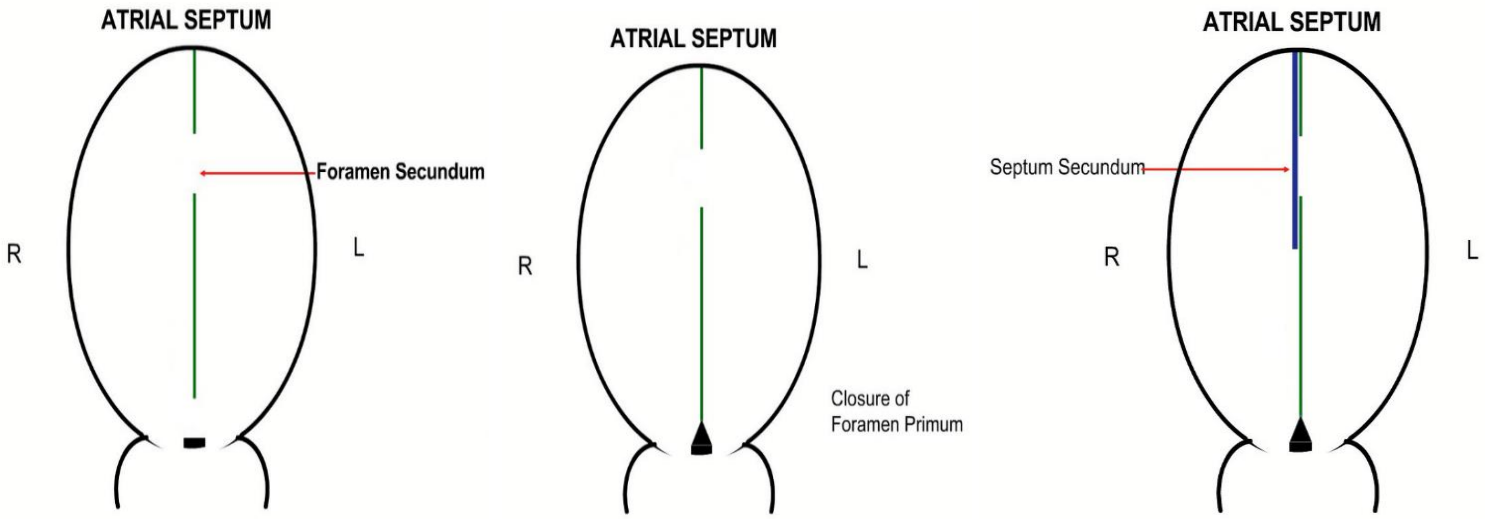
- The foramen secundum forms in the upper part of septum primum as a result of programmed cell death.

- This new opening is the second foramen; it shunts blood right-to-left.

D. Septum Secundum:

- The septum secundum grows from the roof downward to the right of the first septum and overlaps the septum primum.

- They later fuse and form the atrial septum.



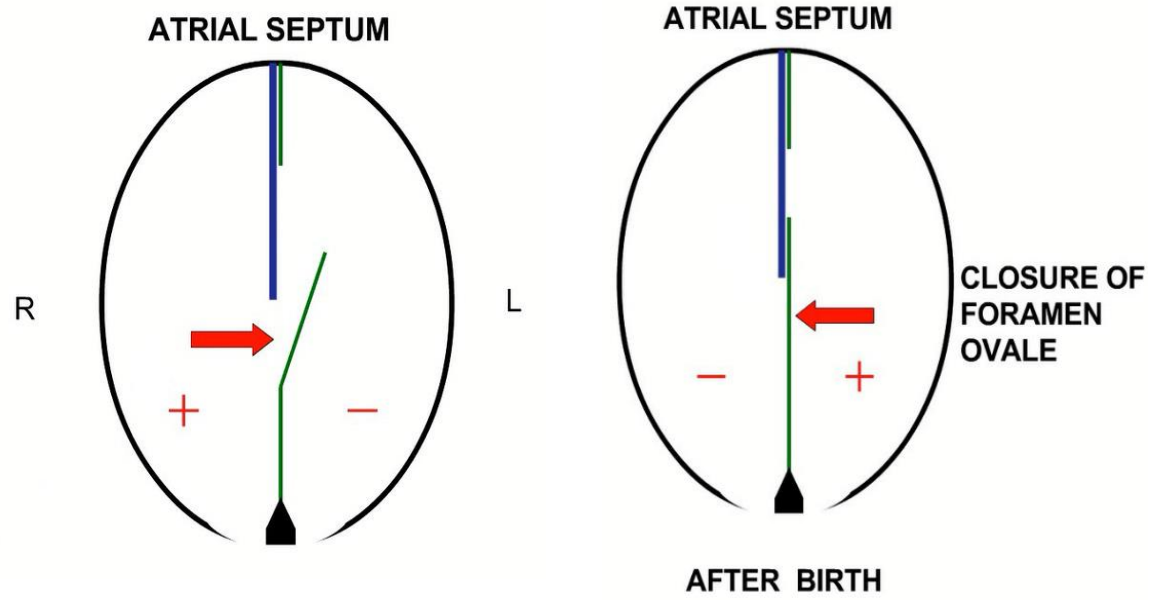
E. Foramen Ovale:

- Foramen ovale is the oval opening in the septum secundum as it overlaps the foramen secundum that provides flow between the two atria.

- At birth, there is a reversal of atrial pressures, with left atrial pressure going higher than the right atrium.

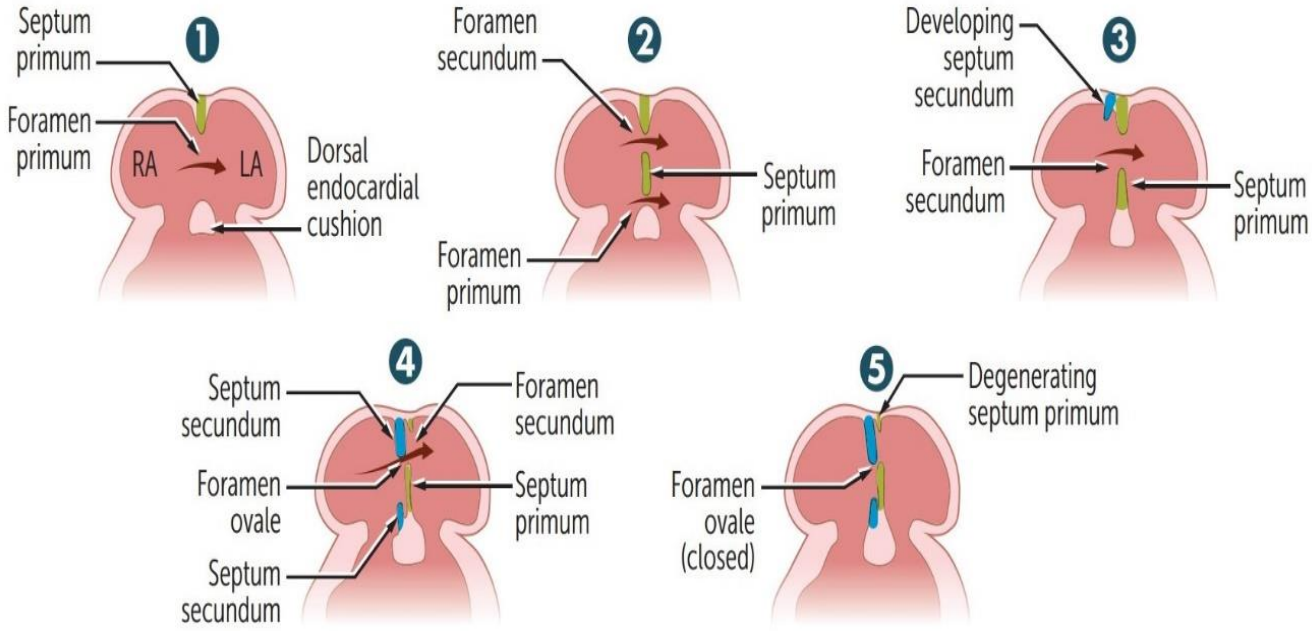
- This results in the closure of foramen ovale by pushing the septum primum against the septum secundum.

- This change in pressure is due to the decrease in the volume of blood and pressure in the right atrium with the cutting of the umbilical vein and the opening of the pulmonary circuit, and the decrease in pulmonary resistance.



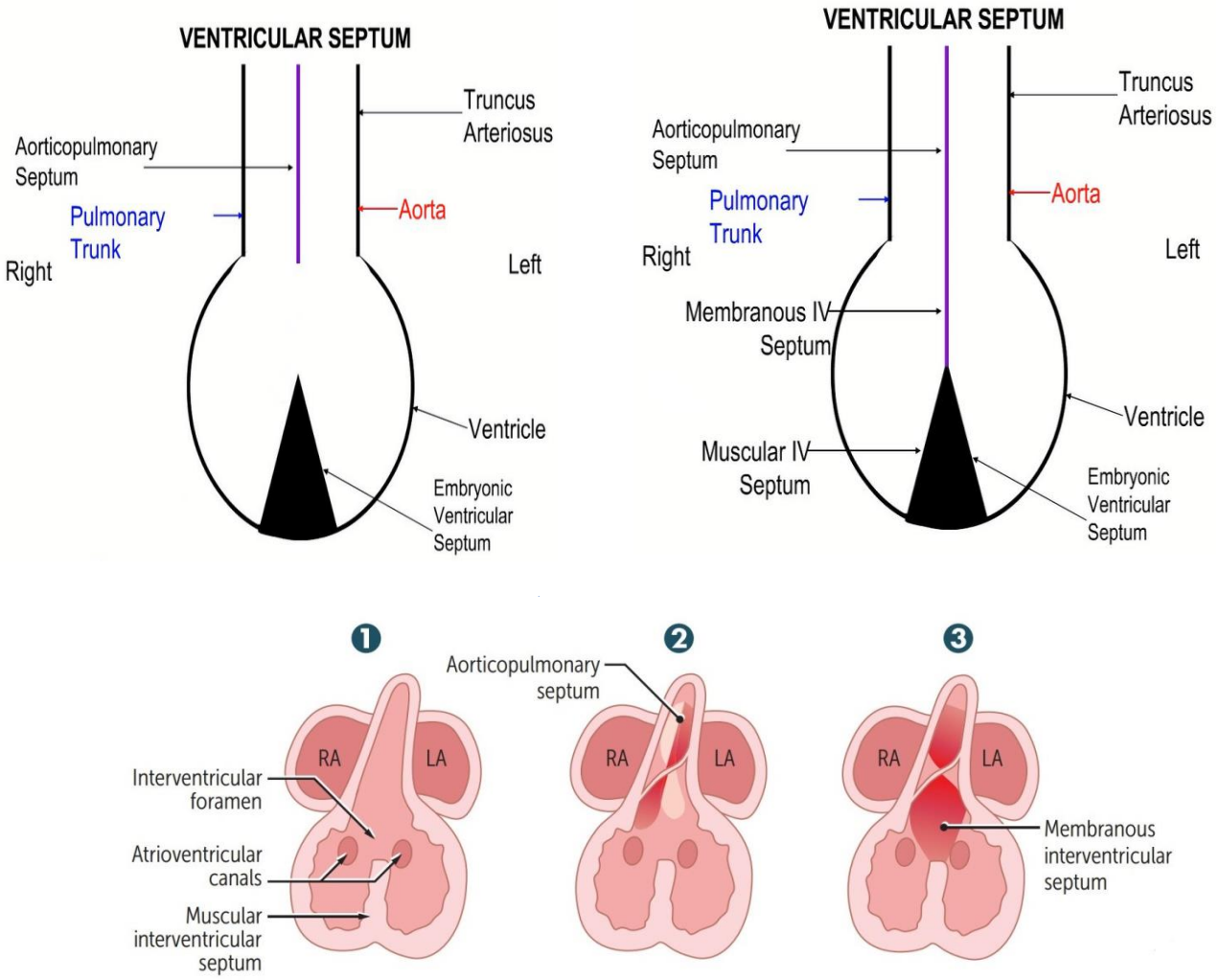
❖ N.B:

- Patent foramen ovale is caused by failure of septum primum and septum secundum to fuse after birth; most are left untreated.
- Can lead to paradoxical emboli (stroke in the setting of venous thromboembolism), similar to those resulting from an ASD.



Septation of Ventricles

- Unlike atrial septation, ventricular septation occurs completely without any prenatal shunting before birth.
- The fully developed interventricular septum is formed by two components: mostly by a thick muscular part and a thin, non-muscular (membranous) part at the superior end.
- The muscular part of the septum forms by an upward growth of muscle from the floor of the primitive ventricle toward the endocardial cushion. It does not reach the cushion and leaves an open IV foramen.
- The membranous part forms mostly from the bulbar ridges (site of neural crest migration) of the endocardial cushions.
- The membranous part closes the IV foramen and completes ventricular septation.
- Growth of endocardial cushions separates atria from ventricles and contributes to both atrial septation and membranous portion of the interventricular septum.



Septation of the Truncus

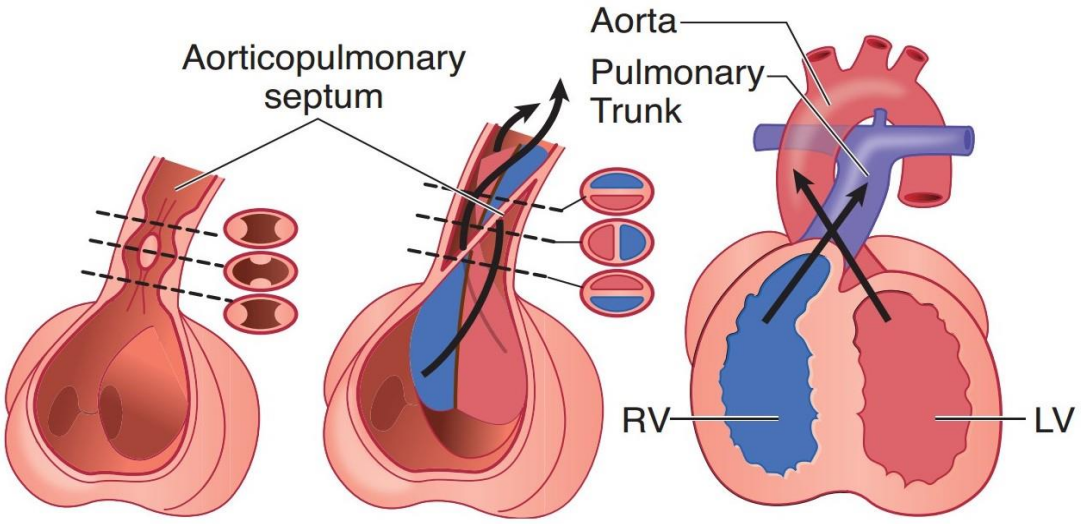
- During the fifth week, pairs of ridges develop from the endocardial cushion and Form on the walls of the truncus.
- The ridges twist around each other as they grow and form a spiral septum within the truncus called the aorticopulmonary septum (AP).
- The spiral septation of the truncus results in the formation of the aorta and pulmonary trunks and the semilunar valves.
- Migration of neural crest cells into the endocardial cushions contributes to the formation of the aorticopulmonary septum, and the neural crest cells play an important role in the development of the septum.
- Defects in the development of the aorticopulmonary septum result in three significant cyanotic congenital heart defects at birth (Transposition of great vessels, Tetralogy of Fallot, Persistent truncus arteriosus).

- Each of these abnormalities has right-to-left shunting thus producing cyanosis.

- Since each of these defects involves the endocardial cushion, they are all related to failure of neural crest cells to migrate to the cushion.

❖ N.B:

- Failure of aorticopulmonary septum to develop in a spiral fashion results in the aorta arising from the right ventricle and the pulmonary trunk arising from the left ventricle (Transposition of the great vessels).
- This causes right-to-left shunting of blood with resultant cyanosis.

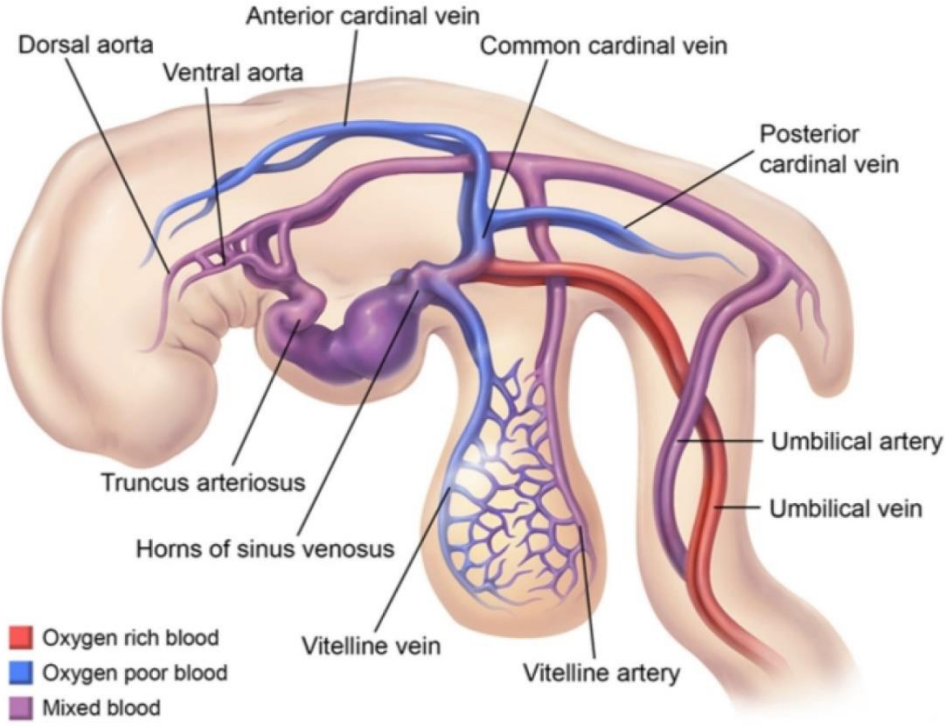


Heart embryology

Embryonic structures	Adult structures
Truncus arteriosus	Ascending aorta and pulmonary trunk
Bulbus cordis	Smooth parts (outflow tract) of left and right Ventricles
Primitive ventricle	Trabeculated part of left and right ventricles
Endocardial cushion	Atrial septum, membranous interventricular septum; atrioventricular (Mitral/tricuspid) and semilunar valves (Aortic/pulmonary)
Primitive atrium	Trabeculated part of left and right atria
Primitive pulmonary vein	Smooth part of left atrium
Left horn of sinus venosus	Coronary sinus
Right horn of sinus venosus	Smooth part of right atrium (sinus venarum)
Right common cardinal vein and right anterior cardinal vein	Superior vena cava (SVC)
Posterior, subcardinal, and supracardinal veins	Inferior vena cava (IVC)

❖ N.B:

- In early embryonic development, the body's veins fall into three main groups: umbilical, vitelline, and cardinal veins.
- The umbilical veins degenerate, the vitelline veins form the veins of the portal system, and the cardinal veins form the veins of the systemic circulation.
- The common cardinal veins of the developing embryo drain directly into the sinus venosus.
- These cardinal veins ultimately give rise to the superior vena cava and other constituents of the systemic venous circulation.

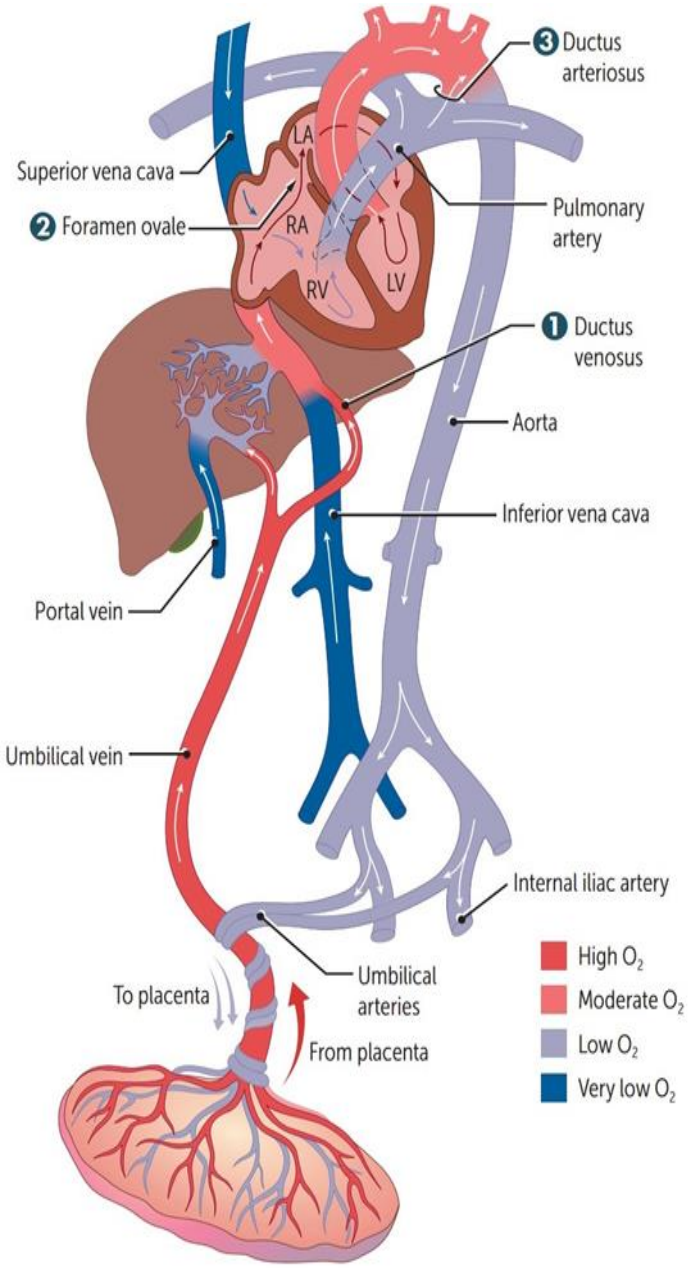


Fetal circulation

- The fetal circulation differs considerably from the adult circulation.
- Oxygenated blood from the placenta is delivered to the fetus via the umbilical vein.
- Thus, the umbilical vein has the highest oxygen content in the fetal circulation (The ligamentum teres is the remnant of the umbilical vein in the adult).
- Blood from the umbilical vein is first delivered to the liver, where it bypasses the hepatic circulation via the ductus venosus and enters the inferior vena cava (IVC).
- From the IVC, blood is delivered to the heart where it is either pumped into the pulmonary circulation or crosses directly from the right heart to the left heart via the foramen ovale.
- A fraction of the blood pumped into the pulmonary circulation may bypass the lungs via the ductus arteriosus and pass directly into the descending aorta.

- From the aorta, blood circulates to all of the fetal tissues.

- Deoxygenated blood is delivered from the fetus back to the placenta by the paired umbilical arteries.



- <u>3 important shunts:</u>

1. Blood entering fetus through the umbilical vein is conducted via the ductus venosus into the IVC, bypassing hepatic circulation.

2. Most of the highly oxygenated blood reaching the heart via the IVC is directed through the foramen ovale and pumped into the aorta to supply the head and body.

3. Deoxygenated blood from the SVC passes through the RA → RV → main pulmonary artery → patent ductus arteriosus → descending aorta; shunt is due to high fetal pulmonary artery resistance.

- Fetal-postnatal derivatives:

AllaNtois → urachus (Urachus is part of allantoic duct between bladder and umbilicus)	**MediaN umbilical ligament**
Ductus arteriosus	Ligamentum arteriosum
Ductus venosus	Ligamentum venosum
Foramen ovale	Fossa ovalis
Notochord	Nucleus pulposus
UmbiLical arteries	MediaL umbilical ligaments
Umbilical vein	Ligamentum teres hepatis (Contained in falciform ligament)

❖ N.B:

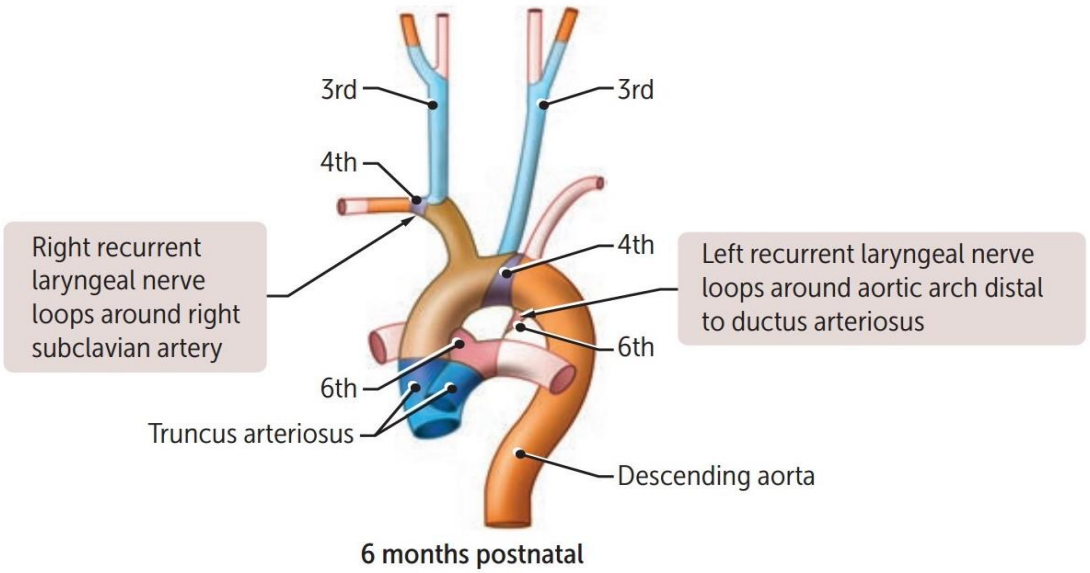
- The ductus arteriosus is an embryonic structure that allows fetal blood to pass directly from the pulmonary artery to the systemic circulation thereby bypassing the pulmonary circulation.
- This vessel typically closes immediately following birth by a process mediated by decreased local prostaglandin E2 (PGE2) levels and increased partial pressures of oxygen.
- Patency of this vessel after birth results in a left to right shunt.
- After the ductus arteriosus closes, it is referred to as the ligamentum arteriosum.
- Indomethacin (prostaglandin inhibitor) can be used to close a PDA, while PGE_2 infusions can be used to maintain patency of this structure in cases of congenital heart disease requiring a patent left-to-right shunt in order to maintain oxygenation (Tetralogy of Fallot, Transposition).
- Prostaglandins E1 and E2 kEEp PDA open.

Aortic arch derivatives

- Develop into arterial system.
- During embryonic development, the head, neck, and upper thorax region develop from a set of arches known as pharyngeal arches.
- Each arch is associated with a cranial nerve and an aortic arch.
- The first aortic arch gives rise to a portion of the maxillary artery, and the second aortic arch gives rise to the stapedial artery, which typically regresses in humans.
- The fifth aortic arch completely regresses, leaving no structures or vestiges in the adult.
- The third aortic arch forms the common and proximal internal carotid arteries.

- The fourth aortic arch gives rise to part of the true aortic arch and a portion of the subclavian arteries.
- The sixth aortic arch gives rise to the pulmonary arteries and the ductus arteriosus.

1st	**Part of maxillary artery (branch of external carotid).** **1st arch is maximal.**
2nd	Stapedial artery and hyoid artery. Second = Stapedial.
3rd	Common Carotid artery and proximal part of internal Carotid artery. C is 3rd letter of alphabet.
4th	On left: aortic arch; on right: proximal part of right subclavian artery. 4th arch (4 limbs) = systemic.
6th	Proximal part of pulmonary arteries and (on left only) ductus arteriosus. 6th arch = pulmonary and the pulmonary-to systemic shunt (ductus arteriosus).



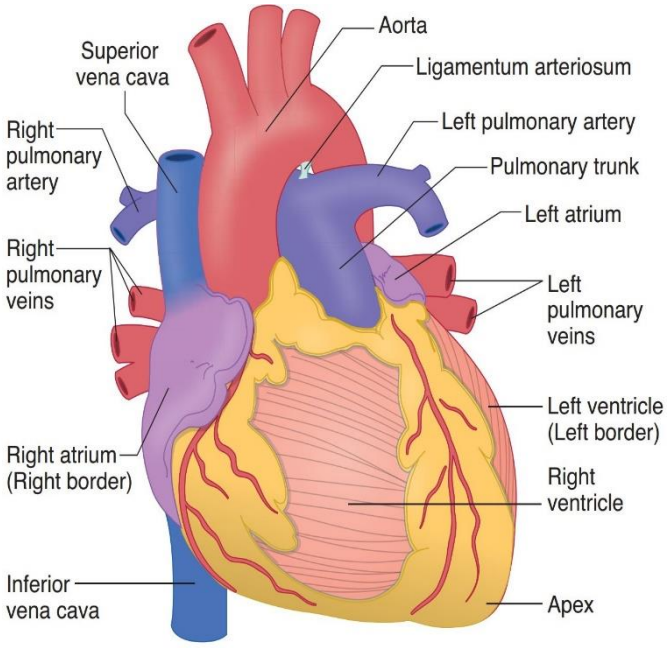
6 months postnatal

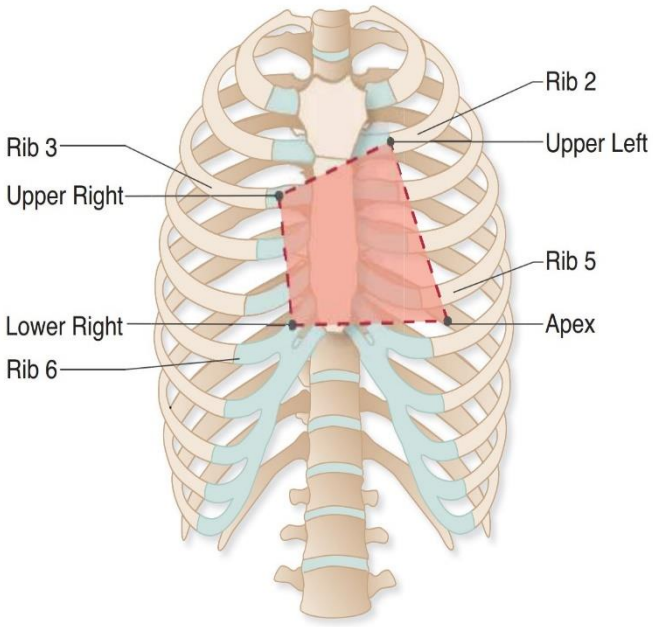
CHAPTER 2

Anatomy

Surface Projections of the Heart

- The heart lies obliquely within the middle mediastinum, mostly posterior to the sternum.
- The anterior (sternocostal) surface is formed primarily by the right ventricle.
- The posterior surface is formed primarily by the left atrium.
- The inferior (diaphragmatic) surface is formed primarily by the left ventricle.
- The right border is formed by the right atrium.
- The left border is mainly formed by the left ventricle.
- The apex is the tip of the left ventricle and is found in the left fifth intercostal space.

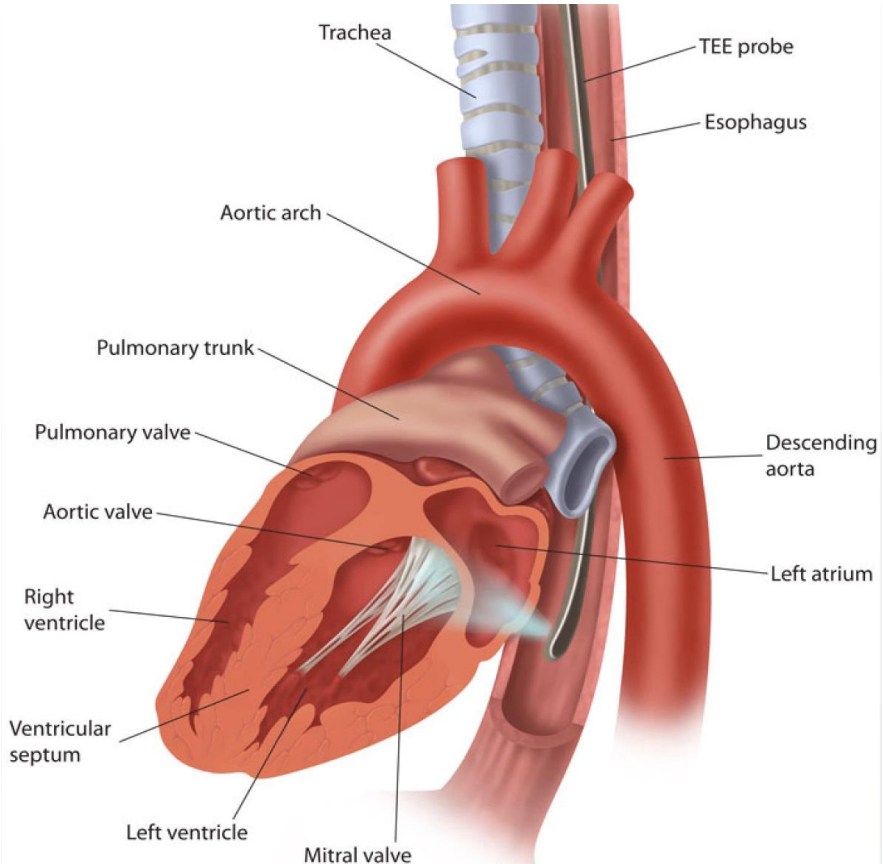




❖ N.B:

1. Transesophageal echocardiography (TEE) uses ultrasound waves generated from within the esophagus to produce clear images of the neighboring cardiac structures.

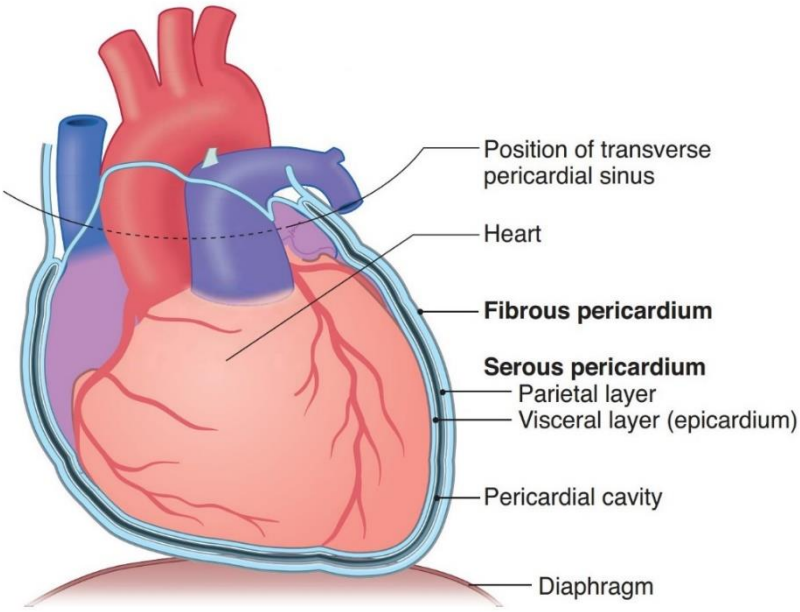
- The left atrium makes up the majority of the heart's posterior surface, with the esophagus passing immediately posterior to the heart.
- Therefore, the esophagus lies within closest proximity to the left atrium.
- This allows the left atrium, atrial septum, and mitral valve to be particularly well visualized on TEE.
- The descending thoracic aorta lies posterior to the esophagus and the left atrium.
- This position permits clear visualization of the descending aorta by transesophageal echocardiography if the probe was rotated so that it faces posteriorly, allowing for the detection of abnormalities such as dissection or aneurysm.



2. Due to its adjacent proximity, conditions that result in left atrial enlargement (atrial fibrillation, mitral stenosis) can cause dysphagia through external compression of the esophagus or hoarseness (due to compression of the left recurrent laryngeal nerve, a branch of the vagus).

Pericardium

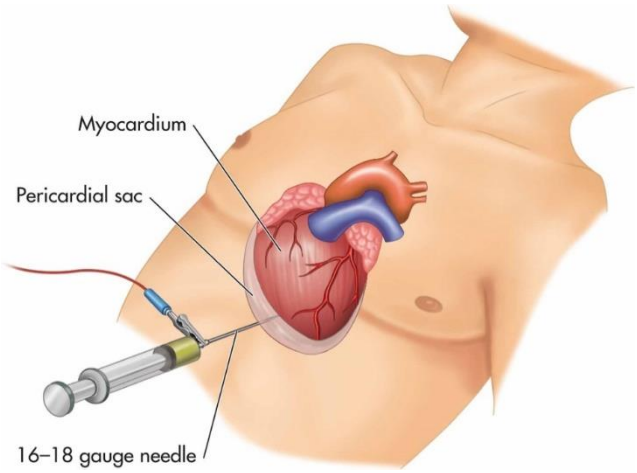
- The pericardium is the serous sac covering the heart and is the only one of the 3 serous membranes that has 3 layers (an outer fibrous layer and a double-layered parietal and visceral serous layers).
- The serous pericardium is double-layered and formed by the outer parietal layer and the inner visceral layer (epicardium) that covers the surface of the heart.
- The fibrous pericardium surrounds the entire heart and the great vessels at the upper aspect of the heart.
- The fibrous pericardium is very strong and maintains the position of the heart within the middle mediastinum.
- The pericardial cavity is the potential space between the parietal and visceral layers containing a small amount of serous fluid that allows free movement of the beating heart.



❖ N.B:

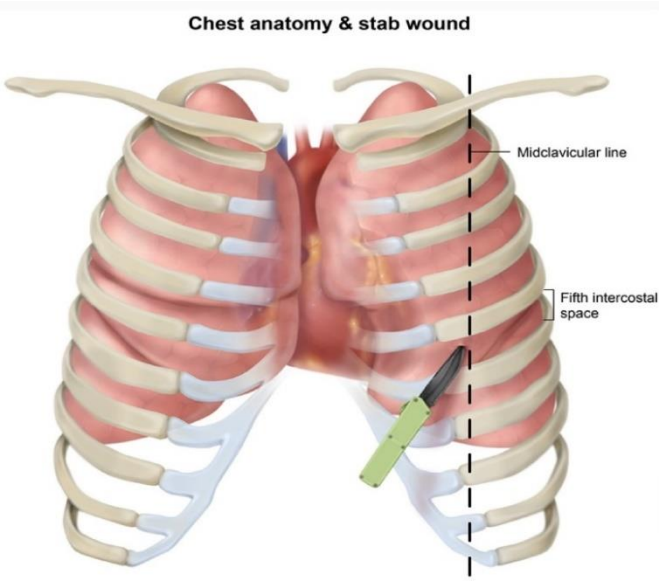
1. Cardiac tamponade is the pathological accumulation of fluids (serous or blood) within the pericardial cavity.

- The fluid compresses the heart and restricts venous filling during diastole and reduces cardiac output.
- A pericardiocentesis is performed with a needle at the left infrasternal angle through the cardiac notch of the left lung to remove the fluid.



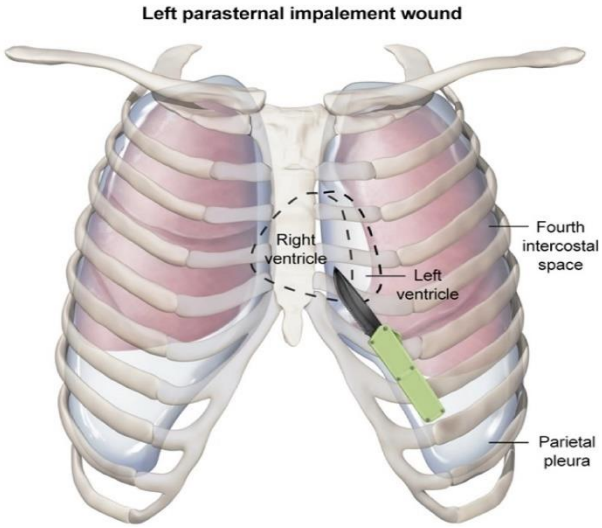
2. Most of the volume of the thoracic cavity is occupied by the lungs.

- The heart is located behind the sternum and its anterior surface is partially covered by the lungs.
- The apex is formed by the left ventricle and is covered by the left lung.
- It lies behind the fifth left intercostal space at the left midclavicular line.
- Penetrating injury involving the fifth intercostal space at the left midclavicular line would most likely injure the left lung.
- Penetration of the left lung at this location could lead to injury of the apex of the heart (left ventricle) as well, if the wound were deep enough.
- All other heart chambers lie medial to the left midclavicular line and would not be affected.



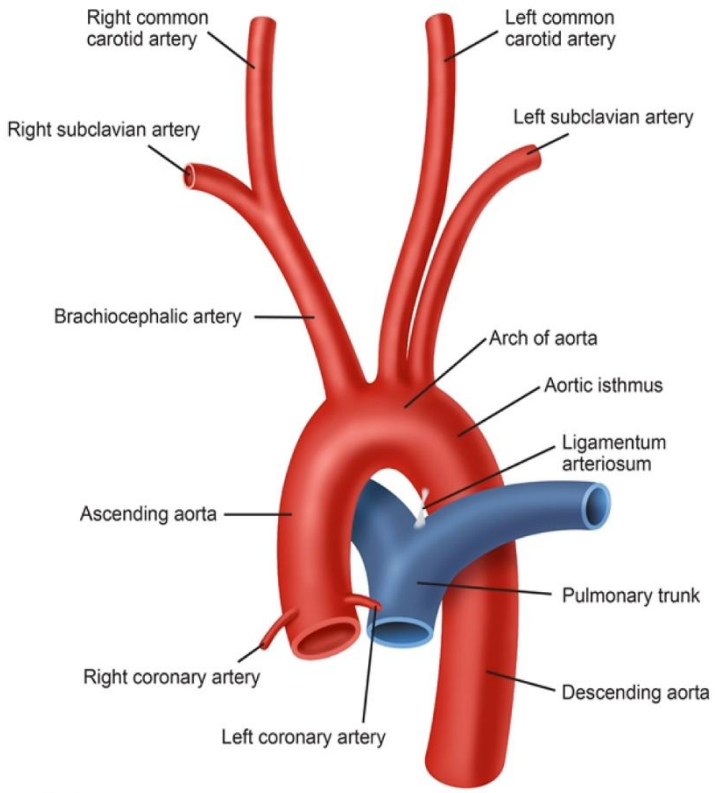
3. A penetrating injury at the left sternal border in the fourth intercostal space along the left sternal border will injure the Right ventricular myocardium.

- It is important to know that the right ventricle composes the majority of the anterior surface of the heart.
- The left lung would not be punctured by a stab wound in this location because there is no middle lobe on the left side, and the superior lobe of the left lung is displaced laterally by the cardiac impression.



4. A motor vehicle accident with sudden deceleration can cause different rates of deceleration between the heart (in a fixed position) and the aorta.

- The most common site of injury is the aortic isthmus, which is the connection between the ascending and descending aorta distal to where the left subclavian artery branches off the aorta.
- Patients typically present with chest pain, back pain, or shortness of breath. However, there can be significant rupture, causing instant death after the trauma.
- Patients who survive the initial rupture may have a widened mediastinum on chest x-ray.



Arterial Supply of the Heart

- The blood supply to the myocardium is provided by branches of the right and left coronary arteries.
- These 2 arteries are the only branches of the ascending aorta.
- Blood flow enters the coronary arteries during diastole.

A. Right coronary artery:

- The right coronary artery courses in the coronary sulcus and supplies major parts of the right atrium and the right ventricle. The branches include the following:
  - Sinoatrial (SA) nodal artery: One of the first branches of the right coronary, it encircles the base of the superior vena cava to supply the SA node (blood supply independent of dominance). Infarct may cause nodal dysfunction (bradycardia or heart block).
  - Right (acute) marginal artery supplies RV.
  - Posterior descending artery (PDA): it is the terminal distribution of the right coronary artery and courses in the posterior interventricular sulcus to supply parts of the right and left ventricles and, importantly, the posterior third of the interventricular septum. The posterior descending artery supplies most of the inferior wall of the left ventricle, which forms the diaphragmatic surface of the heart. PDA also supplies blood to the atrioventricular (AV) node via the AV nodal artery (dependent on dominance):

B. Left main coronary artery: The left main coronary artery divides into the left anterior descending (LAD) and circumflex coronary arteries, which supply most of the anterior and left lateral surfaces of the heart.

- Left anterior descending (LAD): it descends in the anterior interventricular sulcus and provides branches to the anterior left ventricle wall, anterior two-thirds of the interventricular septum, bundle of His, and apex. The LAD is the most common site of coronary occlusion.

- The circumflex artery (LCX): courses around the left border of the heart in the coronary sulcus and supplies the left border of the heart and ends on the posterior aspect of the left ventricle and supplies the posterior-inferior left ventricular wall.

- Coronary dominance is determined by the coronary artery supplying the posterior descending artery (PDA), which also supplies blood to the atrioventricular (AV) node via the AV nodal artery.

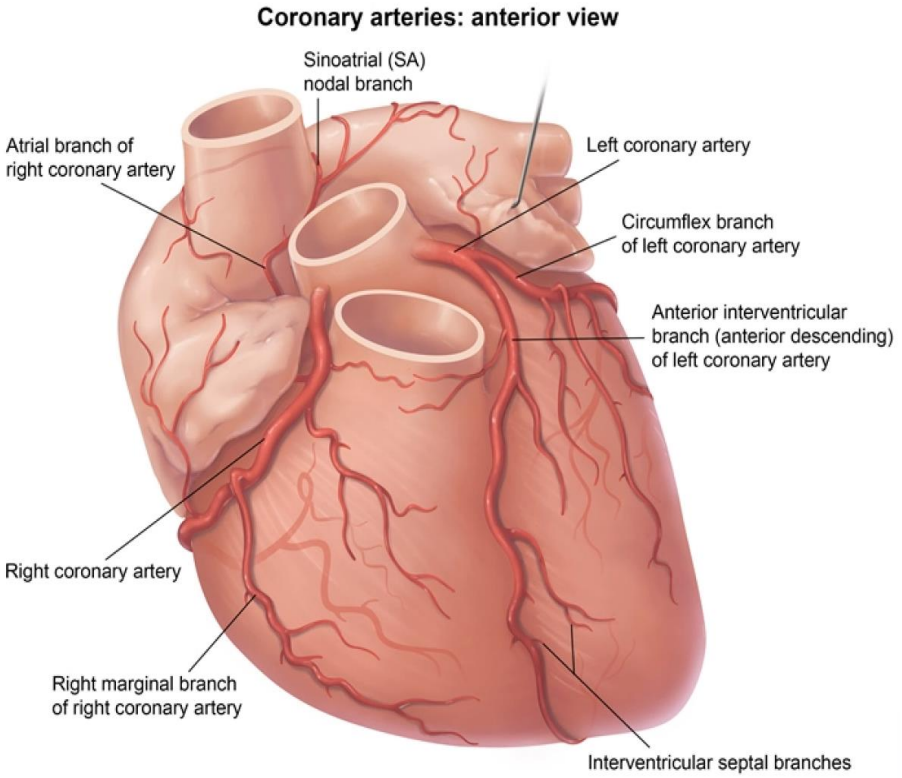
- In 85% of individuals, the right coronary artery gives rise to the posterior descending artery. These patients are said to have right dominant coronary circulation.

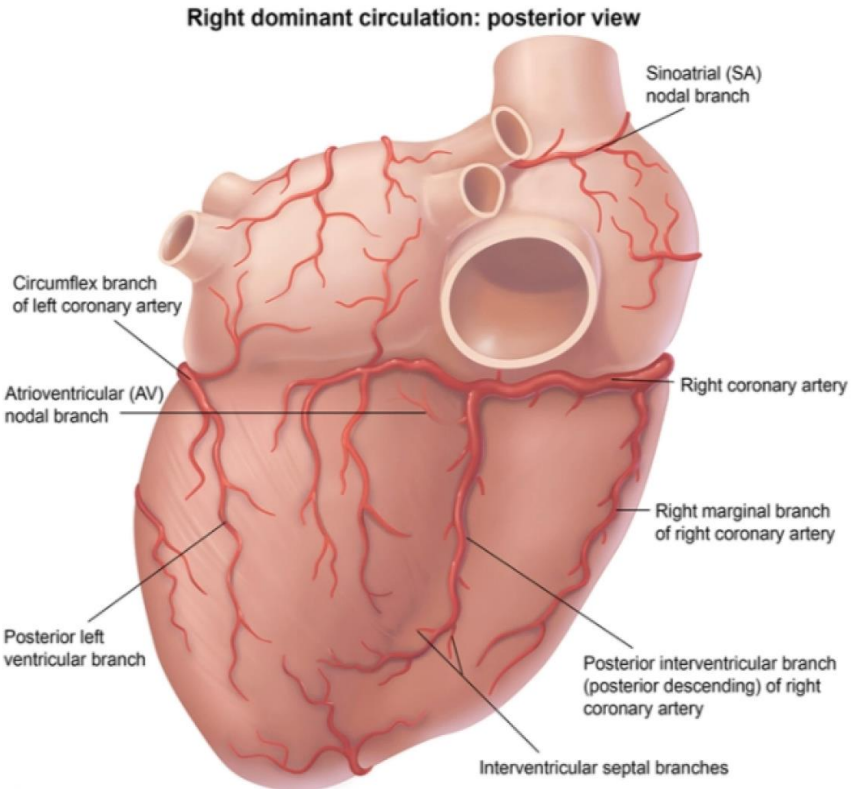
- In approximately 8% of patients, the posterior descending artery arises from the circumflex branch of the left main coronary artery; these patients have left dominant circulation.

- Both right coronary and left circumflex artery in 7% of the population (codominant).

- Because the AV nodal artery usually arises from the posterior descending artery:

- In left dominant coronary circulation: the atherosclerotic lesion is most likely in the left circumflex artery.
- In right dominant coronary circulation: the atherosclerotic lesion is most likely in the right coronary artery.

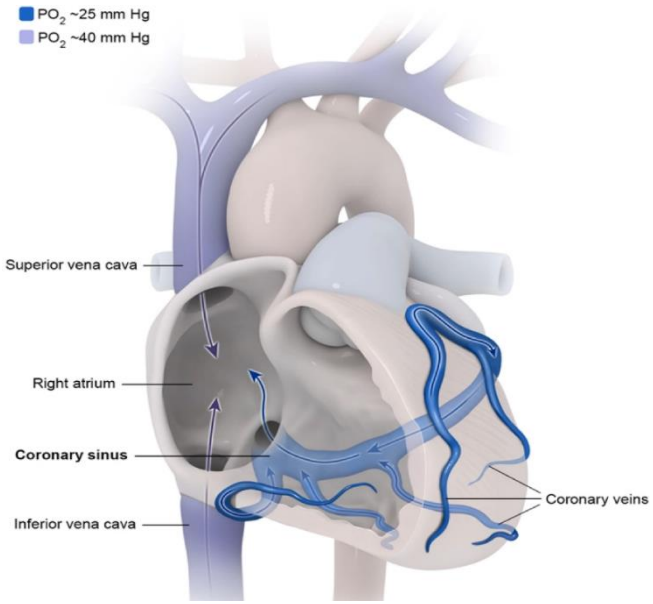




❖ N.B:

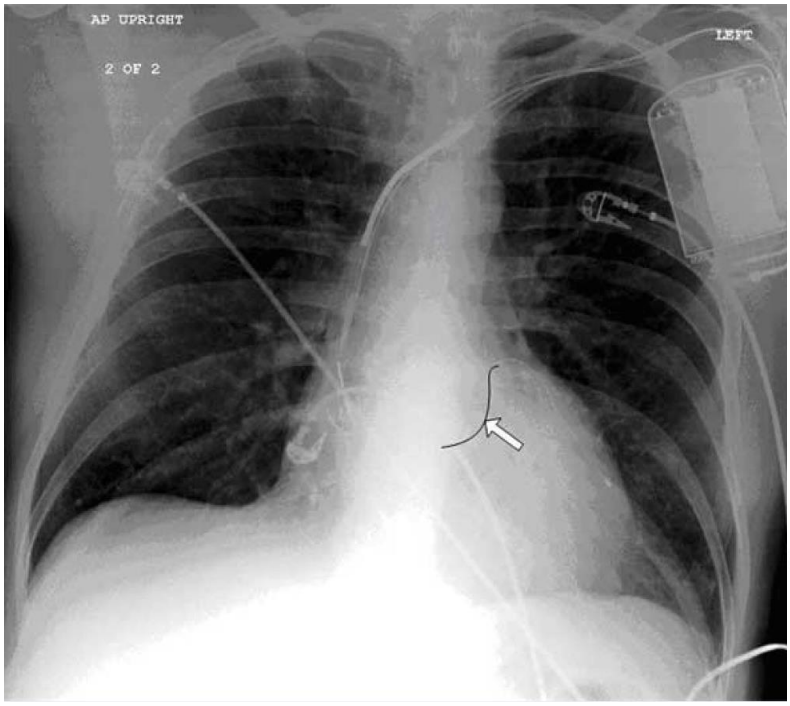
1. The coronary sinus is the main vein of the coronary circulation; it lies in the posterior coronary sulcus.
   - It drains to an opening in the right atrium.
   - It develops from the left sinus venosus.
   - The coronary sinus communicates freely with the right atrium and therefore may become dilated secondary to any factor that causes right atrial dilatation.
   - The most common such factor is pulmonary artery hypertension, which leads to elevated right heart pressures.

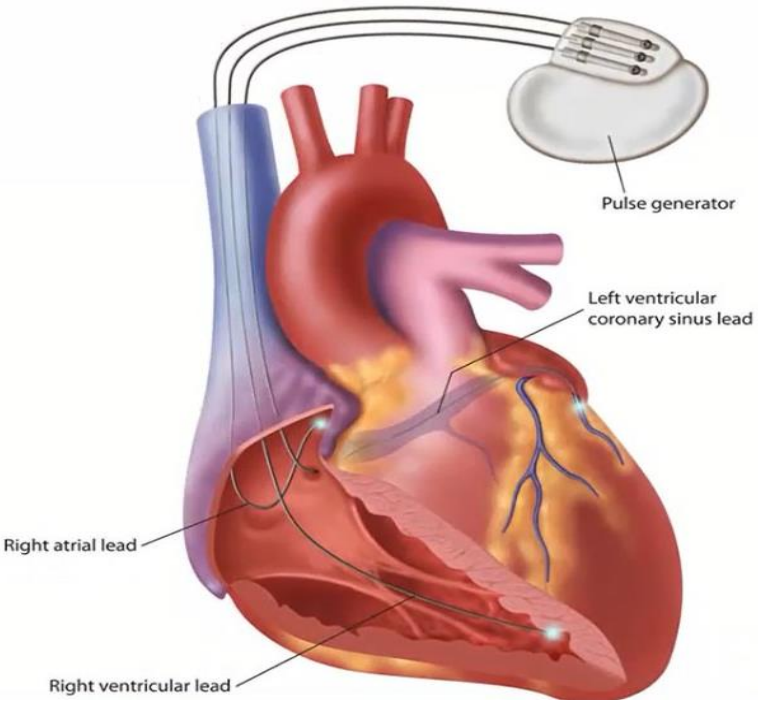
2. Myocardial oxygen extraction exceeds that of any other tissue or organ; therefore, the cardiac venous blood in the coronary sinus is the most deoxygenated blood in the body.



3. Biventricular pacemaker is a special pacemaker which is used to synchronize the contractions of the left ventricle with the right ventricle to improve the ejection fraction in patients with severe and moderately severe symptoms of heart failure.

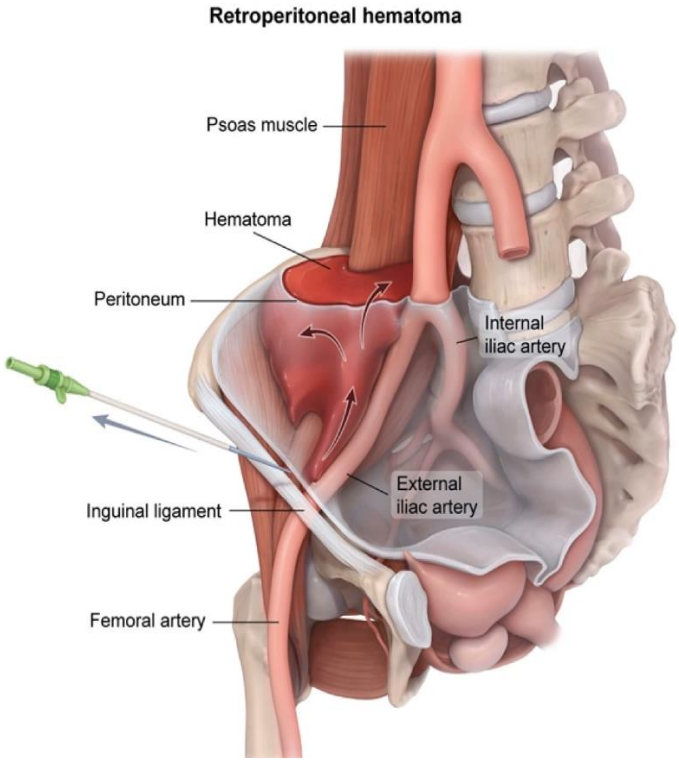
- It is a device that requires 2 or 3 leads.
- If 3 leads are used, the first 2 are placed in the right atrium and right ventricle.
- The third lead is used to pace the left ventricle.
- Right atrial and ventricular leads are easy to place as they only need to traverse the left subclavian vein and superior vena cava to reach these cardiac chambers.
- In contrast, the lead that paces the left ventricle is more difficult to position.
- The preferred transvenous approach involves passing the left ventricular pacing lead from the right atrium into the coronary sinus, which resides in the atrioventricular groove on the posterior aspect of the heart.
- It is then advanced into one of the lateral venous tributaries in order to optimize left ventricular pacing.





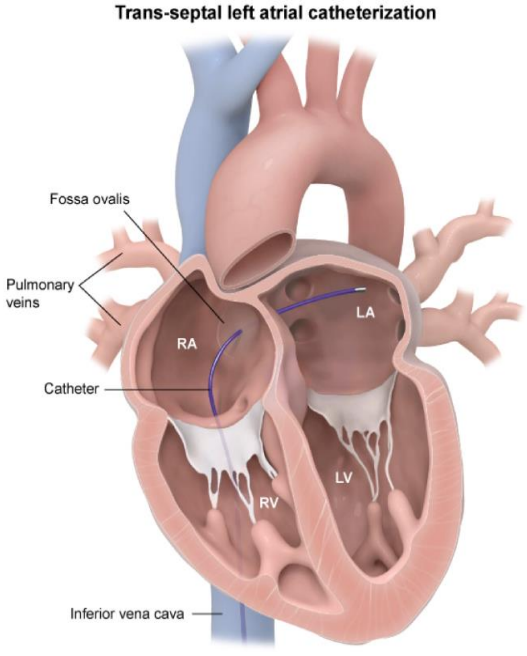
4. Cardiac catheterization requires vascular access through either the common femoral artery (CFA) or radial artery.

- When cannulating the CFA, the optimal entry site is the middle below the inguinal ligament.
- Arterial puncture above the inguinal ligament increases the risk of retroperitoneal hemorrhage as the area is directly over the retroperitoneal space.
- Bleeding in the retroperitoneal space cannot be controlled with manual compression and can lead to significant hemorrhage.
- Patients typically develop hemodynamic instability with significant hypotension, drop in hematocrit, and/or ipsilateral flank pain.
- Retroperitoneal hemorrhage is the most common cause of unexpected mortality after cardiac catheterization, and prompt recognition and treatment can prevent further complications.



5. To access the left side of the heart through right heart catheter, cardiac venous catheters must cross the interatrial septum at the site of the foramen ovale.

- Entry into the left atrium allows for direct measurement of left atrial pressure and for access to arrhythmogenic foci on the left atrial myocardium or pulmonary veins. Following the procedure, the small atrial septal defect created by the catheter typically closes spontaneously.
- A venous catheter traveling from the femoral vein to the heart passes through the iliac vein and inferior vena cava to reach the right atrium.
- Once in the right atrium, structures within the right side of the heart and the pulmonary arteries are readily accessible. However, because the pulmonary capillaries are far too small to pass through, the left side of the heart must be accessed by traversing the interatrial septum.
- The interatrial septum is traversed at the site of the foramen ovale, which in adults is typically covered by a thin membrane of fibrous tissue that can be easily punctured.



Diaphragm

- Structures perforating diaphragm:

- At T8: IVC, right phrenic nerve.
- At T10: esophagus, vagus (CN 10; 2 trunks).
- At T12: aorta, thoracic duct, azygos vein.

- I (IVC) ate (8) ten (10) eggs (esophagus) at (aorta) twelve (12).

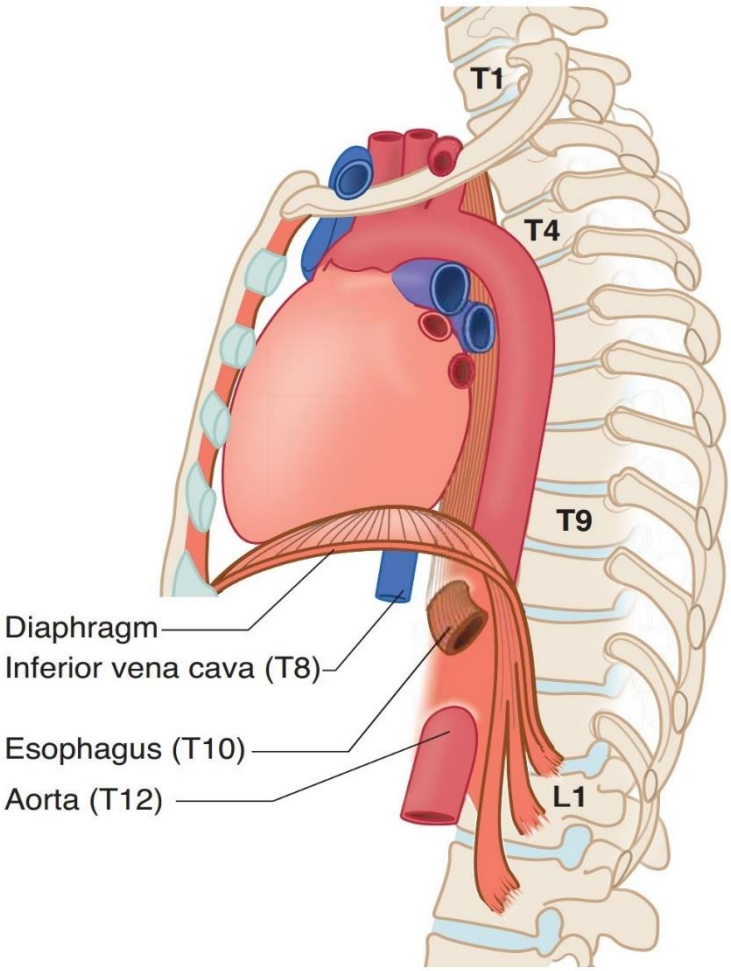
- Diaphragm is innervated by C3, 4, and 5 (phrenic nerve).

- C3, 4, 5 keeps the diaphragm alive.

- Pain from diaphragm irritation (air, blood, or pus in peritoneal cavity) can be referred to shoulder (C5) and trapezius ridge (C3, 4).

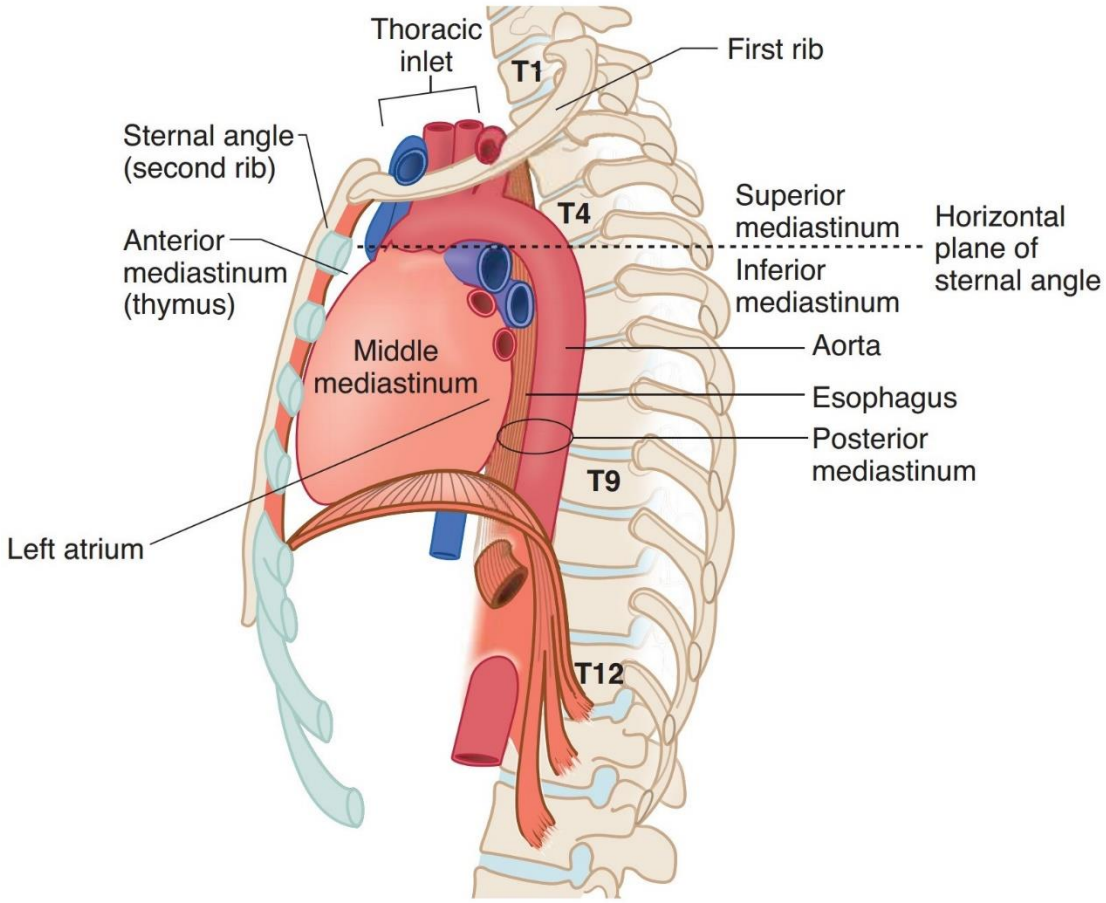
- Other bifurcations:

- The common carotid bifourcates at C4.
- The trachea bifourcates at T4.
- The abdominal aorta bifourcates at L4.



Imaging

- The mediastinum is the central, midline compartment of the thoracic cavity.
- It is bounded anteriorly by the sternum, posteriorly by the 12 thoracic vertebrae, and laterally by the pleural cavities.
- Superiorly, the mediastinum is continuous with the neck through the thoracic inlet; and inferiorly, is closed by the diaphragm. The mediastinum contains most of the viscera of the thoracic cavities except from the lungs (and pleura) and the sympathetic trunk.
- The mediastinum is divided into superior and inferior mediastina by a plane passing from the sternal angle (of Louis) anteriorly to the intervertebral disc between T4 and T5 posteriorly.
- The sternal angle and plane are important clinical landmarks. The inferior mediastinum is classically subdivided into anterior, middle, and posterior mediastina.



Divisions of the Mediastinum

A. Anterior Mediastinum:

- The anterior mediastinum is the small interval between the sternum and the anterior surface of the pericardium. It contains fat and areolar tissue and the inferior part of the thymus gland.

B. Posterior Mediastinum:

- The posterior mediastinum is located between the posterior surface of the pericardium and the T5-T12 thoracic vertebrae. Inferiorly, it is closed by the diaphragm.

- There are 2 important structures coursing within the posterior mediastinum:
  - Thoracic (descending) aorta.
  - Esophagus.

C. Middle Mediastinum: The middle mediastinum contains the heart and great vessels and pericardium.

D. Superior Mediastinum:

- The superior mediastinum is located between the manubrium of the sternum, anteriorly, and the thoracic vertebrae T1-4, posteriorly. As with all mediastina, the parietal pleura and the lungs form the lateral boundary.

- The relationships of these structures in the superior mediastinum are best visualized in a ventral to dorsal orientation between the sternum anteriorly and the vertebrae posteriorly:

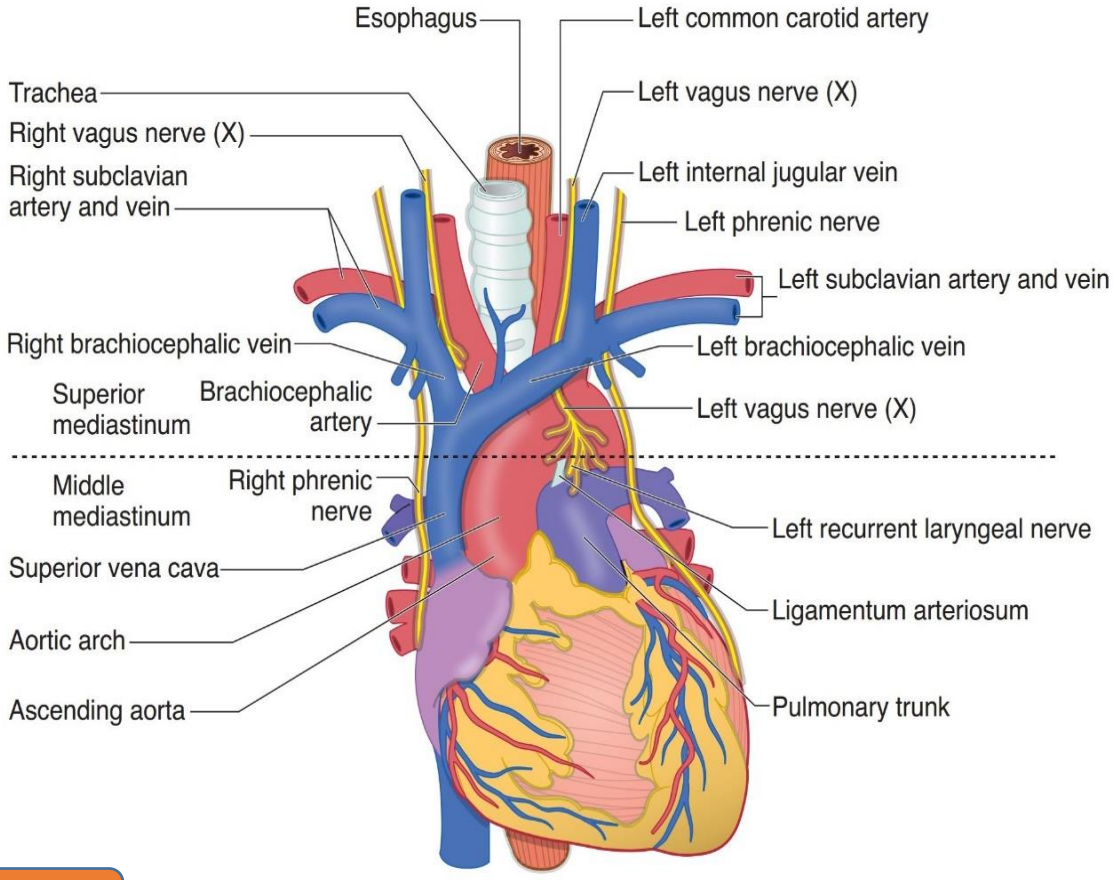
1. Thymus: located posterior to the manubrium, usually atrophies in the adult and remains as fatty tissue

2. Right and left brachiocephalic veins: The 2 veins join to form the superior vena cava posterior. The superior vena cava descends and drains into the right atrium.

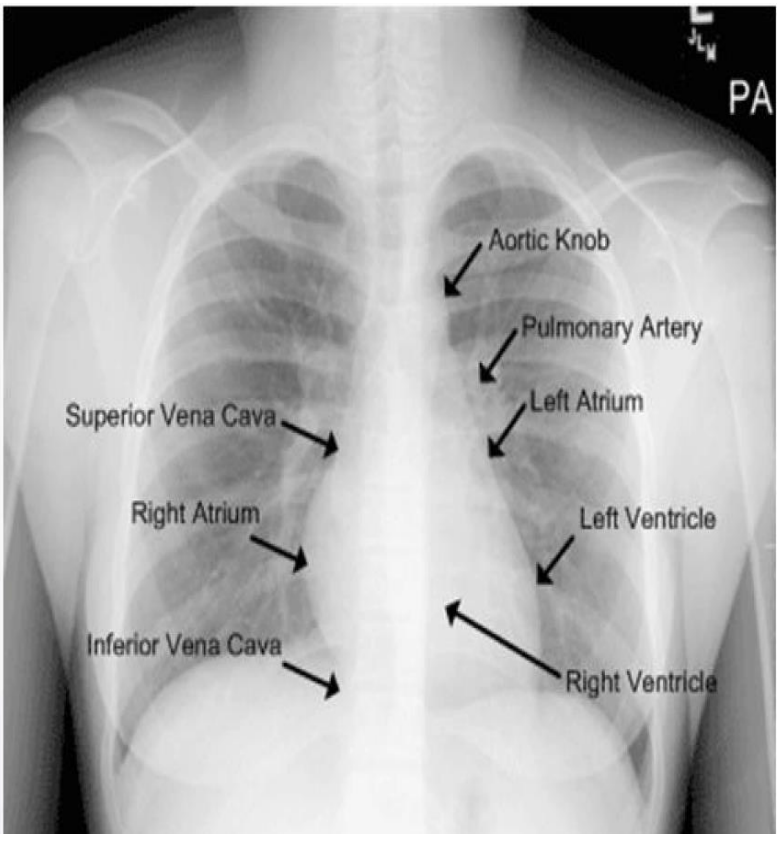
3. Aortic arch and its 3 branches:
   - Aortic arch begins and ends at the plane of the sternal angle and is located just inferior to the left brachiocephalic vein.
   - As a very important radiological landmark, the origins of the 3 branches of the aortic arch (brachiocephalic, left common carotid, and left subclavian) are directly posterior to the left brachiocephalic vein.

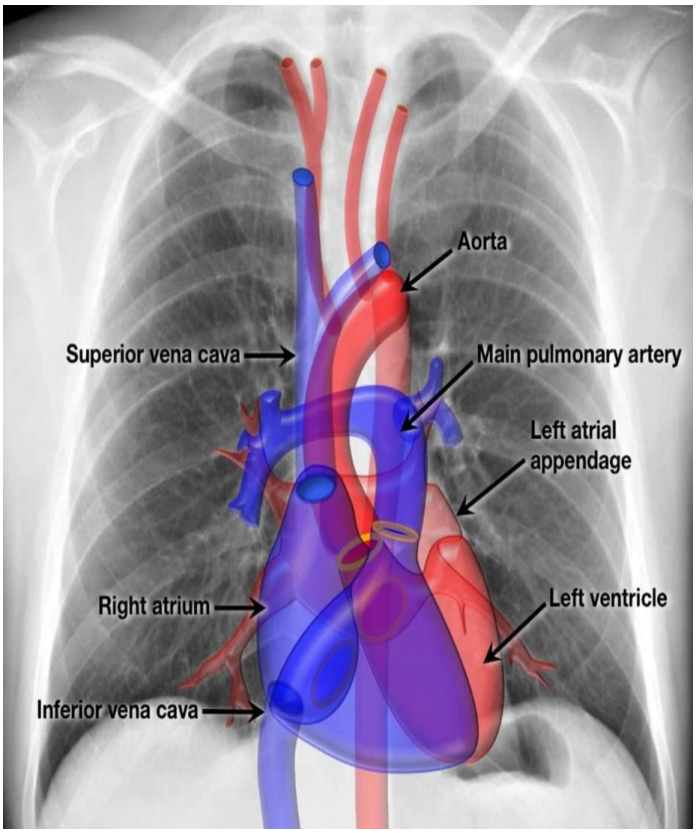
4. Trachea: Lies posterior to the aortic arch and bifurcates at the level of T4 vertebra to form right and left primary bronchi.

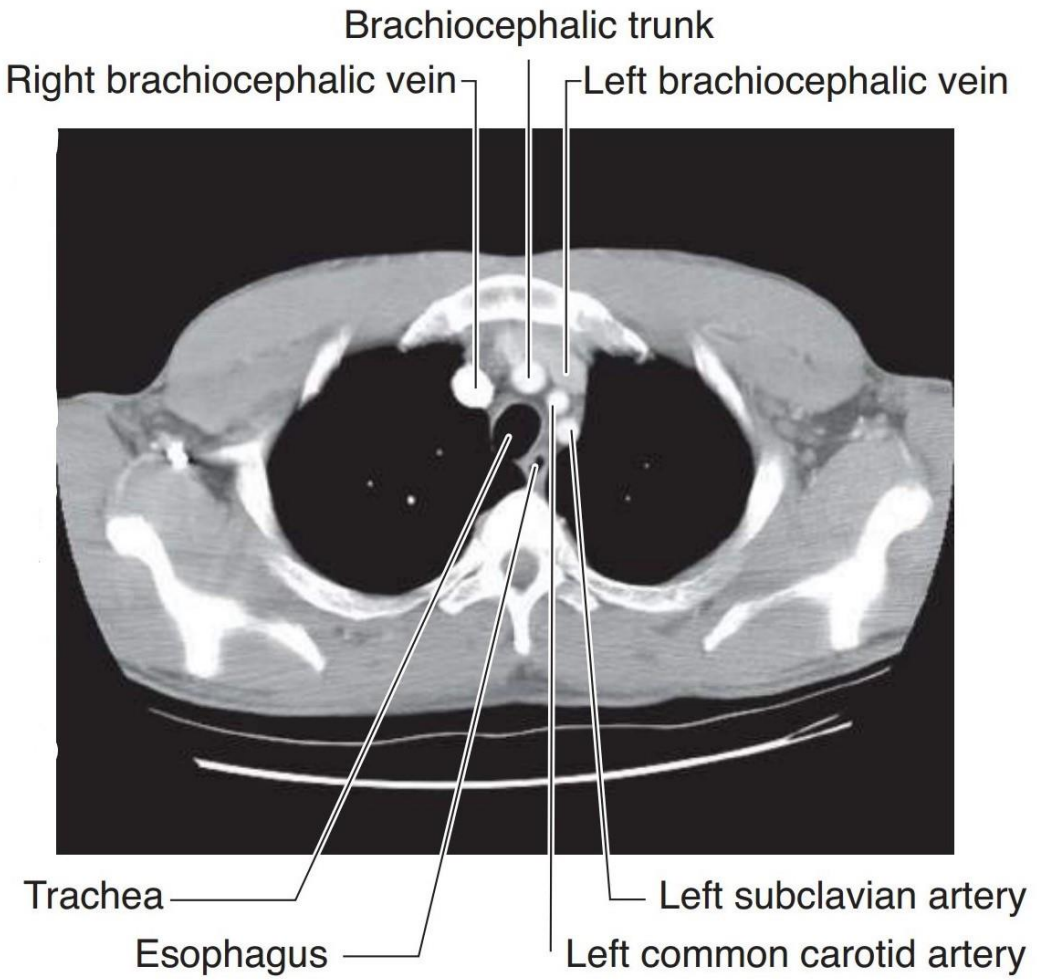
5. Esophagus: Lies posterior to the trachea and courses posterior to left primary bronchus to enter the posterior mediastinum.

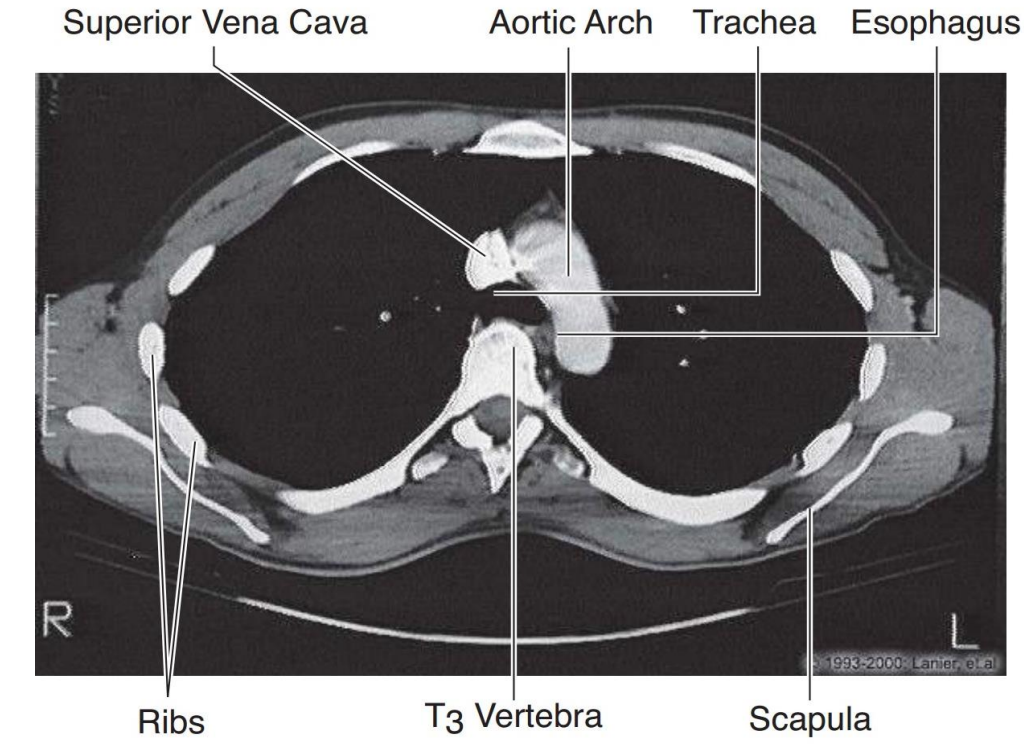

Esophagus
Left common carotid artery
Trachea
Left vagus nerve (X)
Right vagus nerve (X)
Right subclavian artery and vein
Left internal jugular vein
Left phrenic nerve
Left subclavian artery and vein
Right brachiocephalic vein
Left brachiocephalic vein
Superior mediastinum
Brachiocephalic artery
Left vagus nerve (X)
Middle mediastinum
Right phrenic nerve
Left recurrent laryngeal nerve
Superior vena cava
Ligamentum arteriosum
Aortic arch
Pulmonary trunk
Ascending aorta

Practicing

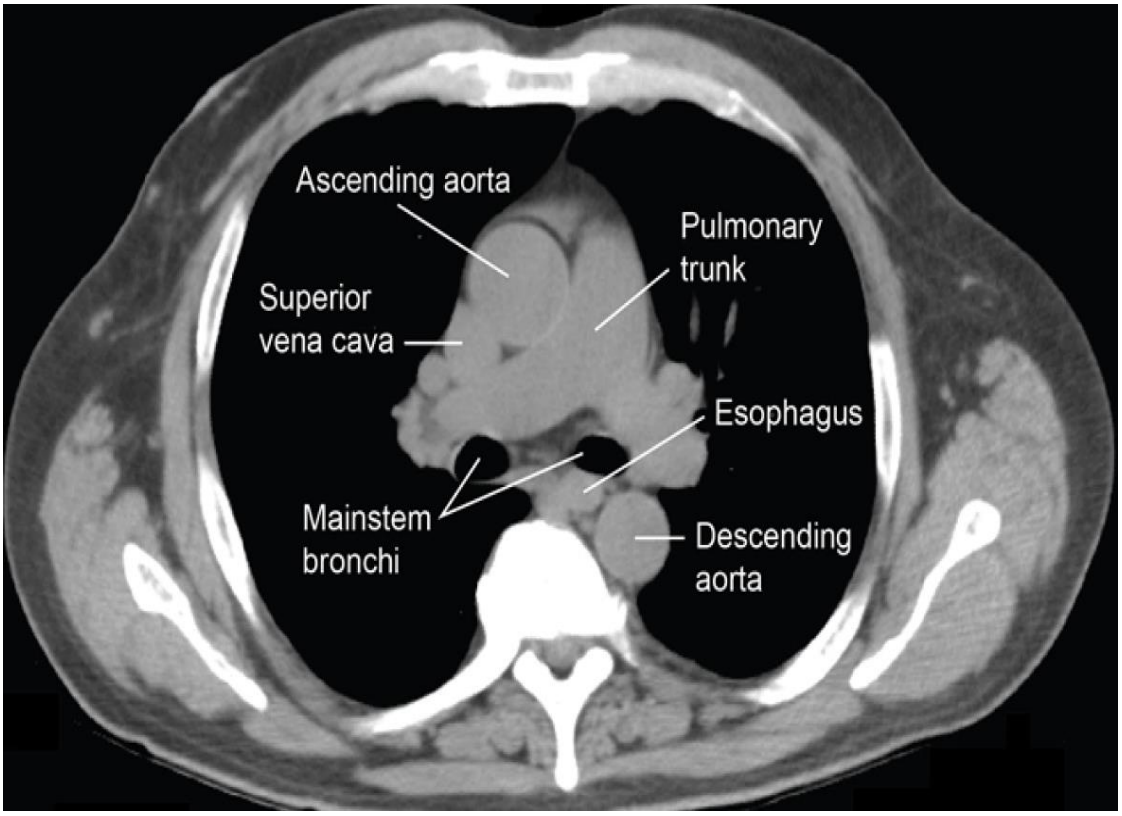

PA
Aortic Knob
Pulmonary Artery
Left Atrium
Superior Vena Cava
Right Atrium
Left Ventricle
Inferior Vena Cava
Right Ventricle

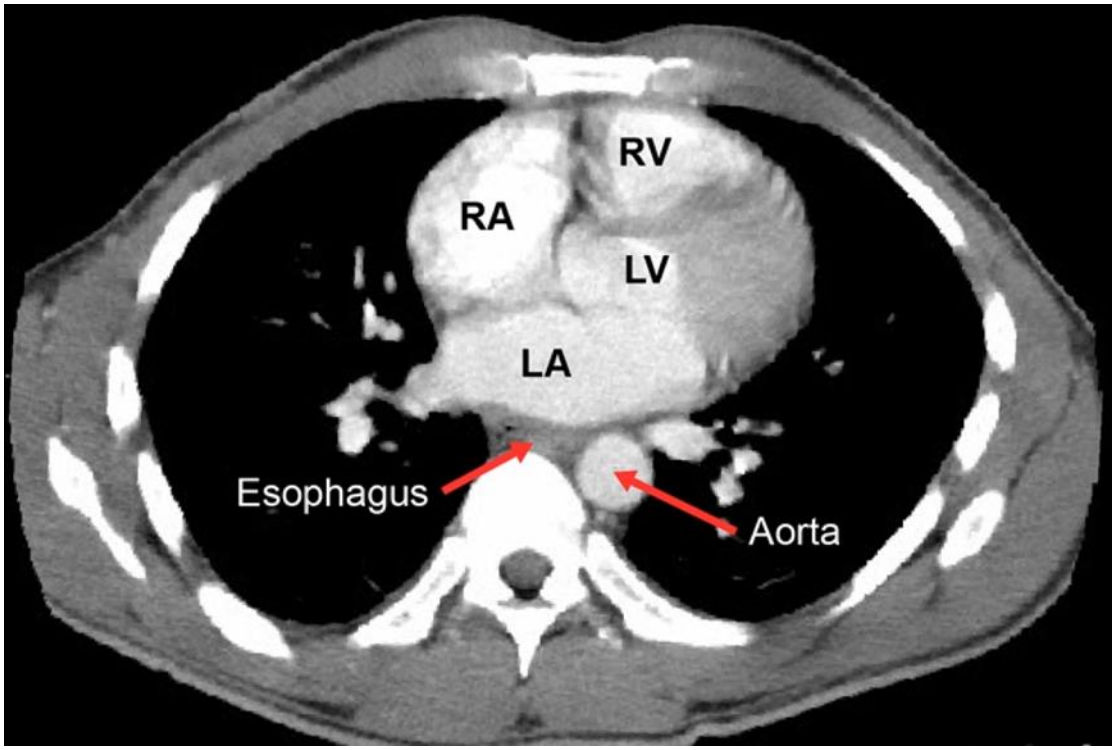

Aorta
Superior vena cava
Main pulmonary artery
Left atrial appendage
Right atrium
Left ventricle
Inferior vena cava


Brachiocephalic trunk
Right brachiocephalic vein
Left brachiocephalic vein
Trachea
Esophagus
Left subclavian artery
Left common carotid artery


Superior Vena Cava
Aortic Arch
Trachea
Esophagus
R
L
Ribs
T3 Vertebra
Scapula

Chest: CT, T3





❖ N.B:

- Cardiovascular dysphagia can result from external compression of the esophagus by a dilated and posteriorly displaced left atrium in patients with rheumatic heart disease and mitral stenosis/regurgitation.

CHAPTER 3

Physiology

Cardiac output

- Stroke volume (SV) is the amount of blood pumped by each ventricle per beat.
- Cardiac output (CO) is the amount of blood pumped by each ventricle per minute.

$$CO = \text{Stroke volume (SV)} \times \text{heart rate}$$

- SV equals the difference between end-diastolic volume (EDV) and End-Systolic volume (ESV).

$$SV = \text{End-diastolic volume (EDV)} - \text{End-systolic volume (ESV)}$$

- Measurement of cardiac output (Fick method): The amount of substance taken by an organ (or by the whole body) per unit of time equals the arterial level of the substance minus the venous level (A-V difference) times the blood flow.

$$\text{Flow} = \frac{Amount\ of\ substance\ taken\ by\ the\ organ}{(A-V)\ difference}$$

- CO can be determined by measuring the amount of O_2 consumed by the body in a given time and dividing this by the A-V difference across the lungs.
- The arterial O_2 content can be measured in a sample obtained from any artery.
- The venous blood sample is taken from the pulmonary artery by means of cardiac catheter.

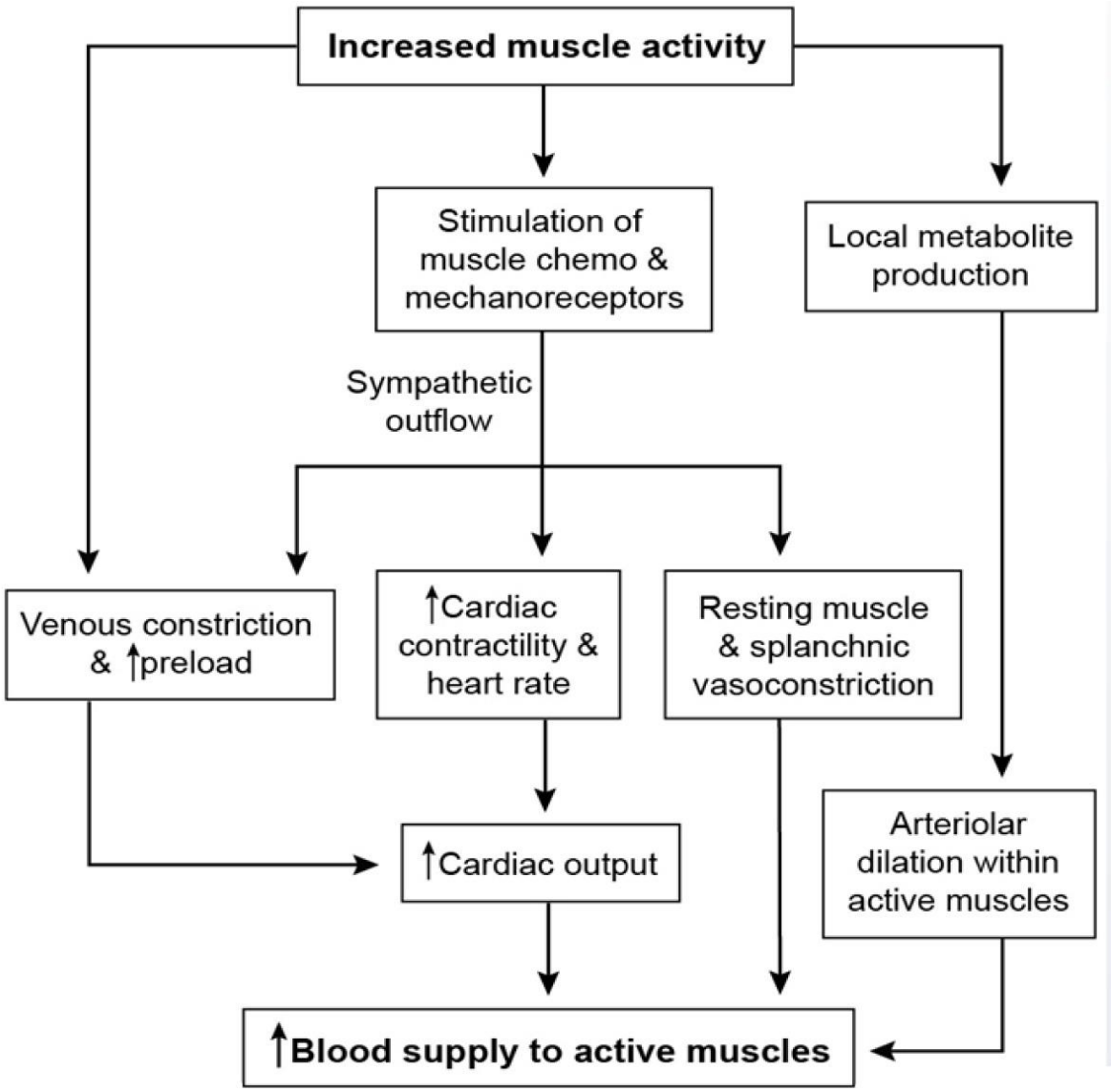
$$CO = \frac{rate\ of\ O2\ consumption}{arterial\ O2\ content - venous\ O2\ content}$$

- Effect of exercise on CO:
- During the early stages of exercise, CO is maintained by ↑ HR and ↑ SV.
- During the late stages of exercise, CO is maintained by ↑ HR only (SV plateaus).
- Diastole is shortened with ↑↑ HR (ventricular tachycardia) → ↓ diastolic filling time → ↓ SV → ↓ CO.

❖ N.B:

1. Stimulation of the sympathetic nervous system is essential during exercise for a number of reasons.
   - First, the increased metabolic demands of the exercising tissue require cardiac output (CO = SV x HR) to increase from a resting rate of 5 L/min to approximately 20 L/min during maximal exertion.
   - Second, in order to supply enough preload to the heart to meet this increased stroke volume, sympathetic stimulation causes contraction of the venous system, increasing venous return to the heart.
   - Third, sympathetic discharge causes contraction of the arterioles in all tissues except the actively working muscles, effectively shunting blood toward the exercising muscle.

- Despite these three sympathetic nervous system effects, the mean arterial pressure typically increases only 20-40 mmHg during full body exercise.
- The mean arterial pressure remains fairly stable during exercise due to an adaptive decrease in the systemic vascular resistance (SVR).
- Exercising muscle releases local vasodilatory factors including adenosine, potassium ions, ATP, CO_2 and lactate.
- There is also a small vasodilatory effect of sympathetic beta receptors.



2. The cardiorespiratory response to exercise includes increased heart rate, cardiac output, and respiratory rate in order to balance the increased total tissue oxygen consumption and carbon dioxide production.

- These coordinated adaptations result in relatively constant arterial blood gas values whereas venous oxygen is decreased and venous carbon dioxide is increased.

Mean arterial pressure (MAP)

- The Poiseuille equation represents the relationship of flow, pressure, and resistance.

$$\text{Flow} = \frac{(P_1 - P_2)\pi r^4}{8\eta l}$$

$$\text{Flow} = \frac{P_1 - P_2}{R}$$

$$R = \frac{8\eta l}{\pi r^4}$$

Flow (volume/time) in a tube
P_1 = Pressure at the beginning of the system
P_2 = Pressure at the end of the system
r = radius of the tube
l = length of the tube
η = viscosity of the fluid
R = resistance

- <u>Resistance factors</u>:

- Vessel length is constant; therefore, changes in length are not a physiologic factor in regulation of resistance, pressure or flow.

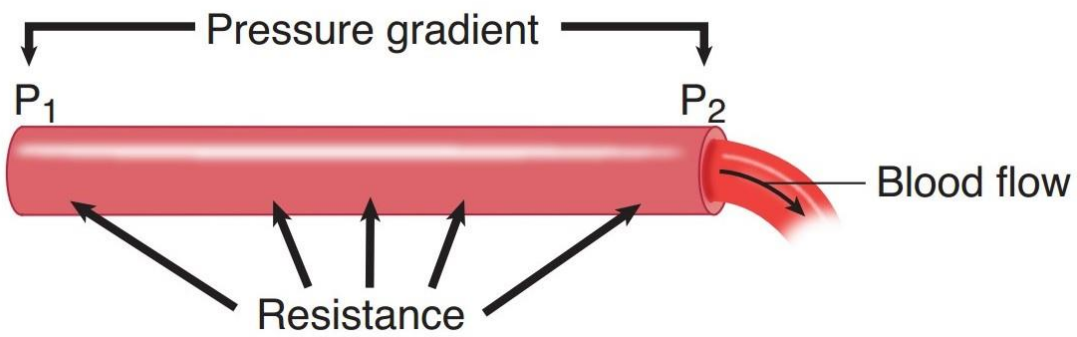
- Tube radius is a much more important factor than length in determining resistance.

- Viscosity is an internal property of a fluid that offers resistance to flow. It is the frictional force between the flowing fluid layers.

- The main determinant of blood viscosity is hematocrit.

- Polycythemia and hyperprotinemic state (multiple myeloma) increase viscosity and TPR.

- Anemia decreases viscosity and TPR.



- Blood flow is directly proportional to the vessel radius raised to the fourth power ($F \alpha r^4$).

- Resistance to blood flow is inversely proportional to the vessel radius raised to the fourth power ($R \alpha \frac{1}{r4}$).

Applying the Poiseuille equation to the systemic circuit, the following is true:

$$F = \frac{P_1 - P_2}{R}$$

F = cardiac output (CO)

P_1 = mean arterial pressure (MAP = 92 mmHg)

P_2 = right atrial pressure (RAP = 2 mmHg)

R = total peripheral resistance (TPR = mainly arterioles)

Since RAP is very small compared to MAP, the equation can be simplified by ignoring this factor. Therefore:

$$CO = \frac{MAP}{TPR}$$

or

$$MAP = CO \times TPR$$

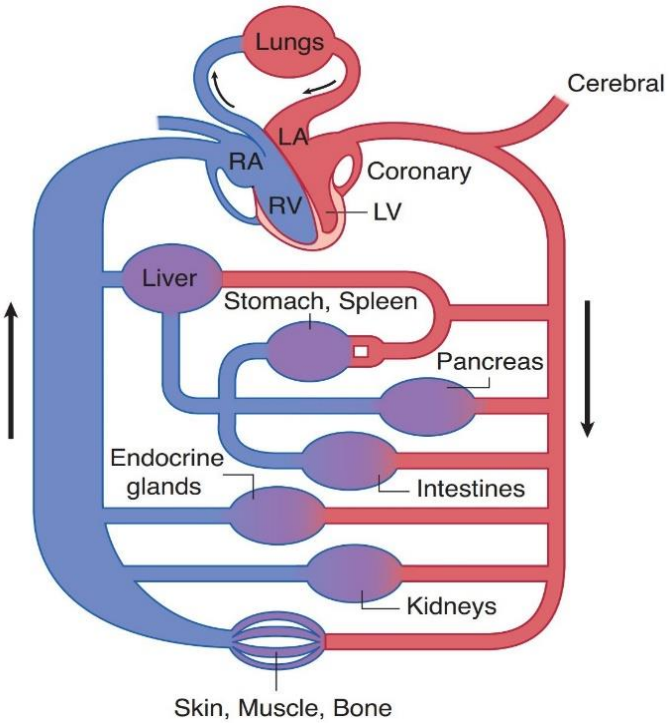
- Total resistance of vessels in series:

- RT =R1 + R2 + R3

- Total resistance of vessels in parallel:

- $\frac{1}{RT} = \frac{1}{R1} + \frac{1}{R2} + \frac{1}{R3}$

- The total resistance for a group of vessels arranged in parallel is equal to one divided by the sum of the inverse values for resistance of each of the contributing vessels.



- Total body circulation can be best described as a parallel circuit, whereas circulation in individual organ is often best described by a series arrangement.

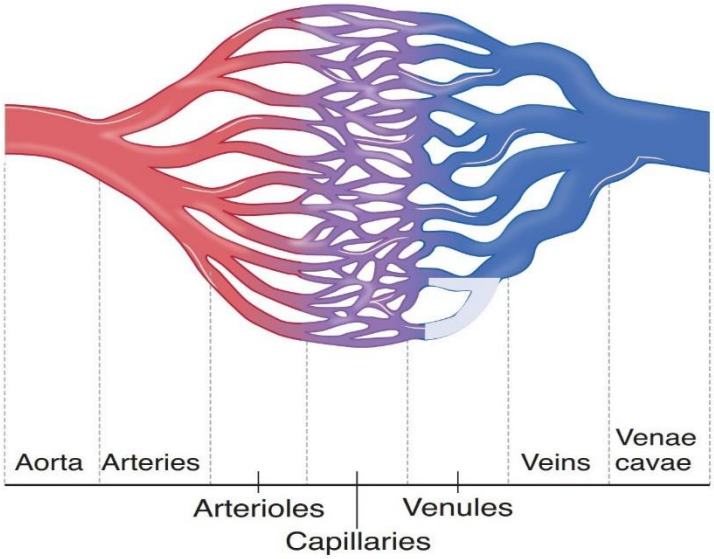
- Removal of organs in parallel arrangement (nephrectomy or amputation) → ↑ TPR and ↓ CO.

- Adding resistance in parallel (obesity) → ↓ TPR.

- Arterioles account for most of TPR. Veins provide most of blood storage capacity.

- Velocity vs. Cross-Sectional area:

- There is always an inverse relationship between velocity and cross-sectional area:
  - Aorta has smallest cross-sectional area and highest velocity.
  - Capillaries have highest total cross-sectional area and lowest flow velocity.
  - The low velocity in the capillaries facilitates the exchange of nutrients and gases with the tissues.



- Systolic Blood Pressure (SP):

- It is the peak pressure in a systemic artery during the cardiac cycle.

- The most important factor determining systolic pressure under most physiological conditions is stroke volume (SV):

↑ SV → ↑ SP; ↓ SV → ↓ SP

- A secondary factor affecting systolic blood pressure is aortic compliance.

- The aorta contains elastic fibers that stretch expanding the aorta during ejection and rebound or recoil during diastole.

- Isolated systolic hypertension (systolic blood pressure >140 mm Hg with diastolic blood pressure <90 mm Hg) is due to age-related stiffness and decrease in compliance of the aorta and major peripheral arteries.

- Diastolic Blood Pressure:

- It is the lowest pressure in a systemic artery during the cardiac cycle.

- The most important factor determining diastolic blood pressure is the resistance of the arterioles (TPR).

↑ TPR → ↑ DP; ↓ TPR, ↓ DP

- Pulse pressure:

- It is the difference between systolic and diastolic blood pressures.

Pulse pressure = systolic pressure – diastolic pressure

- Pulse pressure is proportional to SV, inversely proportional to arterial compliance.

- ↑ Pulse pressure in hyperthyroidism, aortic regurgitation, aortic stiffening (isolated systolic hypertension in elderly), obstructive sleep apnea (↑ sympathetic tone), exercise (transient).

- ↓ pulse pressure in aortic stenosis, cardiogenic shock, cardiac tamponade, advanced heart failure (HF).

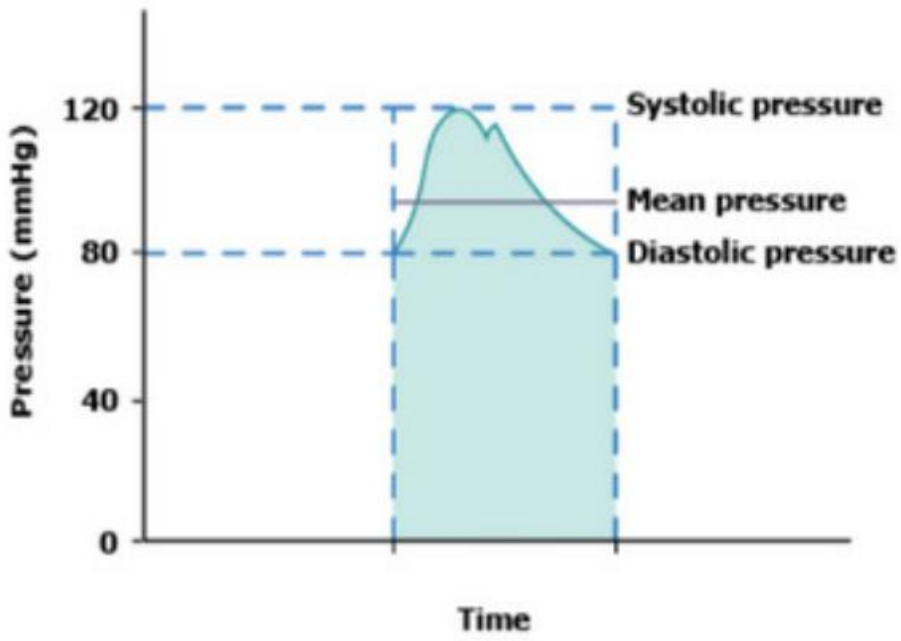
- MAP:

- It is the average pressure in the artery over the complete cardiac cycle.

- The shape of the pressure wave shows mean pressure to be closer to diastolic than it is to systolic pressure. Diastolic pressure is a better index of mean pressure than is systolic pressure.

- Mean pressure can be approximated from the following formula:

MAP = 2⁄3 diastolic pressure + 1⁄3 systolic pressure = DBP + 1/3 PP



Cardiac output variables

A. Stroke volume:

- Systolic performance of the ventricles (stroke volume) actually means the overall force generated by the ventricular muscle during systole.

- An important factor influencing this systolic performance is the number of cross-bridges cycling during contraction.

- The greater the number of cross-bridges cycling, the greater the force of contraction.

- Systolic performance is determined by 3 independent variables:

1. The preload factor, also known as the Frank-Starling mechanism (The preload effect can be explained on the basis of a change in sarcomere length).
2. The contractility factor, which, under acute conditions, is calcium dynamics.
3. The afterload factor, which is defined as the "load" that the heart must eject blood against.

- Mnemonic: Stroke Volume affected by Contractility, Afterload, and Preload (SV CAP).

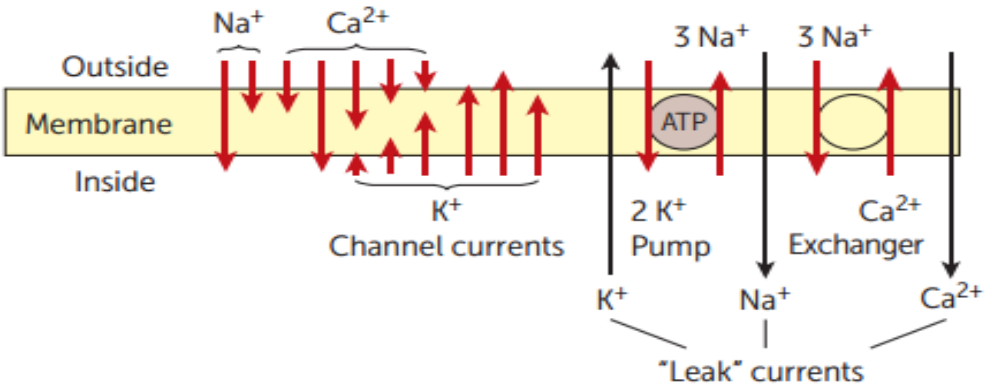
- ↑ SV with:

- ↑ Contractility (exercise).
- ↑ Preload (early pregnancy).
- ↓ Afterload.

B. Contractility:

- Contractility (and SV) ↑ with:

- Catecholamines → inhibition of phospholamban → ↑ Ca entry into sarcoplasmic reticulum → ↑ Ca-induced Ca release.
- ↑ intracellular Ca.
- ↓ extracellular Na (↓ activity of Na/Ca exchanger).
- Digitalis (blocks Na/K pump →↑ intracellular Na → ↓ Na/Ca exchanger activity → ↑ intracellular Ca).



- Contractility (and SV) ↓ with:

- β1-blockade (↓ cAMP).
- HF with systolic dysfunction.
- Acidosis.
- Hypoxia/hypercapnia (↓ Po_2/↑ Pco_2).
- Non-dihydropyridine Ca_2 channel blockers

❖ N.B:

- Phospholamban is an inhibitor of cardiac muscle sarcoplasmic reticulum Ca ATPase (SERCA) in the unphosphorylated state, but inhibition is relieved upon phosphorylation of the protein.
- The relief of inhibition on Ca ATPase leads to faster Ca uptake into the sarcoplasmic reticulum → contractility.

C. Preload:

- Amount of blood loaded into left ventricle prior to each contraction.

- Preload approximated by ventricular EDV; depends on venous tone and circulating blood volume.

D. Afterload:

- Forces resisting flow out of left ventricle.

- Afterload approximated by MAP.

- Flow out of left ventricle ↓ if:

- Blood pressure is high (↑ TPR).
- Outflow obstruction (Aortic stenosis, HOCM)

- VAsodilators (hydrAlAzine) ↓ Afterload (Arterial).

- ACE inhibitors and ARBs ↓ both preload (↓ aldosterone) and afterload (↓ angiotensin).

- ↑ afterload → ↑ pressure →↑ wall tension per Laplace's law.

- LV compensates for ↑ afterload by thickening (hypertrophy) in order to ↓ wall tension.

- Chronic hypertension (↑ MAP) → LV hypertrophy.

- Myocardial oxygen demand:

- MyoCARDial O_2 demand is ↑ by:

  - ↑ Contractility.
  - ↑ Afterload (proportional to arterial pressure).
  - ↑ heart Rate.
  - ↑ Diameter of ventricle (↑ wall tension).

- Ejection fraction:

- Usually presented as the percentage of the ventricular volume ejected during systole.

$$EF = \frac{SV}{EDV} = \frac{EDV - ESV}{EDV}$$

- Left ventricular EF is an index of ventricular contractility; normal EF is ≥ 55%.

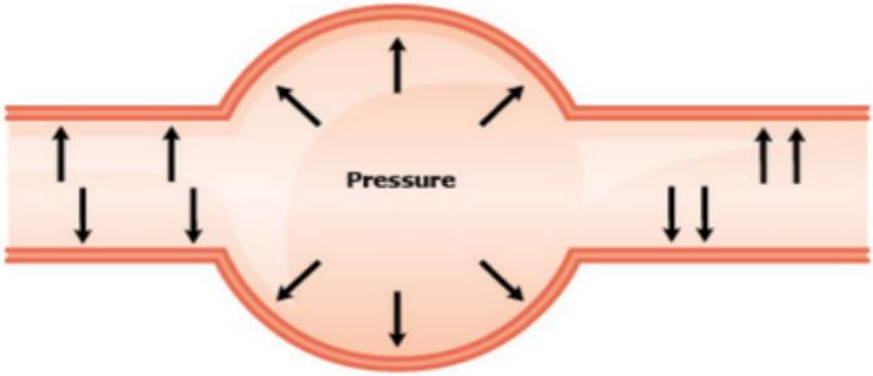
- EF ↓ in systolic HF; usually normal in diastolic HF.

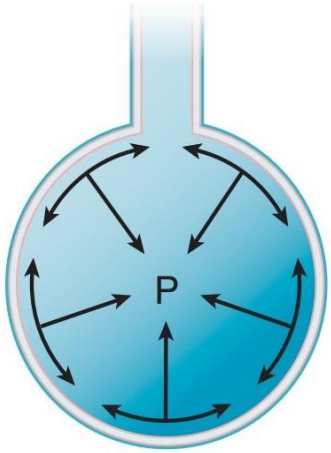
- Wall tension:

- Wall tension is a stretching force that develops in response to vessel pressure.

- Wall tension follows Laplace's law:

$$\text{Pressure} \propto \frac{\text{tension}}{\text{radius}}$$





Wall tension = pressure × radius

- The aorta is the artery with the greatest wall tension (greatest pressure and radius).

- Peripherally, because arterial radius decreases, wall tension also decreases.

- Aortic aneurysm is an abnormal localized vessel dilation.

- The greater radius of the aneurysm, compared to adjacent regions, means a greater wall tension; this wall tension increases further as the aneurysm enlarges.

- A hypertensive episode also increases an aneurysm's wall tension.

- Aortic aneurysms are most commonly located in the abdominal aorta, and it is in this location that they have the greatest likelihood of rupture.

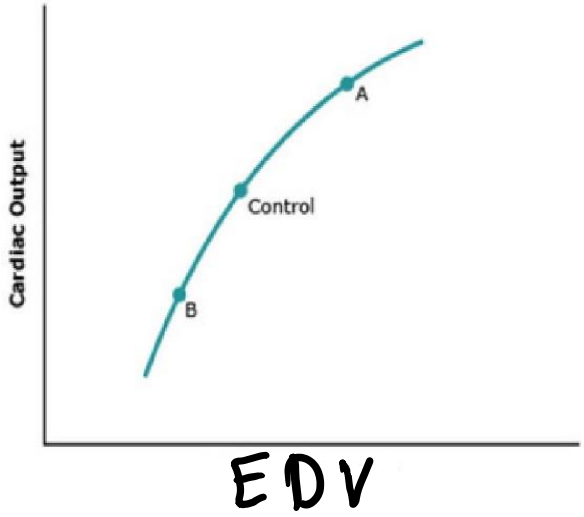
Ventricular function curves

- Ventricular function curves are an excellent graphical depiction of the effects of preload versus contractility and afterload.

- Cardiac function curves describe the heart's pumping ability.

Single Cardiac function curve

- Normal (control) curve:



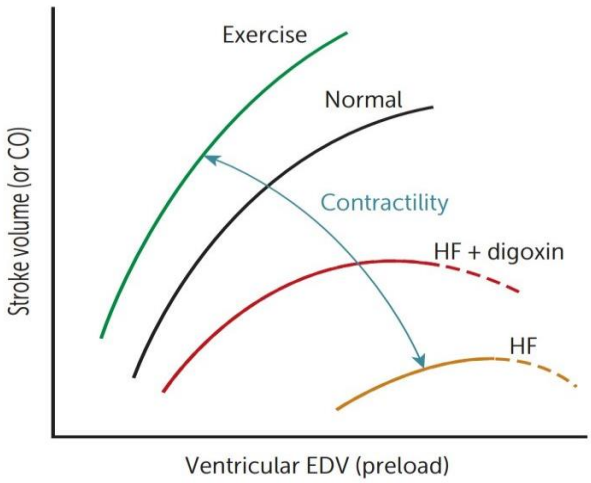
- Control → A: Increase in performance is due to increased preload, contractility unchanged.

- Control → B: Decrease in performance is due to decreased preload, contractility unchanged.

Starling curve

- Contractility ↑ with catecholamines, positive inotropes (digoxin).

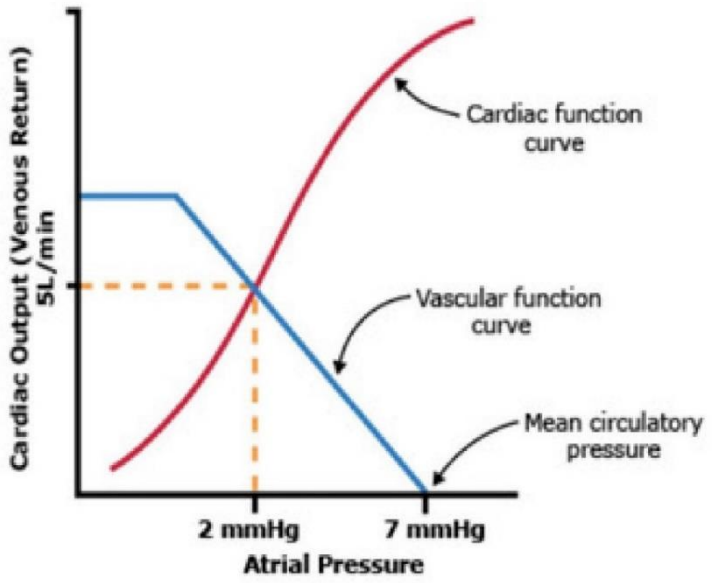
- Contractility ↓ with loss of myocardium (MI), β-blockers (acutely), non-dihydropyridine Ca channel blockers, dilated cardiomyopathy.



Cardiac and vascular function curves

- Vascular function curves (venous return curves) describe the peripheral factors affecting the flow through the circuit.

- The cardiovascular system operates at the intersection of the two curves, which is the equilibrium point for the system (venous return and CO are equal).



- **Ventricular function curve:**

- Y-axis is CO.

- X-axis is EDV (a marker of preload).

- **Vascular function curve:**

- Y-axis is VR.

- X-axis is RAP (the downstream pressure for VR).

- The curve shows that as RAP increases, VR decreases. This is because RAP is the downstream pressure for VR. As RAP increases, the pressure gradient for VR falls, which in turn decreases VR. Thus, RAP has a negative impact on VR.

- **Means systemic pressure (mean circulatory pressure):**

- X-intercept for the VR curve is mean circulatory pressure (mean systemic pressure).

- This is the pressure in the circulation when there is no flow (when the heart stops).

- MSP is the upstream pressure for VR. Thus, when RAP = MSP, flow (VR) is zero. Normal value of MSP is about 7 mmHg.

- MSP is directly related to blood volume and inversely related to venous compliance.

- Increasing vascular volume (infusion; activation of RAAS) or decreasing venous compliance (sympathetic stimulation) increases MSP, causing a right shift in the VR curve. Thus, either of these changes enhances filling of the ventricles (move up the Frank-Starling curve) and CO.

- Decreasing vascular volume (hemorrhage; burn trauma; vomiting; diarrhea) or increasing venous compliance (inhibit sympathetics; alpha block; venodilators) decreases MSP, causing a left shift in the VR curve. Thus, either of these changes reduces filling of the ventricles (move down the Frank-Starling curve) and CO.

A. Inotropy:

- Changes in contractility → altered SV → altered CO/VR and RA pressure (RAP).

- Examples:

1. Catecholamines, digoxin ⊕.
2. Uncompensated HF, narcotic overdose ⊖.

B. Venous return:

- Changes in circulating volume or venous tone → altered RA pressure for a given CO.

- Mean systemic pressure (x-intercept) changes with volume/venous tone.

- Examples:

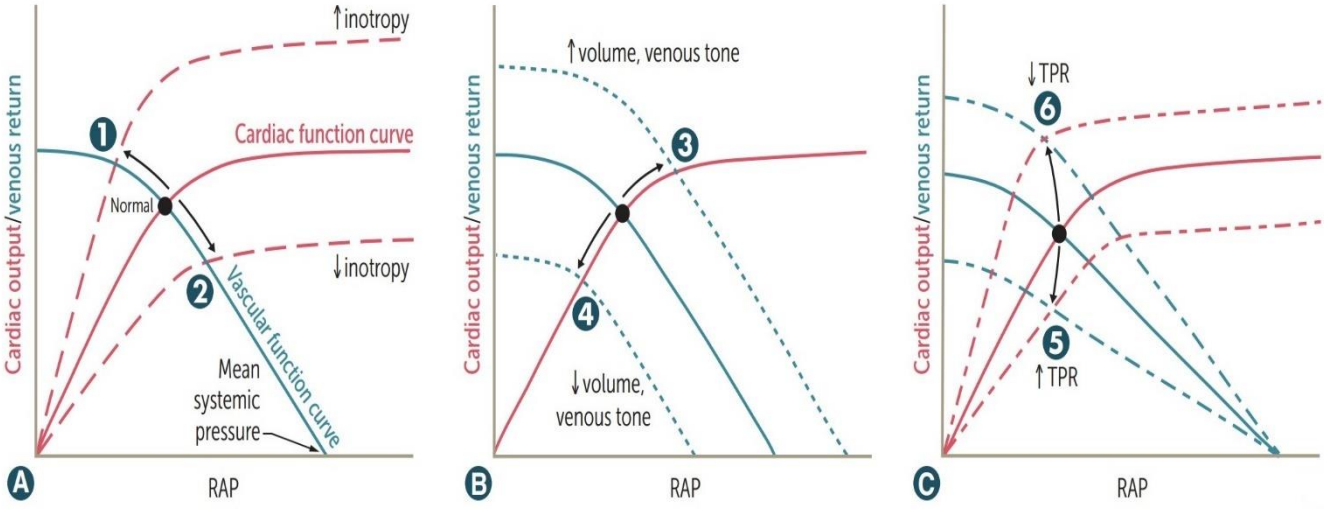
3. Fluid infusion, sympathetic activity ⊕.
4. Acute hemorrhage, spinal anesthesia ⊖.

C. Total peripheral resistance:

- At a given mean systemic pressure (x-intercept) and RA pressure, changes in TPR → altered CO.

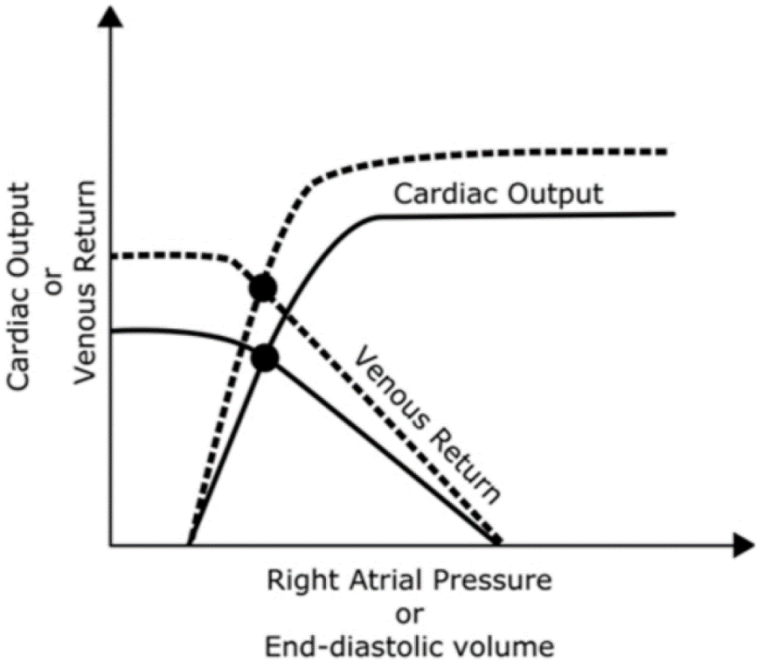
- Examples:

5. Vasopressors ⊕.
6. Exercise, AV shunt ⊖.



❖ N.B:

- Arteriovenous (AV) shunts result from the formation of AV fistulas.
- An AV fistula is an abnormal communication between an artery and a vein that bypasses the arterioles, the major source of resistance in the vascular system.
- Thus, AV shunts allow blood under arterial pressure to directly enter the venous system.
- AV fistulas can be congenital or acquired (secondary to penetrating injuries or iatrogenically created for dialysis access).
- Acutely, an arteriovenous fistula causes a decrease in TPR (increased slope of both the cardiac function curve and the venous return curve), which results in an increased cardiac output and an increased venous return. However, the venous return curve does not immediately shift along the x-axis.
- Over time, the sympathetic nervous system and kidneys will begin to compensate for a chronic fistula by increasing cardiac contractility, vascular tone, and circulating blood volume. These changes further increase the cardiac function curve as well as increase the mean systemic pressure, resulting in a rightward shift of the venous return curve on the x-axis.
- High-volume AV shunts can eventually result in high-output cardiac failure.



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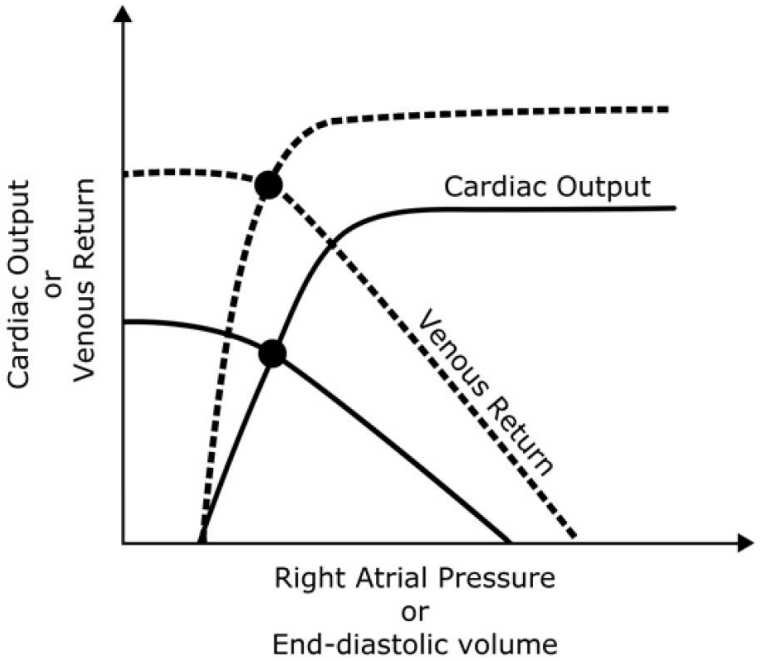
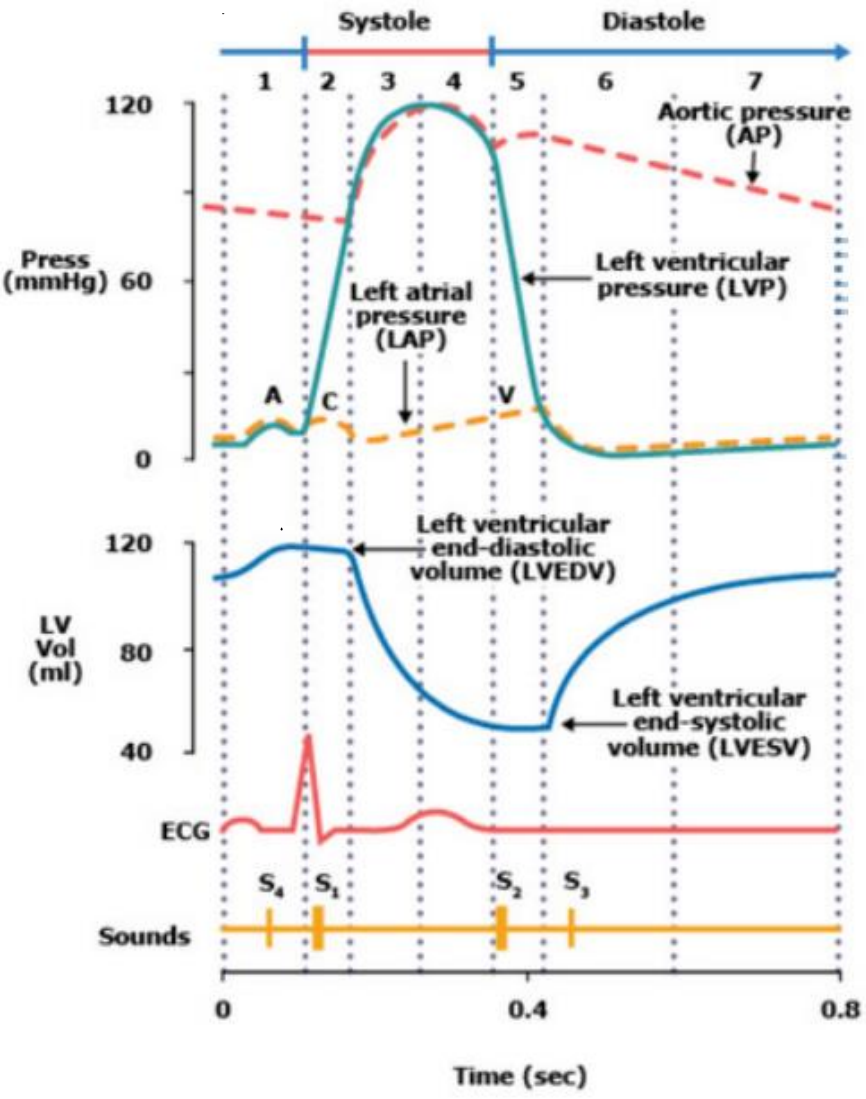


[chronic]

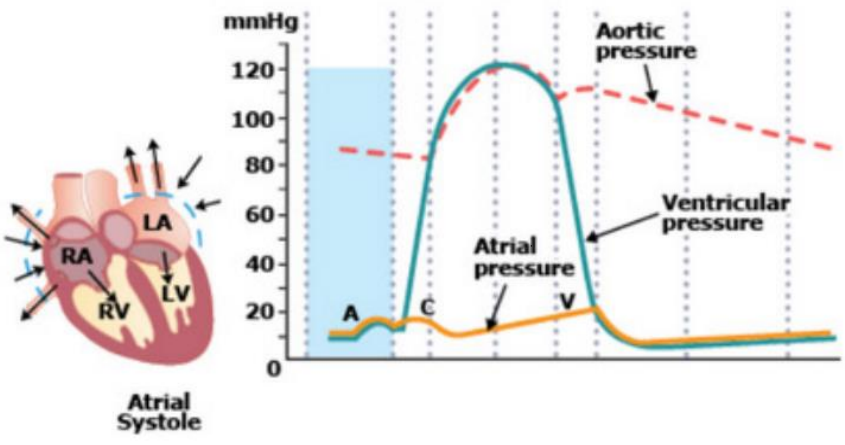
Normal Cardiac Cycle

- The Figure illustrates the most important features of the complete left sided cardiac cycle.



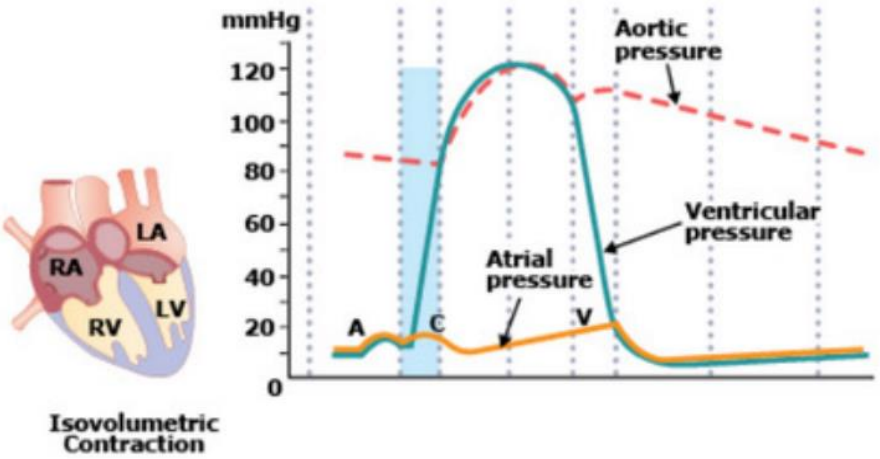
- The cardiac cycle for the left heart can be divided into a number of phases and events:

A. Late Diastolic Filling:



- Minor contribution to LV filling at rest.
- Atrial contraction.
- "A wave" on the venous pulse
- S4 if presents. It coincides with atrial contraction against a stiff ventricle, as seen in concentric hypertrophy.
- Mitral valve open.

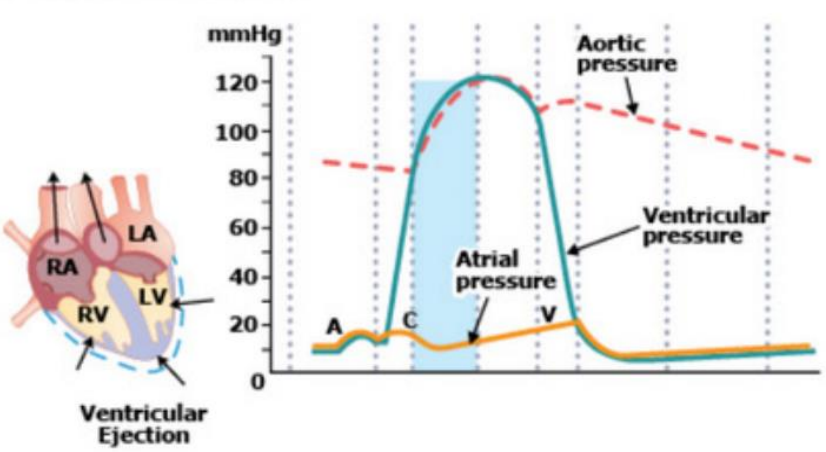
B. Isovolumetric Contraction:



- Closure of the mitral valve (S1) and start of isovolumetric contraction.
- Both mitral and aortic valves closed and pressure rising.
- Ventricular volume constant = end-diastolic volume (EDV).
- Ventricular depolarization (QRS)

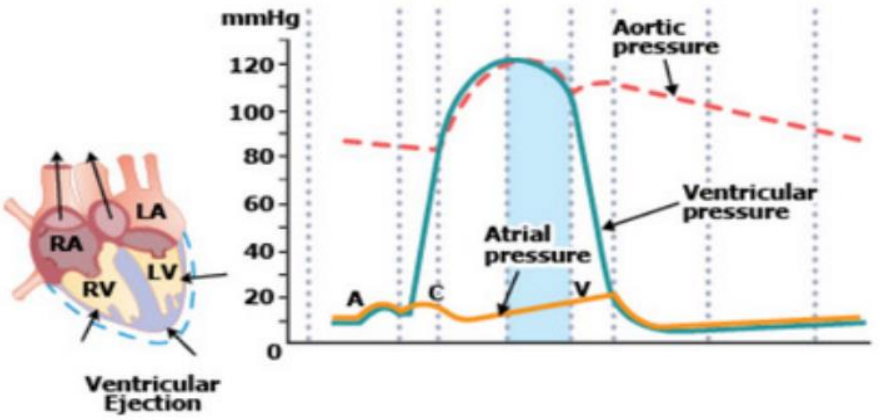
C. Ejection Phase:

1. Early ejection phase:



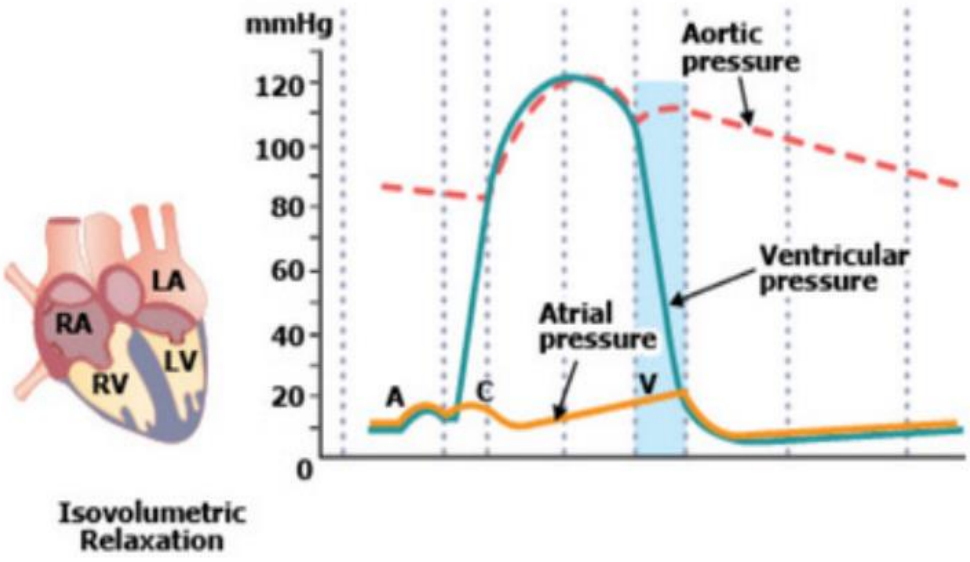
- Aortic valve opens because ventricular pressure exceeds aortic pressure.
- Ejection phase begins.
- Most of the blood ejected early in this phase (rapid ejection) when aortic and ventricular pressures are rising.
- Peak ventricular pressure = peak aortic pressure (systolic blood pressure).

2. Late ejection phase:



- Reduced ejection as aortic and ventricular pressure starts to decline.
- Volume ejected = stroke volume (SV), phase terminated when aortic valve closes (S2).
- Creates dicrotic notch (secondary upstroke in the descending part corresponding to the transient increase in aortic pressure upon closure of the aortic valve).
- Aortic valve closes because ventricular pressure declines below aortic pressure.

D. Isovolumetric Relaxation:

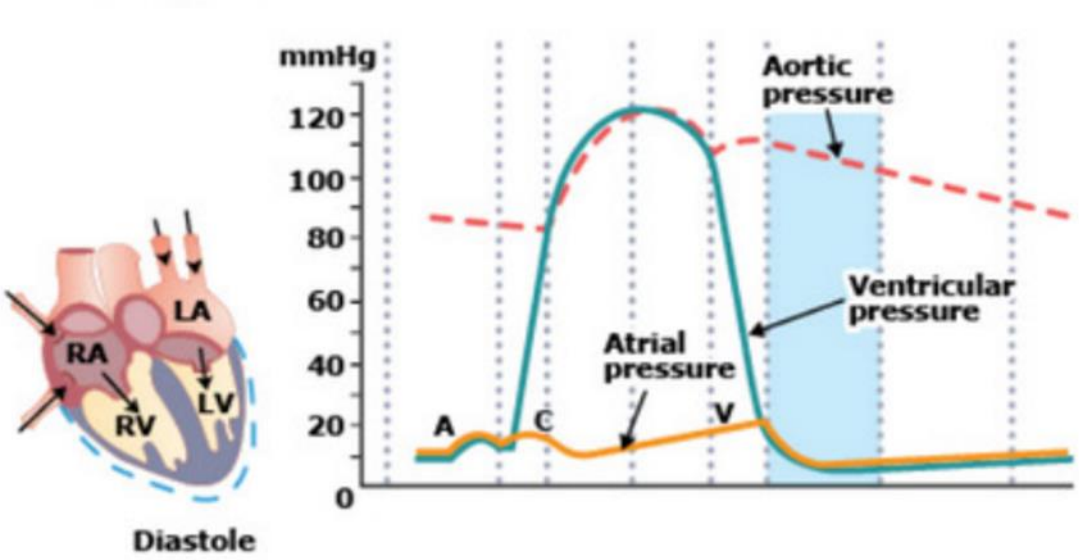


- Begins with closure of the aortic valve.
- Both aortic and mitral valve closed, and pressure declines.
- Ventricular volume constant = end-systolic volume (ESV).
- SV = volume of isovolumetric contraction (EDV) - volume of isovolumetric relaxation (ESV).
- EF (ejection fraction) = SV/EDV normal resting value 55- 65%.

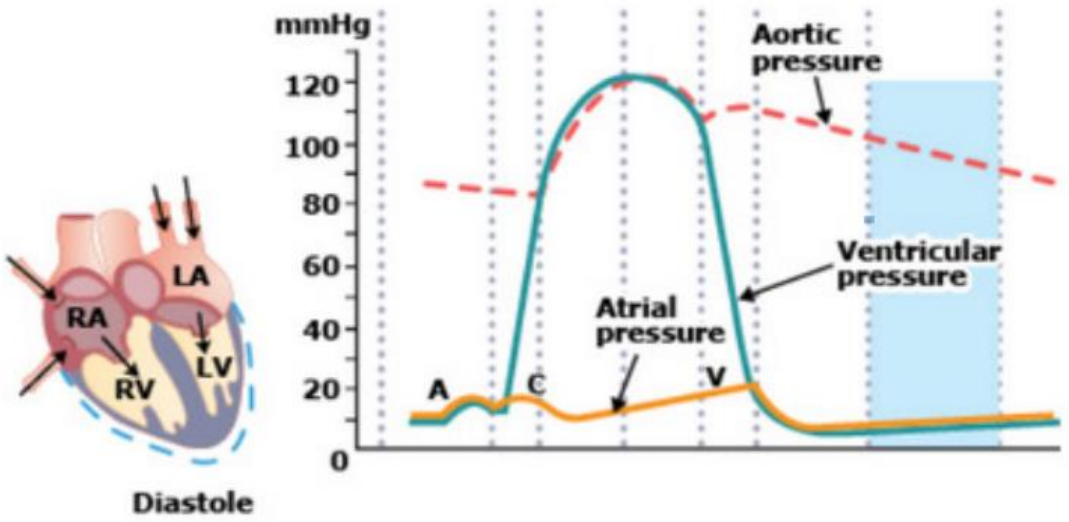
E. Filling Phase:

1. Early diastolic filling:

- Mitral valve opens because pressure in the ventricle decreases below atrial pressure.
- Rapid filling from the atrium and S3 if present (often associated with a volume-overloaded ventricle as heart failure).



2. Mid-diastolic filling:



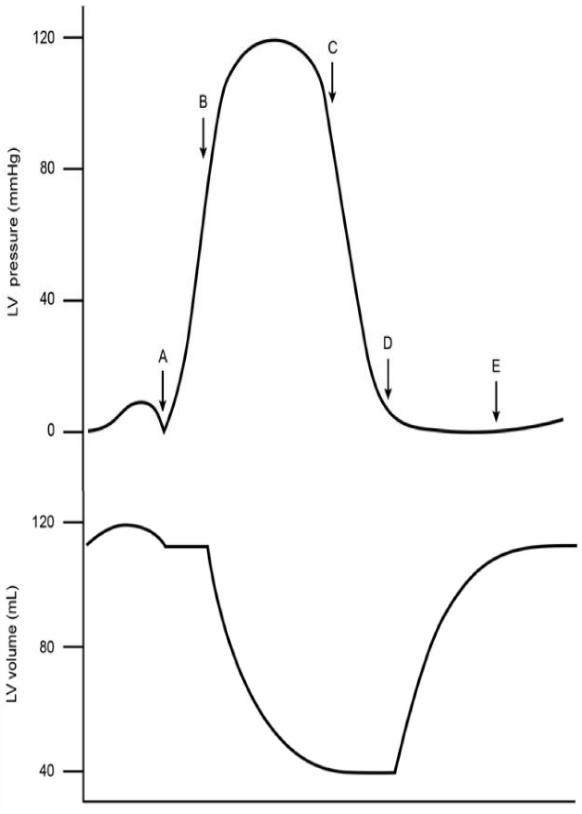
- Period of reduced filling.

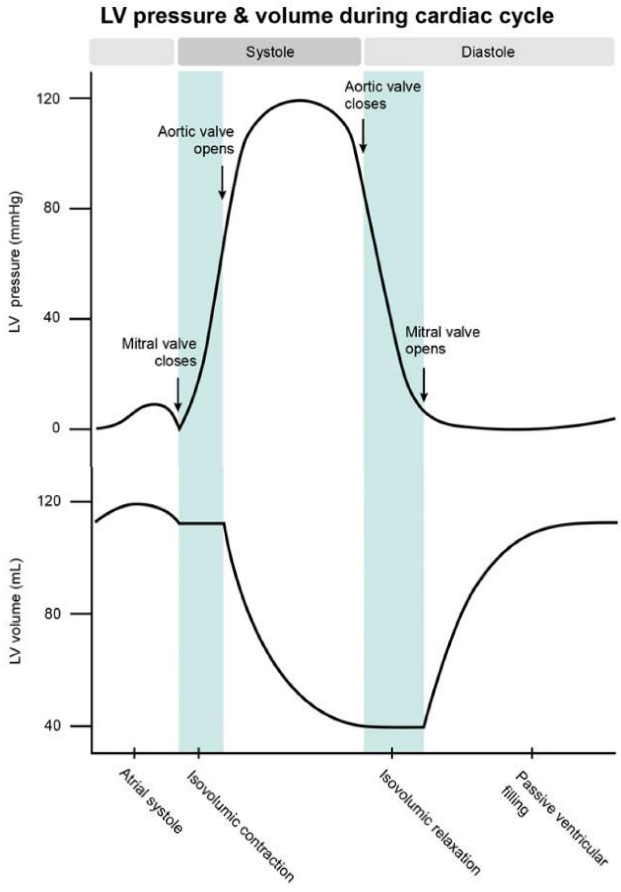
- Ventricular filling in equilibrium with venous return.

❖ N.B:

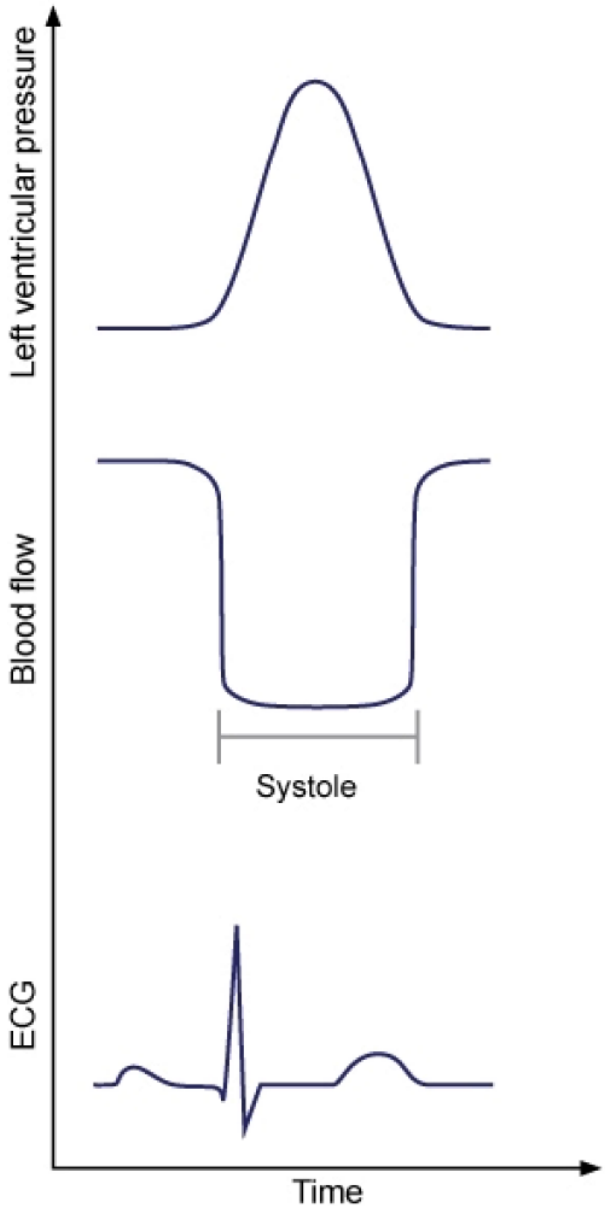
1. The graph below depicts the left ventricular pressure and volume during the cardiac cycle. Together these graphs can be used to plot the various phases of the cardiac cycle.

- First, on the left, is atrial systole. In this phase, blood is forcefully expelled from the atria into the ventricles causing the slight increase in ventricular pressure and volume seen on the far left of the graph.
- Next, the mitral valve closes causing a slight depression of the ventricular pressure curve (marked as point A below).
- The ventricle then begins to contract. The segment between points A and B corresponds to isovolumetric contraction. During this time the ventricular pressure increases but the ventricular volume remains the same because the aortic and mitral valves are closed.
- When the ventricular pressure exceeds the diastolic systemic blood pressure, the aortic valve opens (point B). Now the ventricular volume begins to decrease sharply as blood is expelled.
- The left ventricular pressure continues to increase between points B and C until the systolic maximum blood pressure is reached.
- When these two values are equal, the aortic valve closes (point C).
- Isovolumetric relaxation occurs between points C and D. The ventricle relaxes and both the aortic and mitral valves are closed.
- At point D, the mitral valve opens, initiating the phase of diastolic filling.

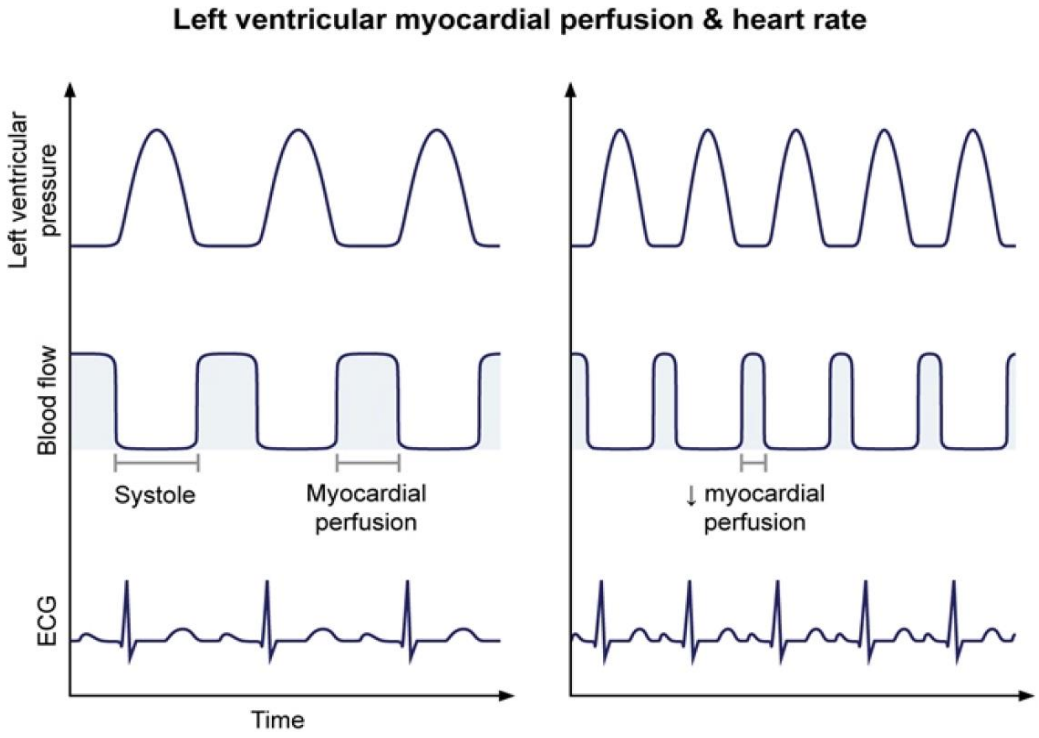




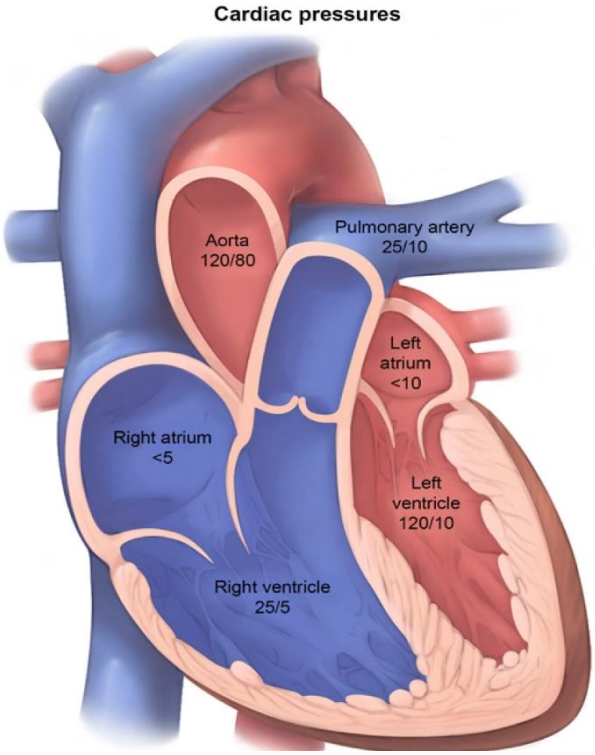
2. The blood flow curves show a cyclical variation in flow during the cardiac cycle, with maximum flow occurring during diastole and minimal blood flow occurring during ventricular systole.
- This blood flow pattern is unique for the left ventricular myocardium.
- The great majority of blood flows through the vascular beds of the left ventricle during diastole, when the vessels are not compressed by myocardial contraction.
- This systolic reduction in blood flow is greatest in the subendocardial myocardium (where wall pressures are the highest), making it the region most prone to ischemia and myocardial infarction.



3. The high systolic intraventricular pressure and wall stress of the left ventricle prevent myocardial perfusion during systole; therefore, the majority of left ventricular myocardial perfusion occurs during diastole. Shorter duration of diastole is the major limiting factor for coronary blood supply to the left ventricular myocardium during periods of tachycardia (exercise).



4. Normal (adult) pressures in the cardiac chambers and pulmonary artery during the cardiac cycle are as follows:



- Recall that, in general, left-sided pressure are greater than right-sided pressures.
- Within the atria, the normal pressure maximum is close to 10 mm Hg.
- Within the right ventricle, the maximum pressure is normally about 25 mm Hg, and within the pulmonary artery, the maximum pressure is normally close to 25 mm Hg.
- The left ventricular and aortic maximum pressures are normally close to the systolic blood pressure.

Heart sounds

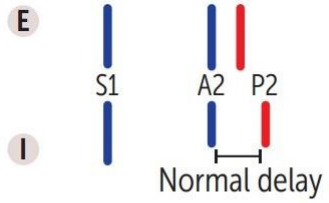
- S1 and S2 are systolic sounds.
- S3 and S4 are diastolic sounds.
- Valves open right side, then left side, but close left, then right.
- A unilateral increase in the output of a ventricle delays the close of valves of S2.
- Stenotic valves open slower and close more slowly (stay open longer)

A. First Heart Sound (S1):

- Closure of mitral, then tricuspid valve.
- Loudest at mitral area.

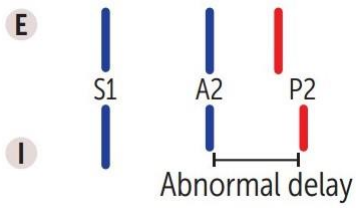
B. Second Heart Sound (S2):

- Closure of the aortic, then the pulmonic valve.
- Two components: A2 aortic valve closure, and P2, pulmonic valve closure.
- Loudest at left upper sternal border.
- An audible splitting of the second sound occurs with a unilateral increase in the output of the right heart that delays the closing of the pulmonic valve, as in inspiration (physiological splitting) and atrial septal defect (flow from left to right).
- Physiologic splitting:
  - Inspiration → drop in intrathoracic pressure →↑ venous return → ↑ RV filling →↑ RV stroke volume →↑ RV ejection time → delayed closure of pulmonic valve.

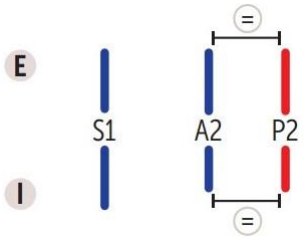


E = Expiration
I = Inspiration

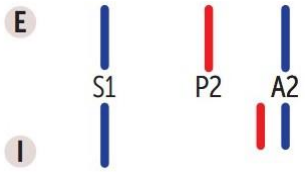
- Wide splitting:
  - Seen in conditions that delay RV emptying (pulmonic stenosis, right bundle branch block).
  - Causes delayed pulmonic sound (especially on inspiration). An exaggeration of normal splitting.



- Fixed splitting:
  - Heard in ASD.
  - ASD → left-to-right shunt → ↑ RA and RV volumes →↑ flow through pulmonic valve such that, regardless of breath, pulmonic closure is greatly delayed.



- Paradoxical splitting:
  - Heard in conditions that delay aortic valve closure (aortic stenosis, left bundle branch block).
  - Normal order of valve closure is reversed so that P2 sound occurs before delayed A2 sound.
  - Therefore, on inspiration, P2 closes later and moves closer to A2, thereby "paradoxically" eliminating the split (usually heard in expiration). On expiration, the split can be heard (opposite to physiologic splitting).



C. Third Heart Sound (S3):
- Occurs during the rapid filling of a very compliant ventricle.
- Normal in children, athletes and pregnancy.
- In older adults, a third heart sound is often associated with a volume-overloaded ventricle (mitral regurgitation, aortic regurgitation, HF).
- A pathological S3, is called a ventricular gallop.

D. Fourth Heart Sound (S4):
- Coincides with atrial contraction against a stiff ventricle.
- An S4 may be present in any condition that causes reduced ventricular compliance (hypertensive heart disease, aortic stenosis, hypertrophic cardiomyopathy).
- It is heard as a low-frequency late diastolic sound that occurs just prior to the first heart sound (S1).

❖ N.B:

1. Left ventricular gallops (S3 and/or S4) are best heard with the bell of the stethoscope (low frequency sound) over the cardiac apex while the patient is in the left lateral decubitus position.

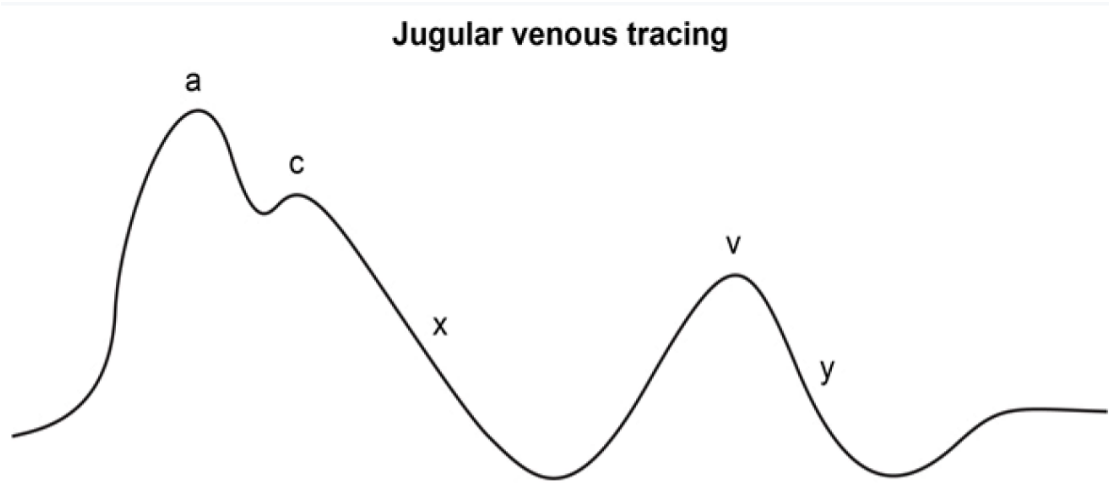
- Listening at end expiration makes the sound even more audible by decreasing lung volume and bringing the heart closer to the chest wall.

2. Paradoxical embolism occurs when a thrombus from the venous system crosses into the arterial circulation via an abnormal connection between the right and left cardiac chambers (patent foramen ovale, atrial septal defect, or ventricular septal defect).

- Atrial left-to-right shunts cause wide and fixed splitting of S2 and can facilitate paradoxical embolism due to periods of transient shunt reversal (during straining or coughing).

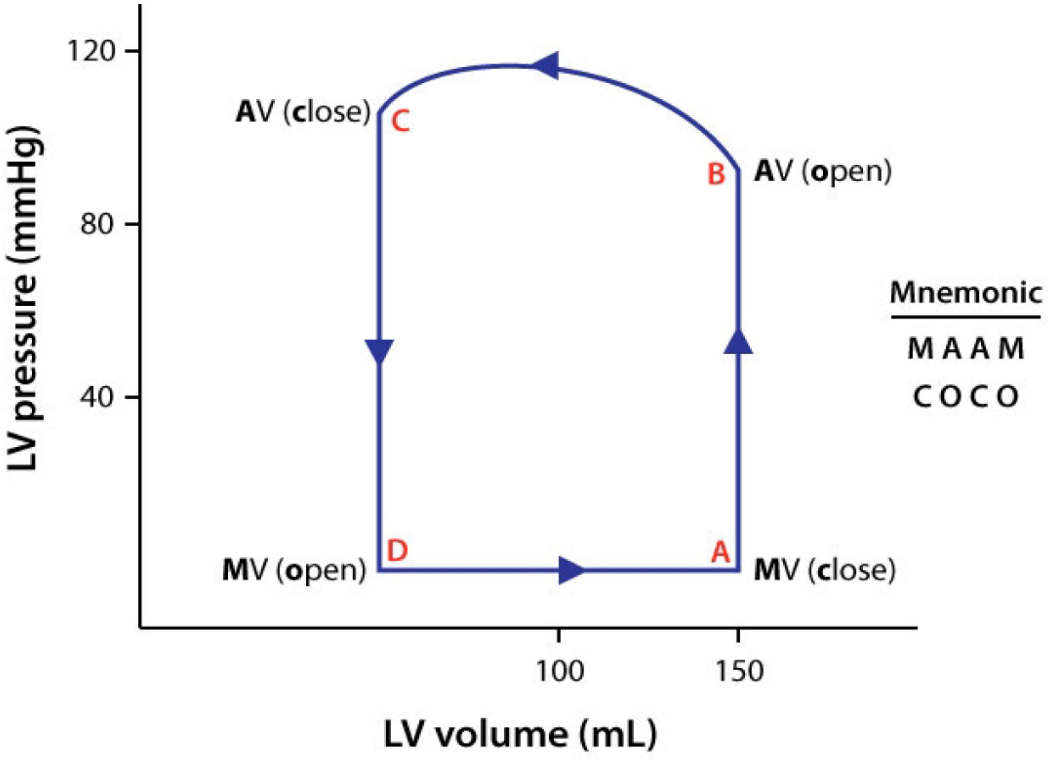
Systemic venous pulse

- A normal jugular venous pulse wave tracing has 3 positive waves (a, c, and v) and 2 negative waves (x and y descent).
- The a wave is generated by atrial contraction (Absent in atrial fibrillation), the c wave is caused by bulging of the tricuspid valve into the right atrium in early systole, and the v wave reflects the passive increase in pressure and volume of the right atrium as it fills in late systole and early diastole.
- Prominent A wave is produced by atrial contraction against high resistance as tricuspid stenosis or high right ventricular pressure due to pulmonic stenosis or pulmonary hypertension.
- Cannon A waves are produced by atrial systole against a closed tricuspid valve (third degree AV block). The tricuspid valve is closed because the very essence of third-degree block is that the atria and ventricles are contracting separately and out of coordination with each other.
- The x-descent is primarily caused by relaxation of the right atrium (Reduced or absent in tricuspid regurgitation and right HF because pressure gradients are reduced).
- The y-descent represents the abrupt decrease in right atrial pressure during early diastole after the tricuspid valve opens and the right ventricle begins to passively fill (Prominent in constrictive pericarditis, absent in cardiac tamponade).



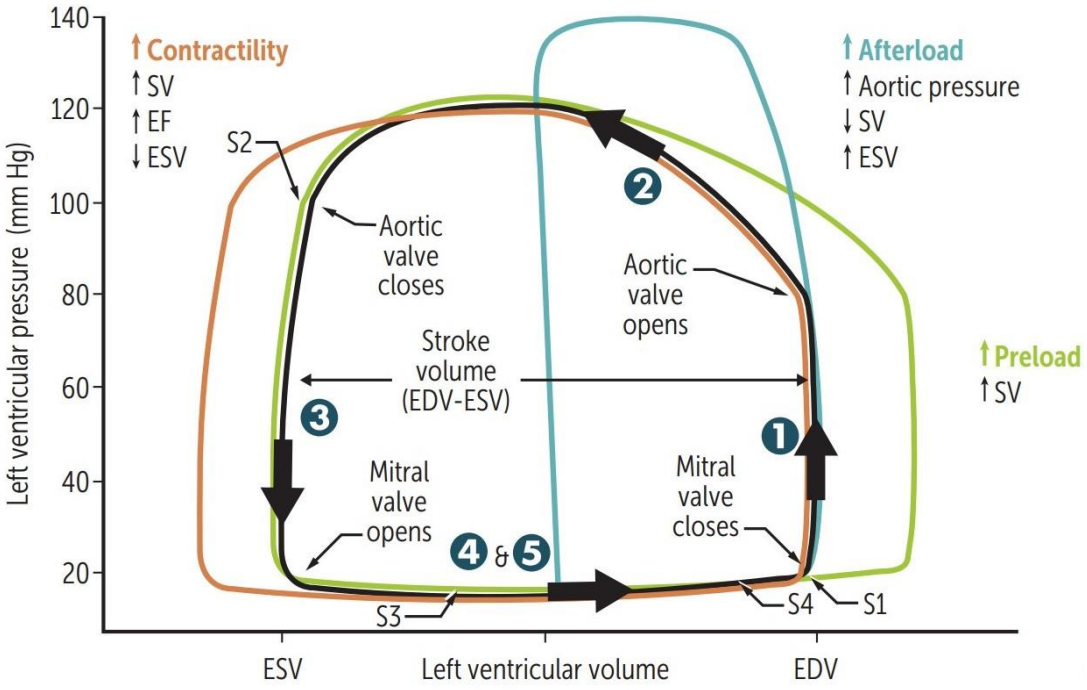
a = Right atrial contraction
c = Bulging of tricuspid valve during right ventricular contraction
x = Right atrial relaxation
v = Continued inflow of venous blood
y = Passive emptying of right atrium after tricuspid valve opening

Pressure- volume loops



A → B = Isovolumetric contraction
B → C = Ventricular ejection
— Ventricular systole

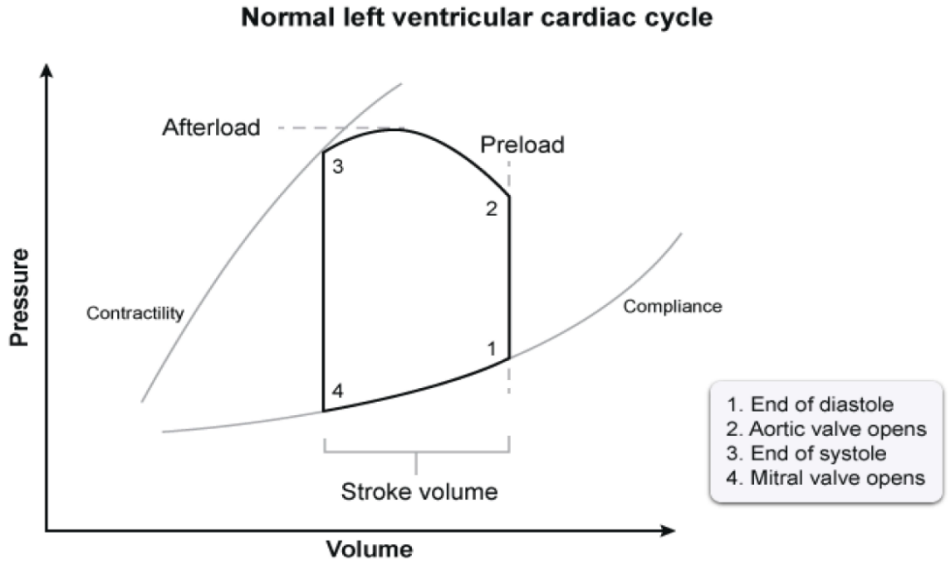
C → D = Isovolumetric relaxation
D → A = Ventricular filling
— Ventricular diastole

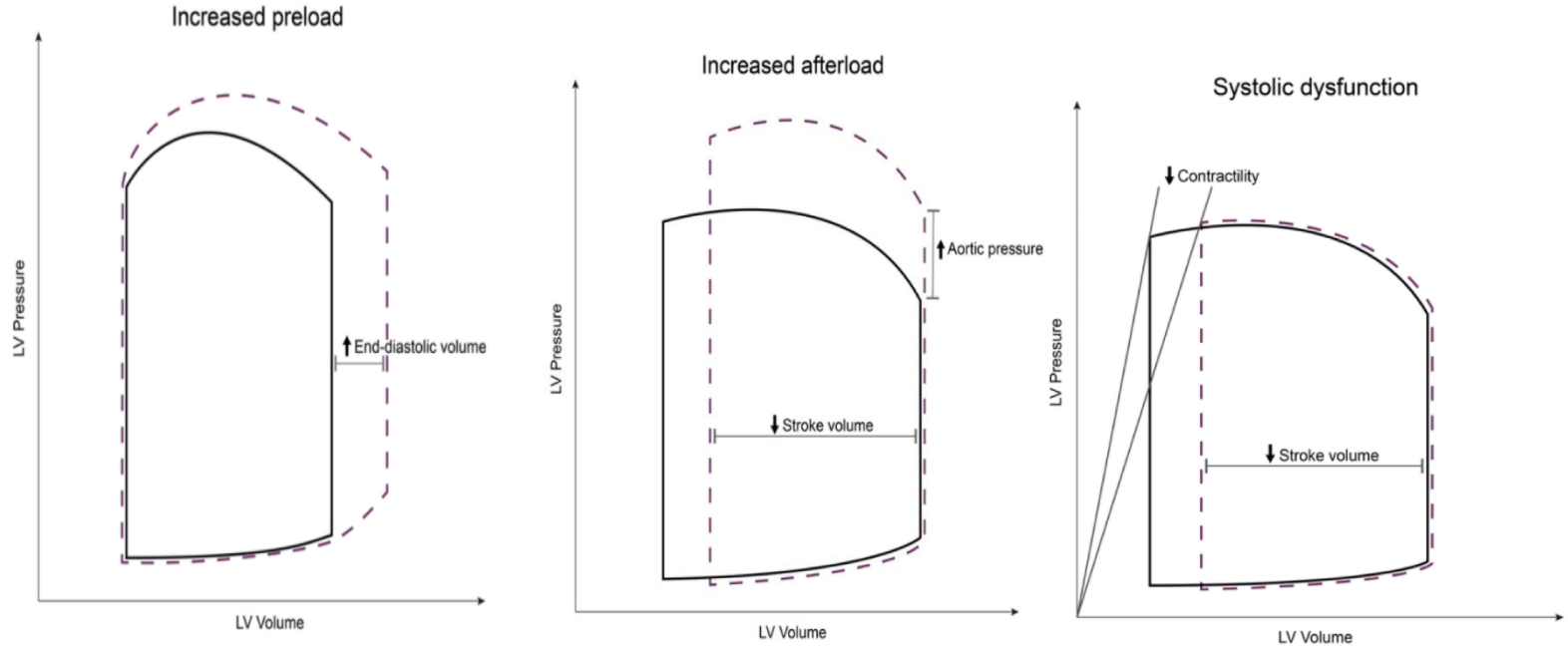


- The ventricular pressure-volume loop depicts the relationship between pressure and volume in the left ventricle during systole and diastole.

- To follow the events in a cardiac cycle, the loop is read in a counterclockwise direction:

1. Isovolumetric contraction: period between mitral valve closing and aortic valve opening; period of highest O_2 consumption.
2. Systolic ejection: period between aortic valve opening and closing.
3. Isovolumetric relaxation: period between aortic valve closing and mitral valve opening.
4. Rapid filling: period just after mitral valve opening.
5. Reduced filling: period just before mitral valve closing.

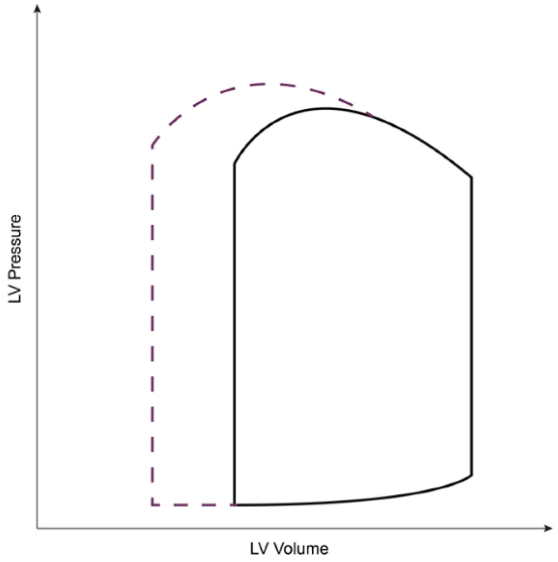




❖ N.B:

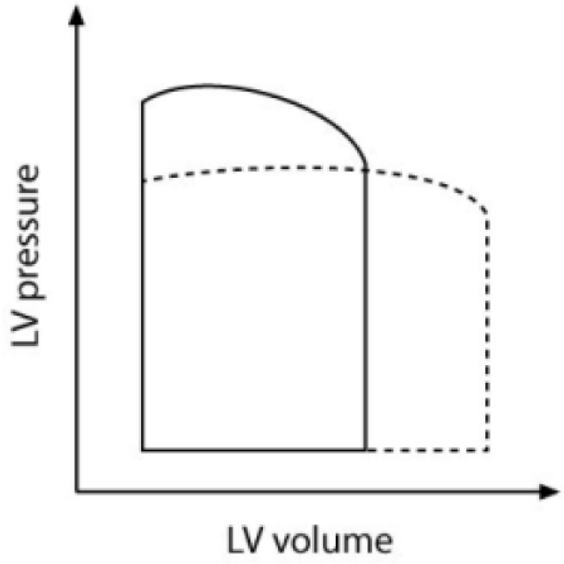
1. The dashed loop reflects an increase in cardiac contractility and stroke volume, as evidenced by the increased ejection volume and higher systolic pressure generated.

- An increased ejection fraction (increased stroke volume) is represented on a ventricular pressure-volume loop as a widening of the graph.
- The isovolumetric relaxation line is shifted to the left indicating less volume remaining in the ventricle after contraction is complete.

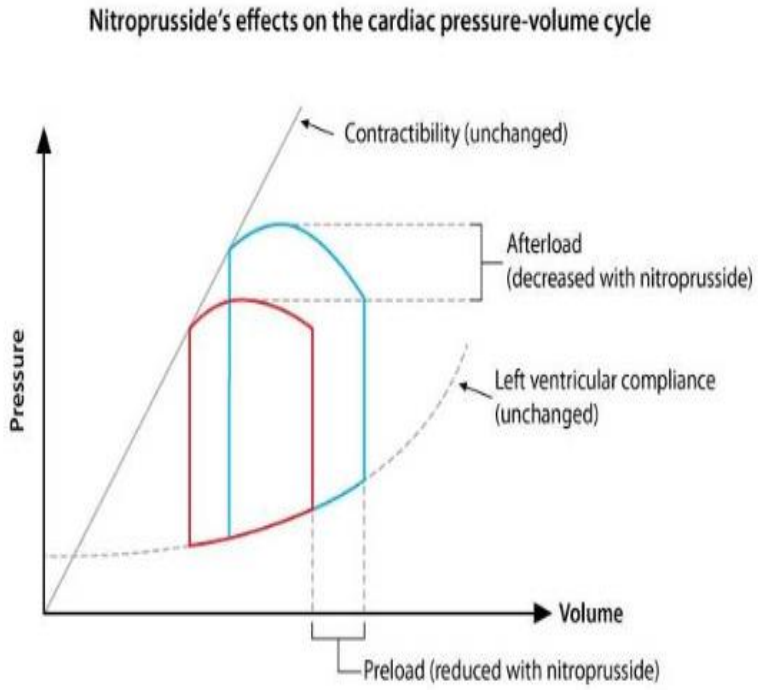


2. AV shunts increase cardiac preload by increasing the rate and volume of blood flow back to the heart.

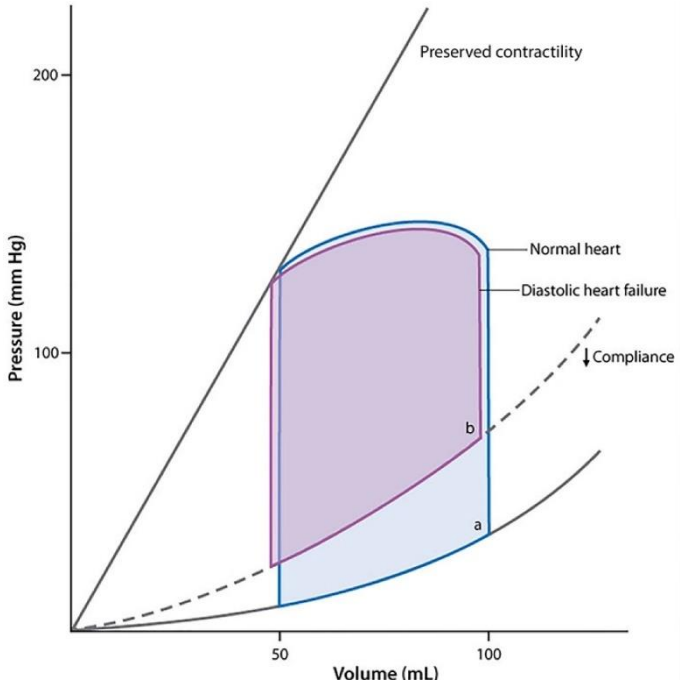
- This is reflected on the ventricular pressure-volume loop by elongation of the diastolic filling segment (bottom line) and a higher end diastolic volume.
- Because AV shunts allow blood to bypass the arterioles, total peripheral resistance is reduced, thus decreasing the afterload as well.



3. Nitroprusside is a short-acting balanced venous and arterial vasodilator.
- As such, it decreases left ventricular (LV) preload and afterload, allowing an adequate cardiac output to be delivered at a lower LV end diastolic pressure (LVEDP).
- The graph below shows a decrease in both LVEDP (preload) and mean systolic intraventricular pressure (afterload) without a reduction in stroke volume.
- Since these changes are balanced, stroke volume is maintained.

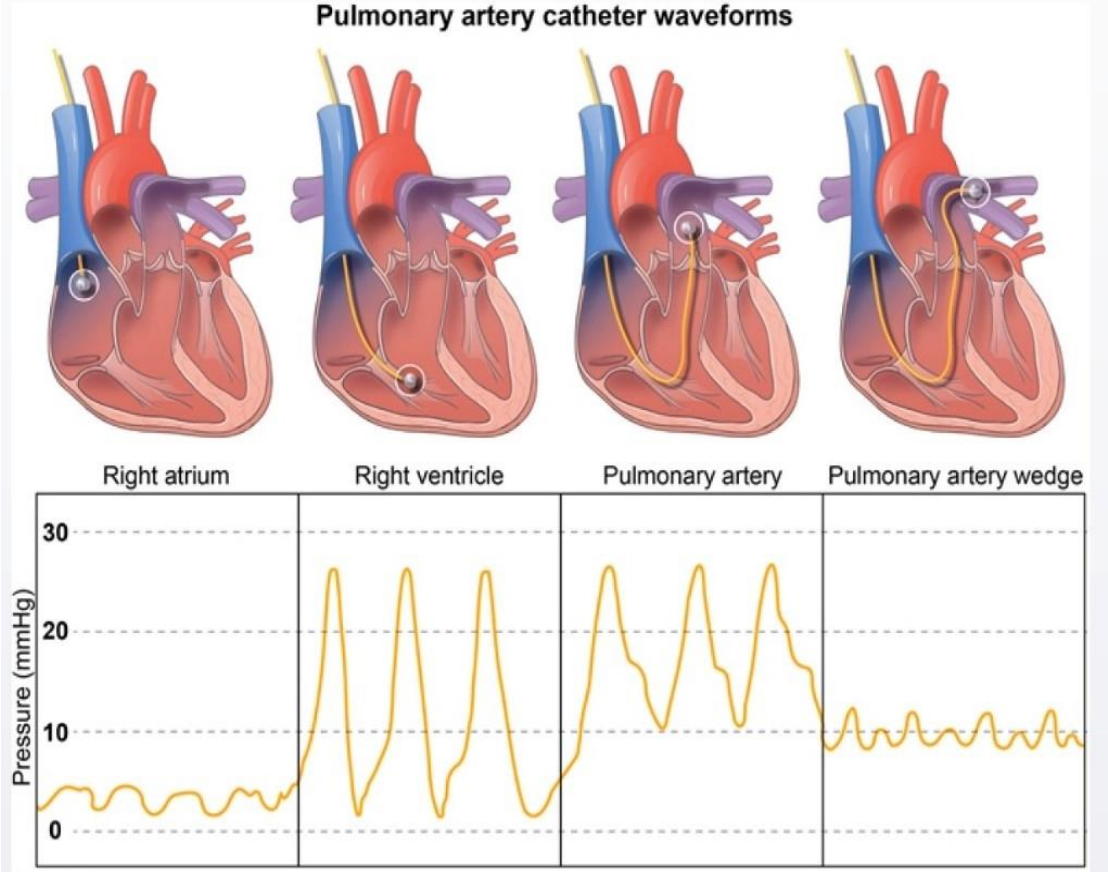


4. Diastolic heart failure (DHF) is caused by decreased ventricular compliance and is characterized by normal left ventricular (LV) ejection fraction, normal LV end-diastolic volume, and elevated LV filling pressures.
- Hypertension, obesity, and infiltrative disorders (transthyretin-related amyloidosis, sarcoidosis) are important causes of DHF.



Pulmonary wedge pressure

- Pulmonary artery catheters (PACs; also called Swan-Ganz or right heart catheters) are used to diagnose pulmonary hypertension and occasionally for management of critically ill patients.
- During pulmonary artery catheterization, the balloon at the distal tip of the catheter is inflated, and the catheter is advanced forward through the right atrium, right ventricle, and pulmonary artery and finally into a branch of the pulmonary artery.
- Once lodged in a pulmonary artery branch, the inflated balloon obstructs forward blood flow, creating a continuous static column of blood between the catheter tip and left atrium.
- Because there is no significant blood flow towards the left atrium (LA) beyond this point of occlusion, the pressure at the tip of the "wedged" pulmonary artery catheter becomes nearly equal to the LA pressure.



Valvular heart diseases

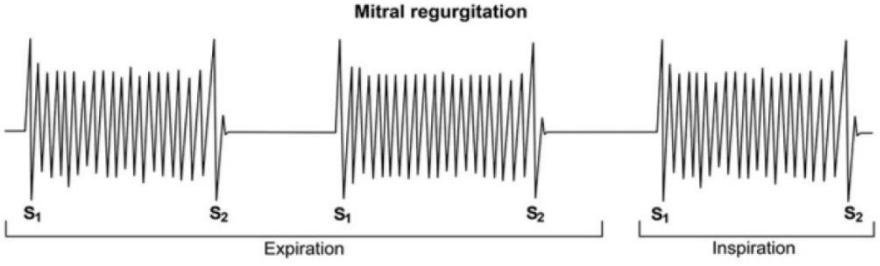
1. Systolic murmurs:

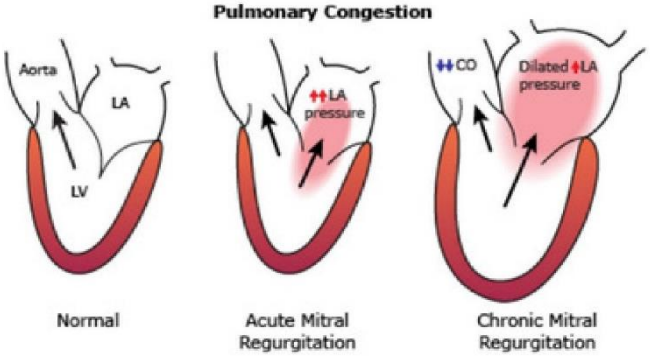
Mitral/Tricusped Regurgitation

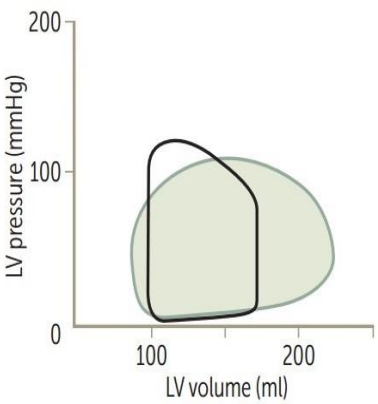
A. Mitral Regurgitation:

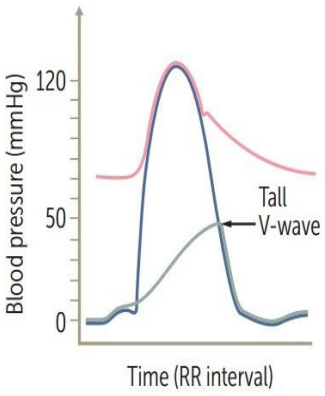
- Closing problem, can involve valve leaflets, mitral annulus, chordae tendineae.
- Causes: MR is often due to ischemic heart disease (post-MI), MVP, LV dilatation, Rheumatic fever and infective endocarditis.
- Murmur: systolic, begins at S1, and continues to S2, holosystolic (pansystolic) high-pitched "blowing murmur".
- Auscultation area: Loudest at apex and radiates toward axilla.
- In patients with mitral regurgitation, some of the blood in the left ventricle is pumped forward through the aortic valve (forward stroke volume), and some is forced backward through the incompetent mitral valve (regurgitant stroke volume). The amount of blood that flows forward is determined in part by the left ventricular afterload.
- As afterload decreases, resistance to blood flow into the aorta is reduced. This diverts blood flow away from the left atrium and toward the aorta, increasing the forward-to-regurgitant volume ratio.
- Arterial vasodilator therapy reduces left ventricular afterload and can reduce heart failure symptoms in patients with mitral regurgitation (although surgery remains the definitive treatment).
- Pathophysiology:

- No isovolumetric contraction (blood flow from the left ventricle to atrium).
- Stroke volume to aorta less than total stroke volume.
- Stroke volume to atrium returns to ventricle in diastole (volume cycles between ventricle and atrium).
- Volume overload (increased preload), dilation, and eccentric hypertrophy of ventricle.









No true isovolumetric phase
↓ ESV due to ↓ resistance and
↑ regurgitation into LA during systole
↑ EDV due to ↑ LA volume/pressure from regurgitation → ↑ ventricular filling
↑ SV

B. Tricuspid:

- Loudest at tricuspid area and radiates to right sternal border.

- TR commonly caused by RV dilatation.

- Rheumatic fever and infective endocarditis can cause either MR or TR.

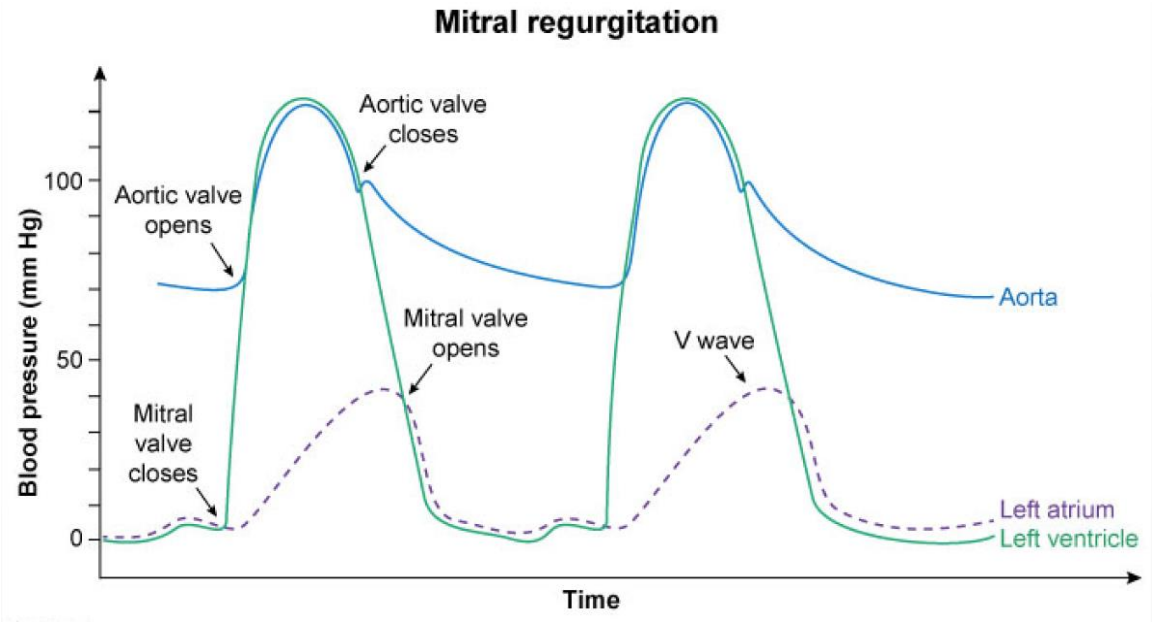
❖ N.B:

1. Among auscultatory findings, the best indicator of severe MR with left ventricular volume overload is the presence of an S3 gallop (volume overload).

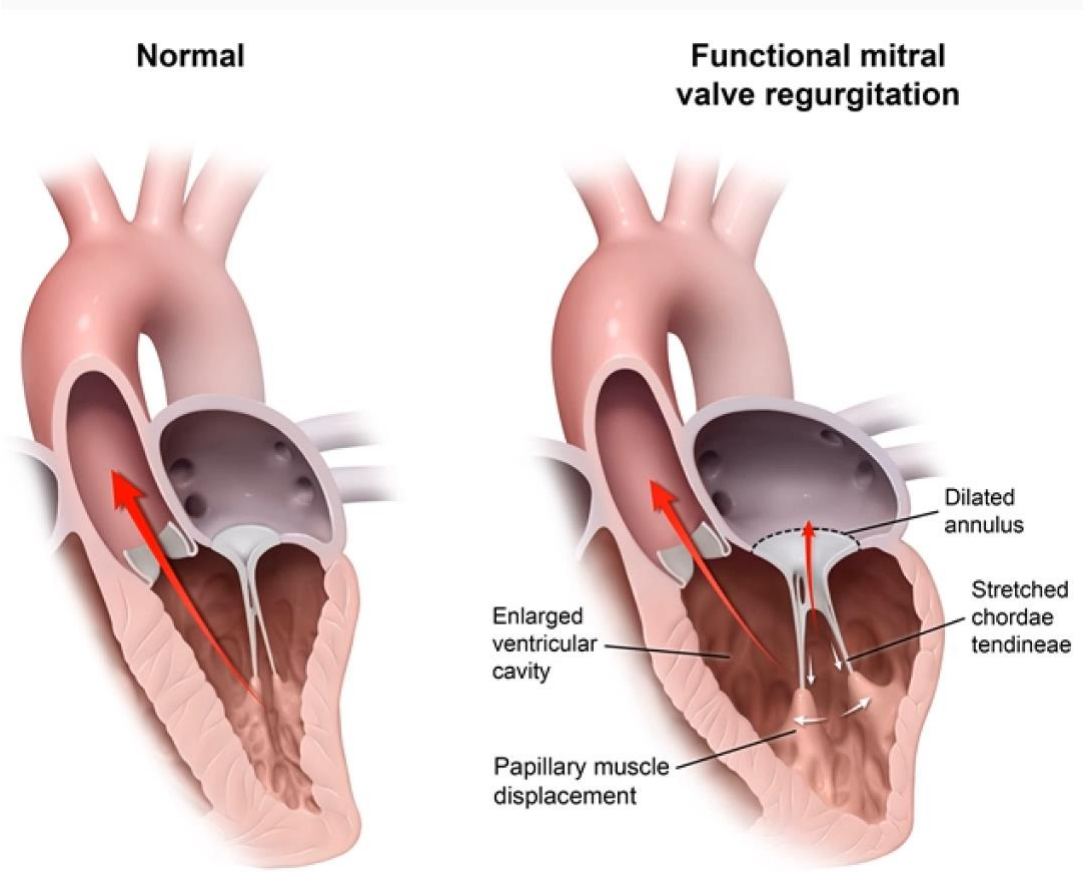
- In cases of severe MR, the left ventricular S3 gallop reflects an increased rate of left ventricular filling due to a large volume of regurgitant flow re-entering the ventricle during mid diastole.

2. In normal individuals, left atrial pressure increases to about 10 mm Hg during systole due to passive filling of the left atrium; this is reflected as the "v wave" on left atrial pressure tracings.

- However, patients with mitral regurgitation have abnormal retrograde blood flow through the mitral valve, which increases filling of the left atrium during systole. This causes elevation of the peak v wave pressure and an earlier upswing than would normally be seen.



3. Decompensated heart failure is a common cause of secondary (functional) mitral valve regurgitation.
- Increased left ventricular end-diastolic volume causes dilation of the mitral valve annulus and restricted movement of the chordae tendineae with subsequent regurgitation.
- Treatment with diuretics and vasodilators can improve heart failure-induced MR.



Aortic Stenosis

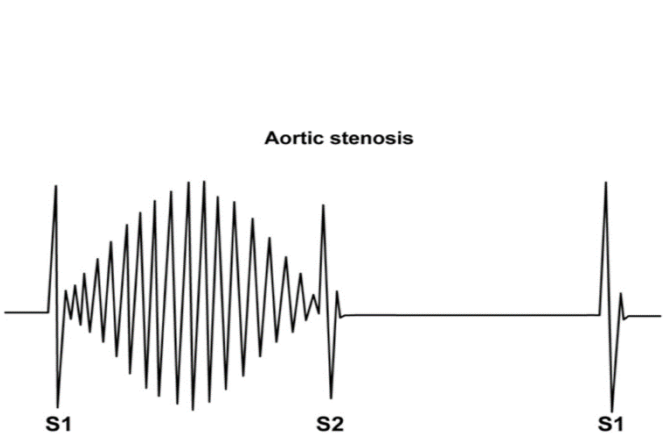
- Opening problem, often caused by degenerative calcific changes in the valve leaflets.
- Causes: Most commonly due to age-related calcification in older patients (> 60 years old) or in younger patients with early-onset calcification of bicuspid aortic valve.
- Murmur: Crescendo-decrescendo systolic ejection murmur (Early ejection click may be present) with soft S_2.
- Auscultation area: Loudest at heart base; radiates to carotids.
- Valve area acts as a major resistant point.
- Left ventricular systolic pressure increases to overcome resistance to flow (afterload).
- Pressure overload leads to a concentric ventricular hypertrophy, reduced chamber size, and a diastolic dysfunction.

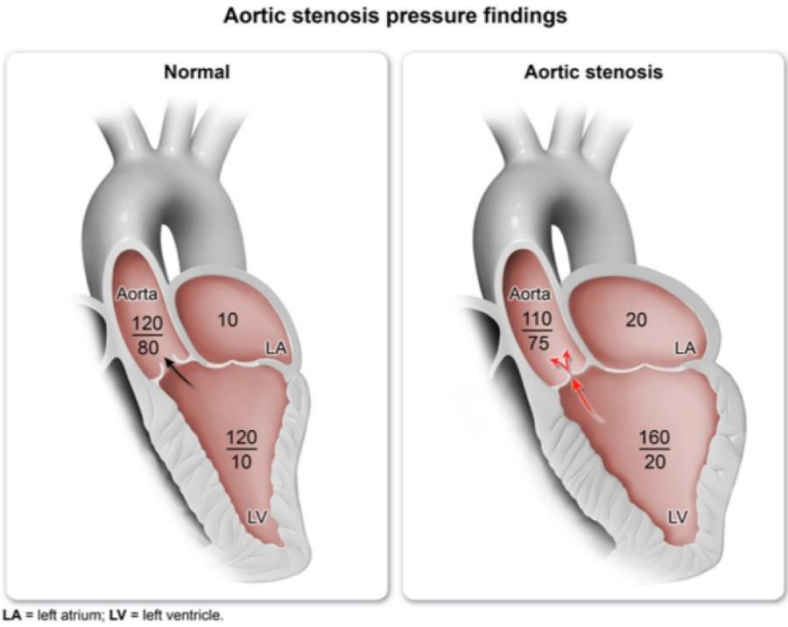
- The most defining characteristic is that left ventricular systolic pressure is significantly higher than aortic systolic pressure.

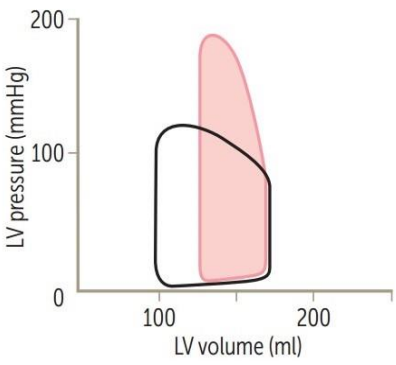
- Presentation:

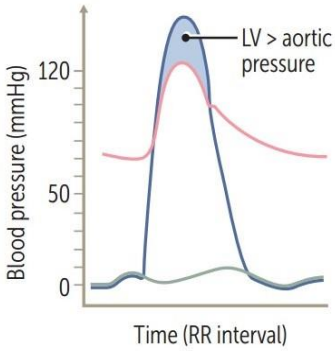
- Can lead to Syncope, Angina, and Dyspnea on exertion (SAD).

- "Pulsus parvus et tardus": pulses are weak with a delayed peak.









↑ LV pressure
↑ ESV
No change in EDV
↓ SV

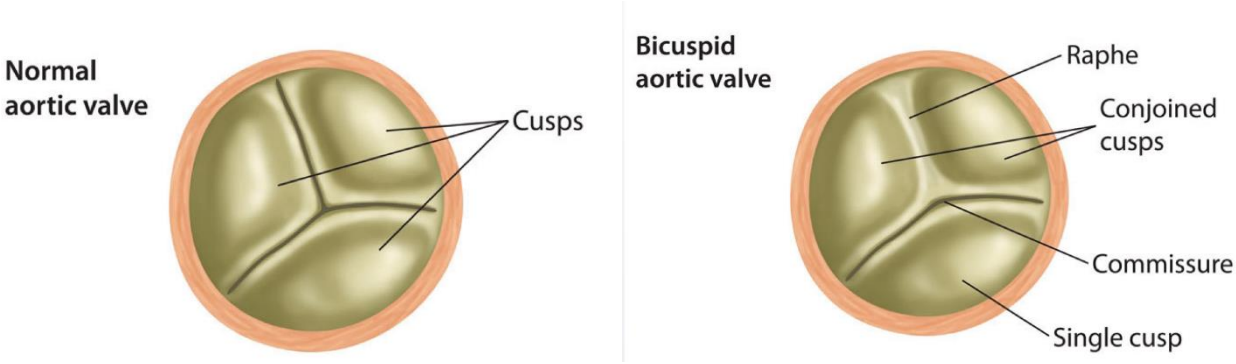
Ventricular hypertrophy → ↓ ventricular compliance → ↑ EDP for given EDV

❖ N.B:

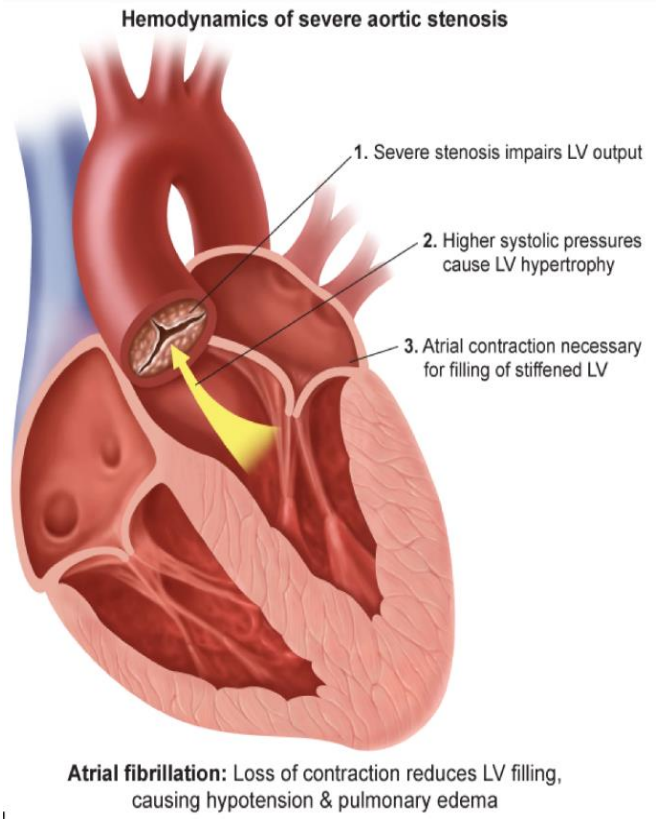
1. Aortic stenosis most commonly results from age-related calcific aortic valve disease (CAVD).
- The early pathogenesis of CAVD closely mimics that of arterial atherosclerosis.
- In the later stages, fibroblasts differentiate into osteoblast-like cells and deposit bone matrix, leading to progressive valvular calcification and stenosis.

2. Bicuspid aortic valves (right and left aortic cusp fusion) occur in approximately 1%-2% of live births, making it one of the most common congenital heart defects.
- The abnormally shaped valve experiences increased hemodynamic stress, which accelerates the normal aging process and causes premature atherosclerosis and calcification of the aortic valve.

- These deposits begin accumulating as early as adolescence and lead to aortic stenosis in >50% of affected patients.
- Symptomatic aortic stenosis develops on average around age 50 (10 years earlier than the average onset of senile calcific aortic stenosis in patients with normal aortic valves).

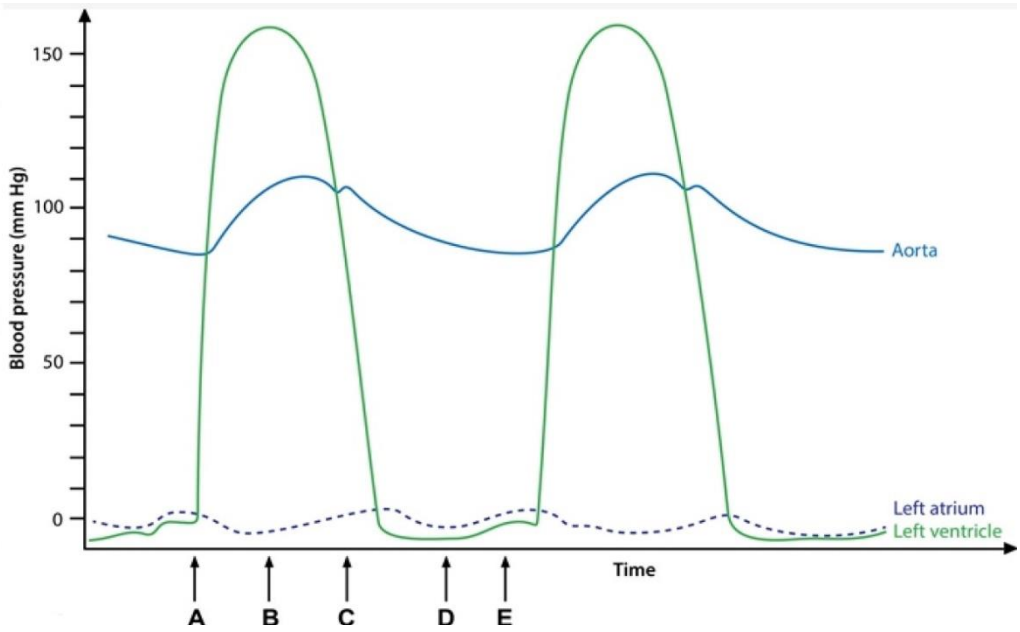


3. Patients with severe AS already have reduced cardiac output due to significant valvular obstruction, which can be exacerbated by the sudden loss of normal atrial contraction that contributes to ventricular filling.
- Atrial contraction is especially important for these patients as many have concentric left ventricular (LV) hypertrophy and therefore reduced LV compliance.
- As a result, they become dependent on atrial contraction to maintain adequate LV filling, without which LV preload can decrease to the point of producing severe hypotension.
- In addition, loss of the atrial kick can result in significantly increased mean pulmonary venous pressure due to buildup of blood in the left atrium and pulmonary veins, leading to acute pulmonary edema.
- As a result, cardioversion is indicated for acute atrial fibrillation in patients with severe AS.



4. This hemodynamic profile shows an abnormal pressure gradient between the left ventricular and aortic pressure tracings during systole (compare to normal), indicating significant aortic stenosis (AS).

- The intensity of the murmur of AS is directly related to the magnitude of the left ventricle to aorta pressure gradient.
- The maximum pressure difference between the left ventricular and aortic pressure tracings is noted at point B and corresponds to the peak intensity of a cardiac murmur during auscultation.



Mitral Valve Prolapse

- Causes: Can be caused by myxomatous degeneration (1° or 2° to connective tissue disease such as Marfan or Ehlers-Danlos syndrome), rheumatic fever, chordae rupture (Post-MI Complication).

- Murmur: Late systolic crescendo murmur with midsystolic click (MC) due to sudden tensing of chordae tendineae as mitral leaflets prolapse into the LA (Chordae cause Crescendo with Click). The murmur is caused by some of the blood leaking back into the left atrium.

- Best heard over apex.

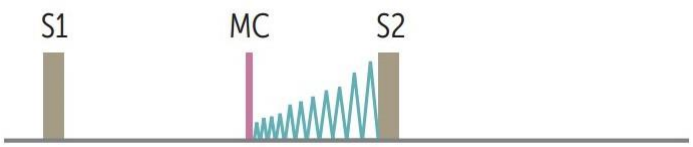
- Most frequent valvular lesion.

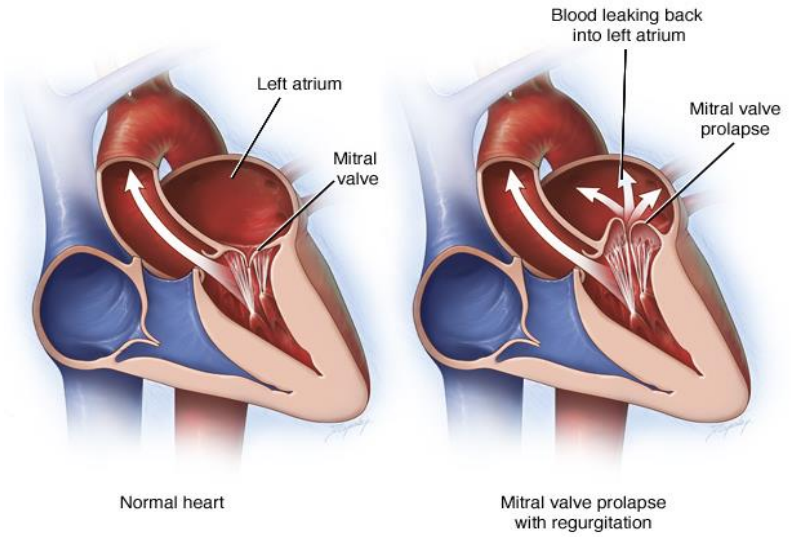
- Presentation:

- Common and usually asymptomatic, ballooning of the mitral valve leaflets into the left atrium during ventricular systole.

- Sometimes accompanied by mitral regurgitation.

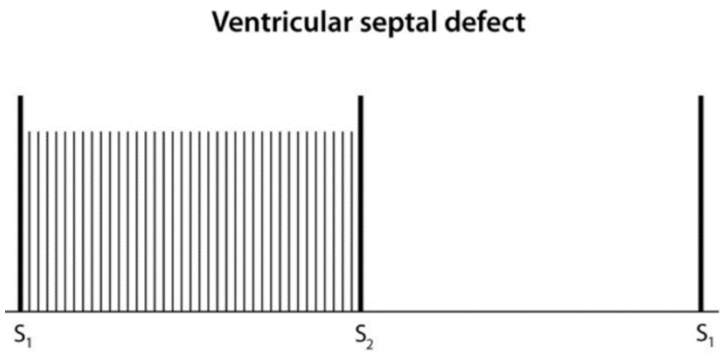
- Can predispose to infective endocarditis.

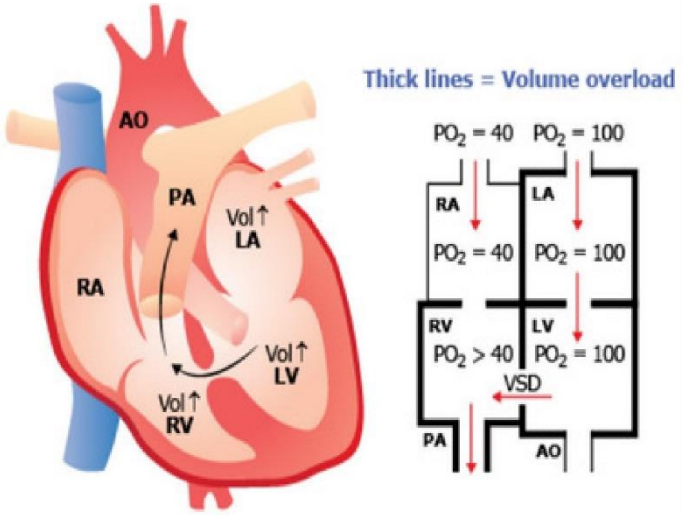




Ventricular Septal Defect (VSD)

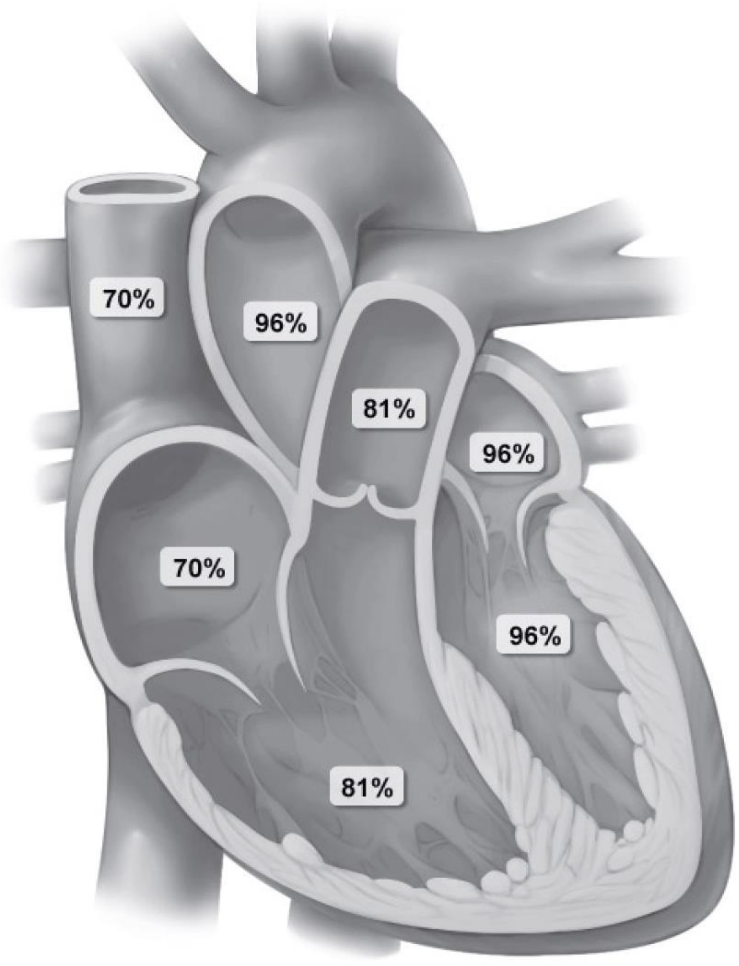
- Murmur: Holosystolic, harsh-sounding murmur.
- Auscultation area: Loudest at tricuspid area.
- Opening in the intraventricular septum.
- Blood flow LV → RV (L → R shunt)
- RV PO_2 > RA PO_2.
- Pulmonary vascular disease ↑ pressure in the right heart and may reverse the shunt (R → L shunt, late cyanosis).





❖ N.B:

- A significant increase in blood oxygen saturation between 2 right-sided vessels or chambers indicates the presence of a left-to-right shunt.
- If such an oxygen step-up occurs between the right atrium and right ventricle, a ventricular septal defect (VSD) is most likely responsible which would allow left ventricular blood to enter the RV during systole.
- Blood is shunted mainly from left to right due to the high-pressure differential, resulting in normal left ventricular SPO_2.

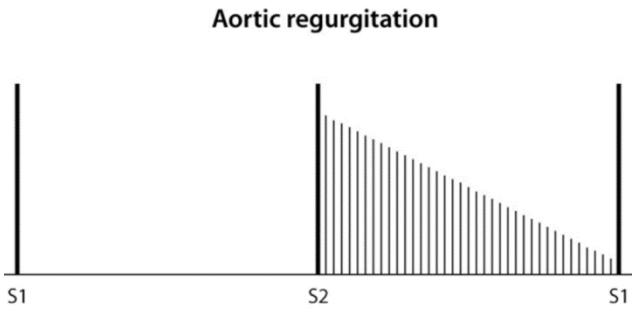


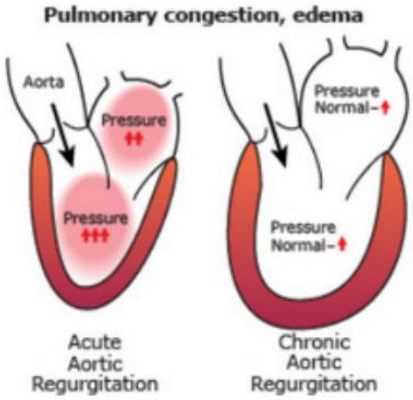
2. Diastolic murmurs:

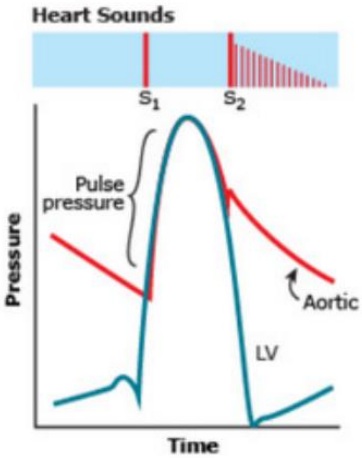
Aortic Regurgitation

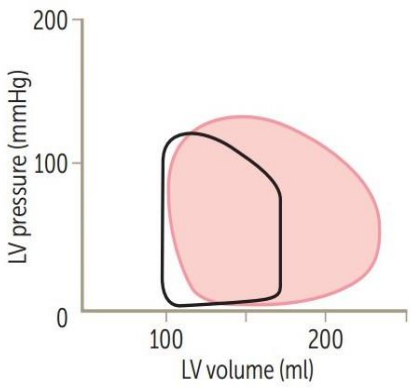
- Closing problem, with retrograde flow from the aorta to left ventricle.
- Causes: Often due to aortic root dilation, bicuspid aortic valve, endocarditis, rheumatic fever.
- Murmur: High-pitched "blowing" early diastolic decrescendo murmur.
- The left ventricular end diastolic volume is increased due to the incompetent aortic valve.
- Presentation:

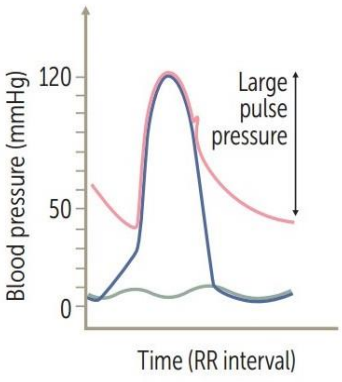
- ↑ stroke volume with retrograde flow produces ↑ systolic blood pressure, but ↓↓ in diastolic blood pressure = ↑↑ pulse pressure (Wide pulse pressure).
- Bounding femoral and carotid pulses marked by abrupt distention and quick collapse ("water-hammer" pulses) are the result of the large pulse pressure.
- Some patients exhibit head-bobbing with carotid pulsations (de Musset sign) due to transfer of momentum from the large left ventricular stroke volume (LVSV) to the head and neck.
- Significant systolic pulsations may also be noticed in other organs (liver, spleen, retina) and the fingertips.









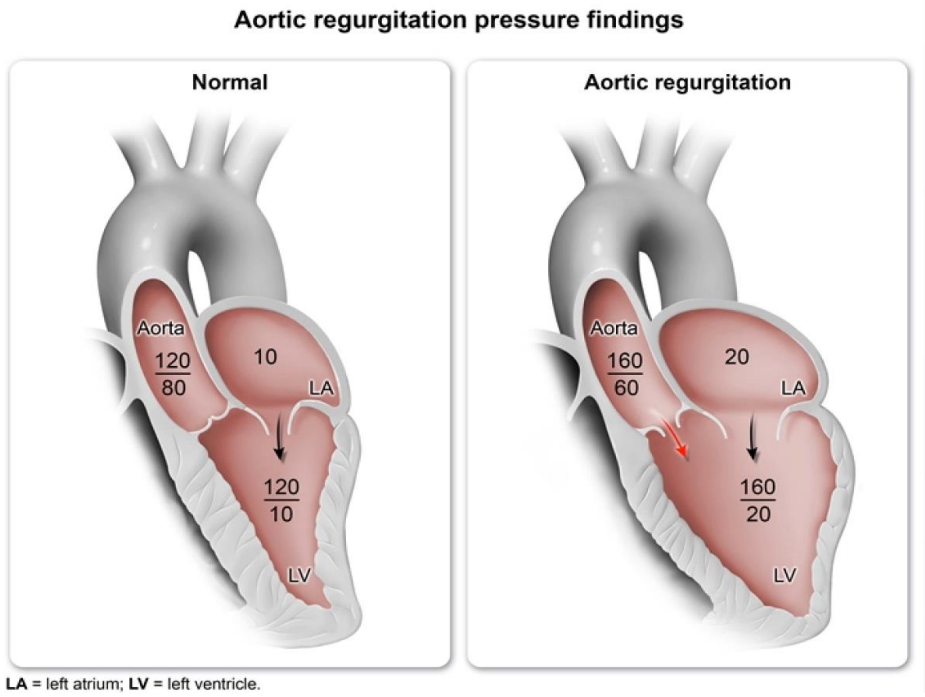


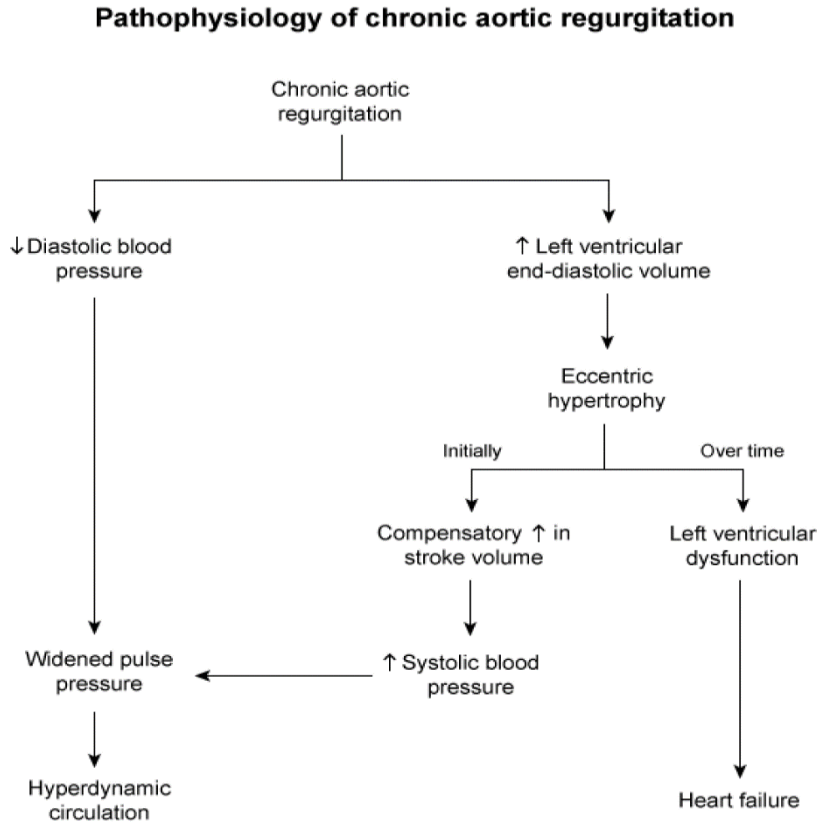
No true isovolumetric phase
↑ EDV
↑ SV

❖ N.B:

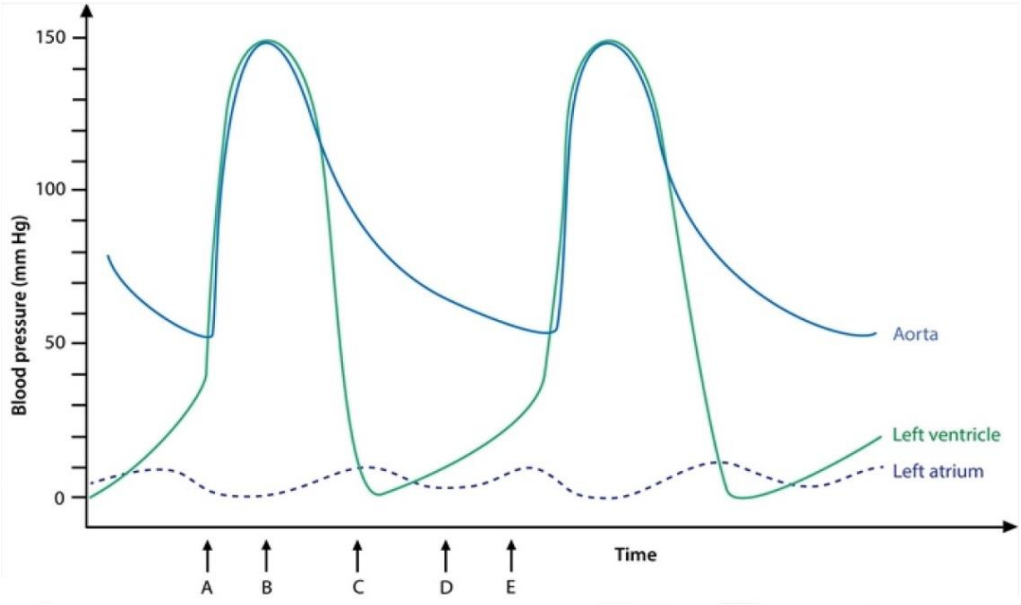
1. Aortic regurgitation causes a rapid fall in aortic pressure during diastole with an increase in left ventricular end-diastolic volume and a compensatory increase in stroke volume.

- These hemodynamic changes create characteristic pressure changes, including reduced aortic diastolic pressure, increased aortic systolic pressure, and increased left ventricular diastolic and systolic pressures.





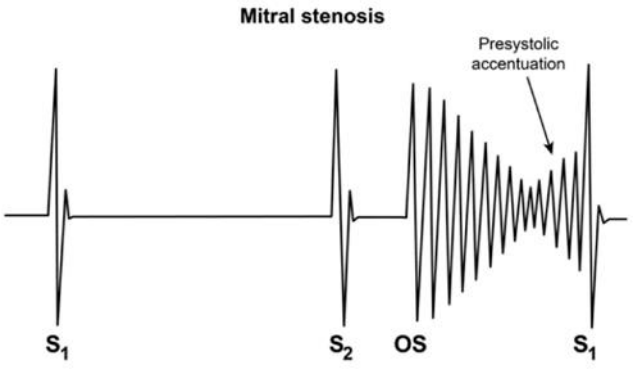
2. The peak intensity of the murmur occurs just after aortic valve closure when the pressure gradient between the aorta and the left ventricle is maximal (point C).

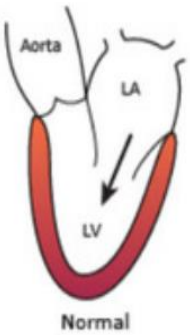


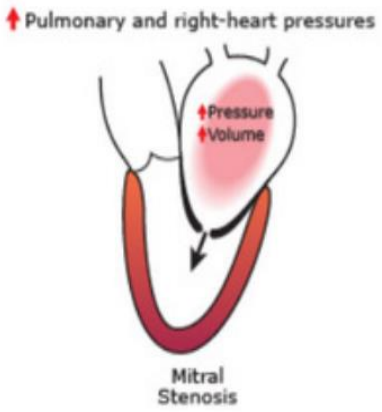
Mitral Stenosis

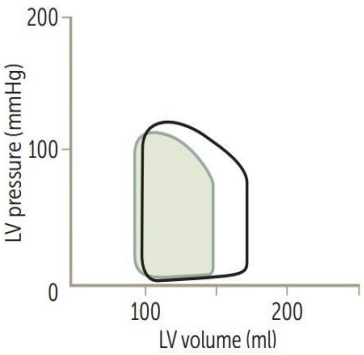
- Opening problem, mitral valve acts as a resistance point, creating a pressure gradient between the left atrium and ventricle during filling phase.
- Causes: Most common cause is rheumatic fever.
- Murmur: Follows opening snap. A mid-diastolic rumbling murmur with presystolic accentuation will be heard after the opening snap.
- Accentuated S1 (mitral valve shuts very forcefully and that is why S1 becomes accentuated)
- Pathophysiology:

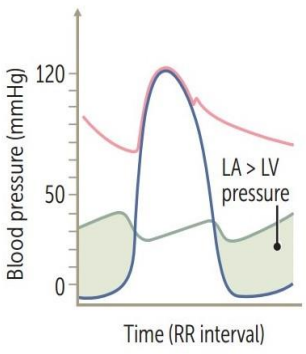
- ↑ left atrial pressure and dilated atrium, which can lead to atrial fibrillation.
- ↑ pulmonary venous, ↑ capillary (edema, dyspnea), ↑ pulmonary arterial pressures.
- Pulmonary hypertension can involve ↑ arteriolar resistance as well.
- Right heart enlargement and hypertrophy.
- Left ventricle of normal or reduced size.









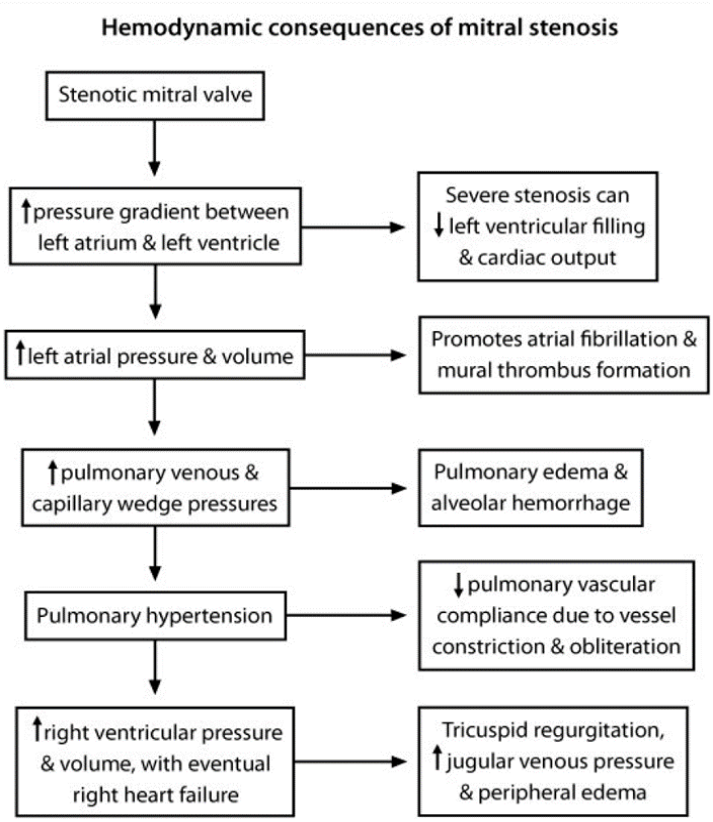


↑ LA pressure
↓ EDV because of impaired ventricular filling
↓ ESV
↓ SV

❖ N.B:

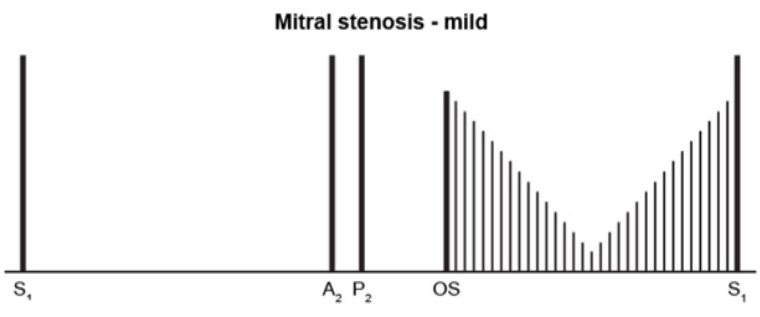
1. Isolated mitral stenosis elevates left atrial diastolic pressure and can therefore cause elevated pulmonary capillary wedge pressure, pulmonary hypertension, decreased pulmonary vascular compliance, right ventricular dilatation, and functional tricuspid regurgitation (Functional tricuspid regurgitation murmur means it's due to right ventricular dilatation not due to fixed valvular lesion and the murmur disappears when the patient takes any drug that decreases the volume overload in right ventricle).

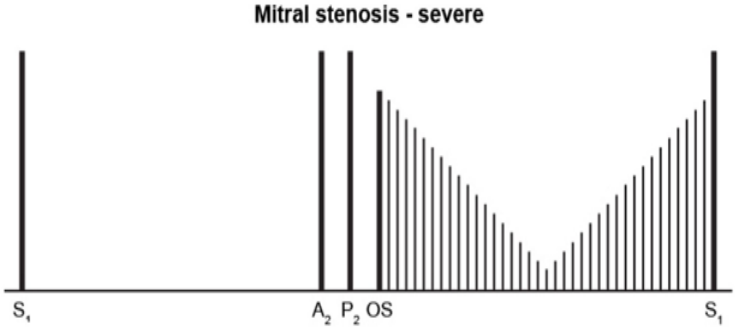
- Diastolic pressure in the left ventricle is usually near normal or even decreased with severe mitral stenosis. Elevated diastolic pressure in left ventricle raises your suspicion about double mitral lesion or concomitant aortic stenosis.



2. On auscultation, the best indicator of mitral stenosis (MS) severity is the length of time between S2 (specifically the A2 component, caused by aortic valve closure) and the opening snap (OS).

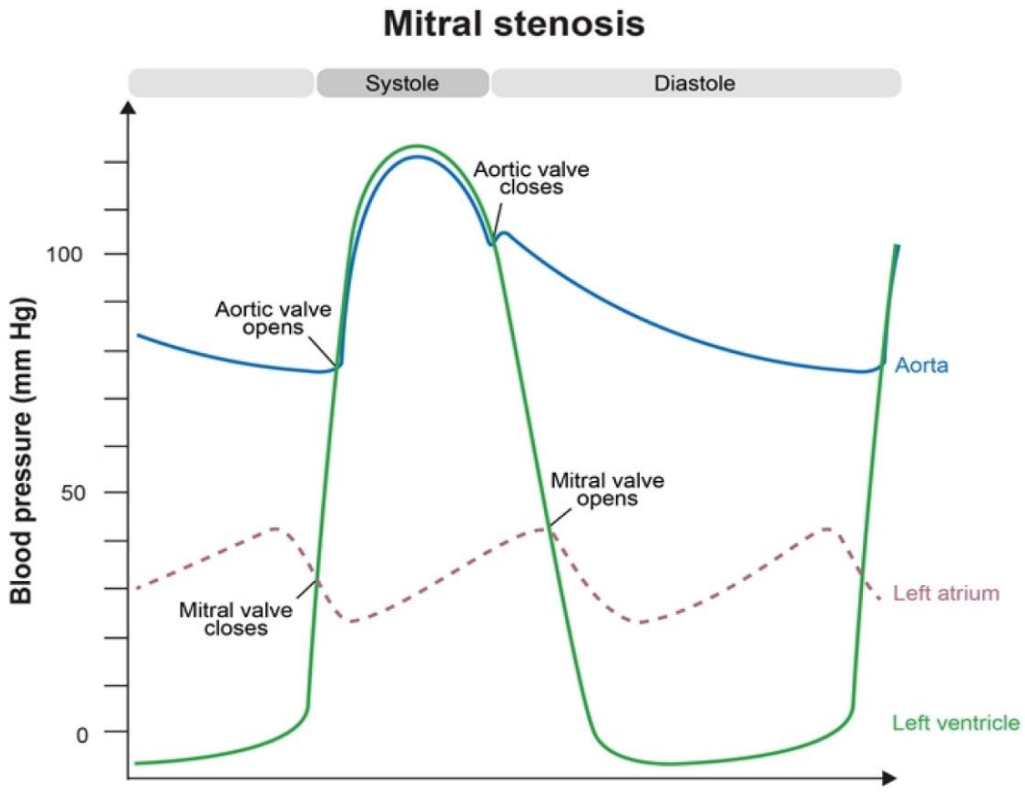
- The OS occurs due to abrupt tensing of the valve leaflets as the mitral valve reaches its maximum diameter during forceful opening.
- As MS worsens, left atrial pressures increase due to impaired movement of blood into the left ventricle.
- Higher pressure causes the valve to open more forcefully; as a result, the A2-OS interval becomes shorter as left atrial pressure increases.





3. During normal diastole, the LA pressure is nearly equal to the left ventricular (LV) pressure since the open mitral valve offers minimal resistance to flow between the two chambers.

- If cardiac catheterization reveals a LA end-diastolic pressure (LAEDP) that is significantly greater than the LVEDP. This abnormal pressure gradient implies increased resistance to flow between the LA and LV, as occurs in mitral stenosis.

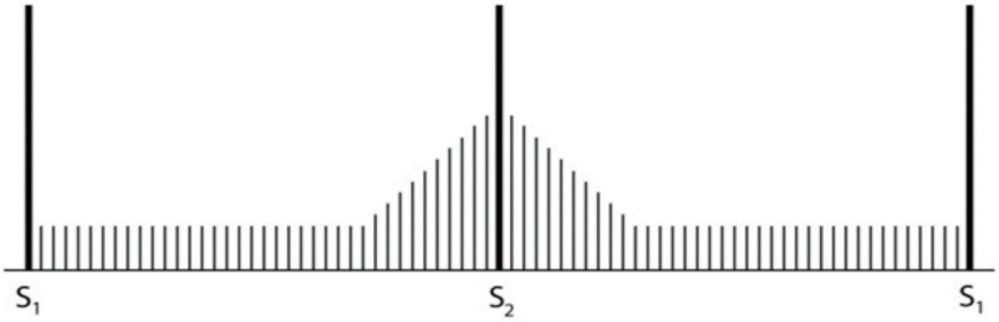


3. Continous murmurs:

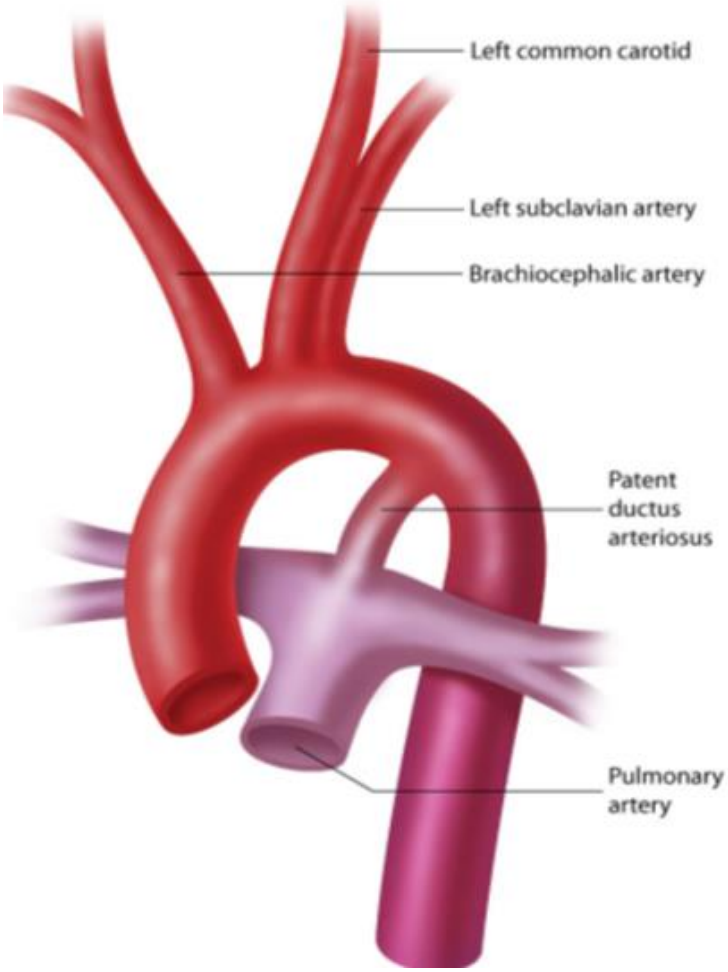
Patent Ductus Arteriosus

- Causes: Often due to congenital rubella or prematurity.
- Murmur: Continuous machine-like murmur. Loudest at S2.
- Connects the pulmonary artery to the descending aorta.
- Constricts after birth due to ↑ PO_2 of blood passing through and ↓ prostaglandins.
- Shunt between the aorta and pulmonary artery (left-to-right shunt no cyanosis).
- Pulmonary vascular disease and ↑ pulmonary arterial pressure shunt reverses (right-to-left shunt-Eisenmenger syndrome).

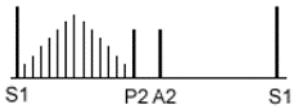
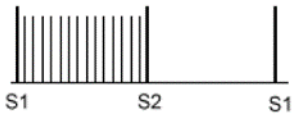
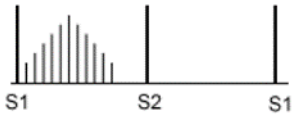
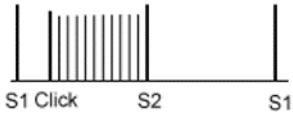
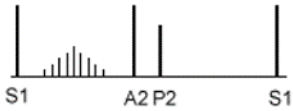
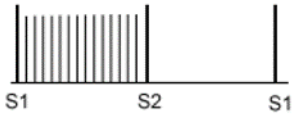
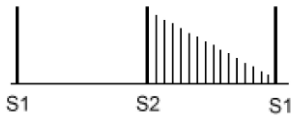
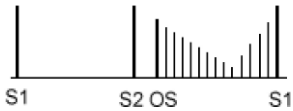
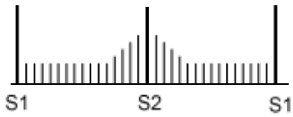
Patent ductus arteriosis



Patent ductus arteriosus

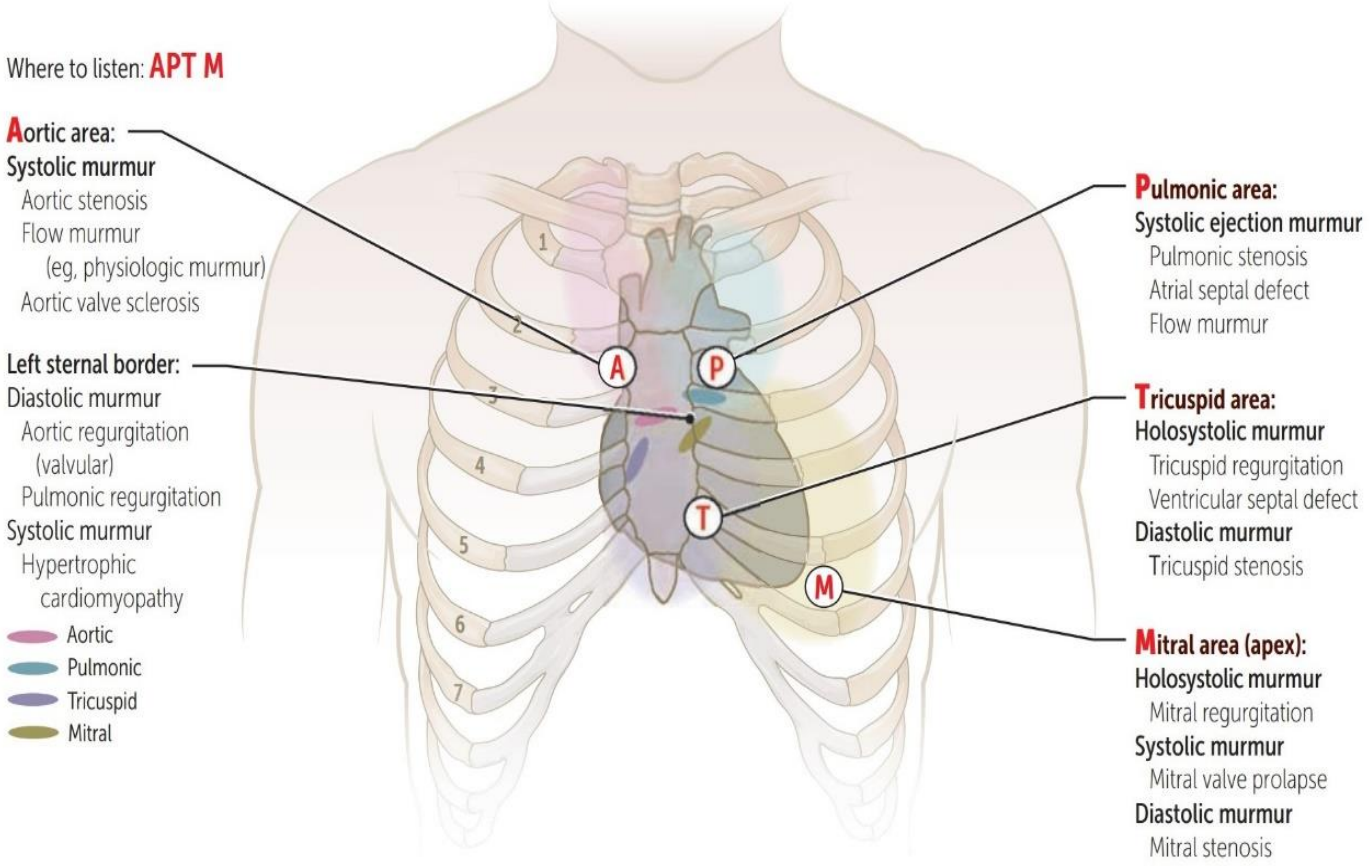


Cardiac murmurs*

Systolic	Aortic stenosis		Crescendo-decrescendo at RUSB, A2 soft & delayed
	Mitral regurgitation		Holosystolic at apex & radiates to axilla
	Hypertrophic cardiomyopathy		Crescendo-decrescendo at mid-left sternal border
	Mitral valve prolapse		Midsystolic click followed by late systolic murmur
	Atrial septal defect		Midsystolic with wide & fixed splitting of S2
	Ventricular septal defect		Holsystolic at left sternal border
Diastolic	Aortic regurgitation		Decrescendo at LUSB (valvular), RUSB (aortic root)
	Mitral stenosis		Opening snap followed by middiastolic rumble with presystolic accentuation
Continuous	Patent ductus arteriosus		Machine-like in interscapular region (posteriorly)

*Pulmonic and tricuspid valve murmurs are similar in character to their aortic and mitral valve counterparts but with different location of optimal auscultation. These murmurs can be further differentiated from their left-sided counterparts by an increase in intensity with inspiration.
LUSB = left upper sternal border; **RUSB** = right upper sternal border.

Auscultation of the heart



Bedside Maneuver	Effect
Inspiration (↑ venous return to right atrium) **Expiration (↑ pulmonary blood flow to the left atrium)**	↑ intensity of right heart sounds ↑ intensity of left heart sounds
Rapid squatting (↑ venous return, ↑ preload, ↑ afterload) **Supine position with leg elevated (↑ venous return, ↑ preload)** **↑ preload → ↑ LV volume**	↑ intensity of most murmurs (↑ flow through stenotic or regurgitant valve) ↓ intensity of hypertrophic cardiomyopathy murmur MVP: later onset of click/murmur
Valsalva (↓ preload), standing up (↓ preload), amyl nitrate (venodilator → ↓ preload) **↓ preload → ↓ LV volume**	↓ intensity of most murmurs (↓ flow through stenotic or regurgitant valve) ↑ intensity of hypertrophic cardiomyopathy murmur MVP: earlier onset of click/murmur
Hand grip (↑ afterload) **↑ Afterload → ↑ LV volume**	↑ intensity of MR, AR, VSD murmurs ↓ hypertrophic cardiomyopathy murmurs and ↓ AS murmur (↓ transaortic valve pressure gradient) MVP: later onset of click/murmur

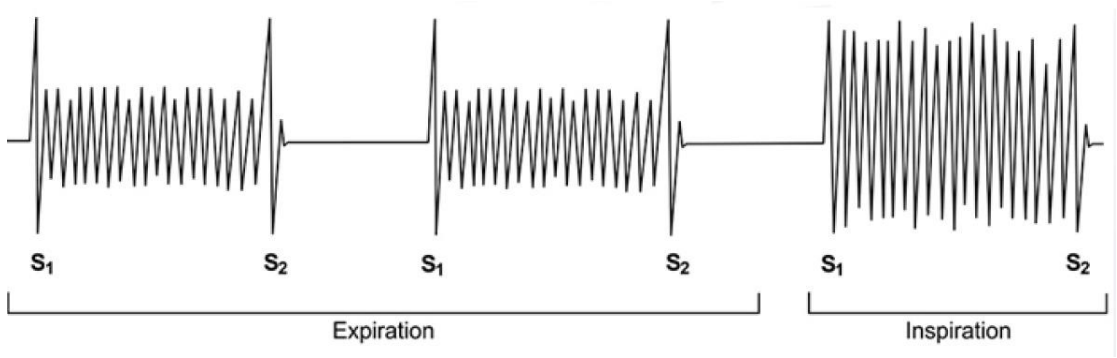
❖ N.B:

1. Position of the patient affects the intensity of the murmur.

- Sitting up and leaning forward accentuates and increases the aortic regurgitation murmur.
- With the patient leaning forward (brings the valve close to the chest wall) and at end expiration (listening during expiration often accentuates left-sided heart murmurs).
- The left lateral decubitus position increases the mitral stenosis murmur.

2. The illustration below represents a holosystolic murmur that increases in intensity during inspiration.

- Holosystolic murmurs are associated with tricuspid regurgitation, mitral regurgitation, and ventricular septal defects.
- The tricuspid valve separates the right atrium and right ventricle, while the mitral valve separates the left atrium and ventricle.
- During inspiration, intrathoracic pressure drops, allowing more blood to return to the right heart.
- Right ventricular stroke volume then increases. Simultaneously, pulmonary vessel capacity is also increased, thereby decreasing the venous return to the left ventricle.
- As a consequence, a tricuspid regurgitation murmur would be expected to increase in intensity during inspiration, while murmurs associated with mitral regurgitation or ventricular septal defects would not. Tricuspid regurgitation is further favored over mitral regurgitation by the fact that tricuspid regurgitation is loudest near the left lower sternal border.
- Mitral regurgitation is heard most prominently over the cardiac apex.
- A ventricular septal defect produces a holosystolic murmur that is typically loudest over the left sternal border in the 3rd or 4th intercostal space.



Nervous reflexes in the control of blood pressure

- The control of blood pressure involves altering the two factors that determine MAP:

$$MAP = CO \times TPR$$

- <u>Baroreceptors:</u>

- Aortic arch transmits via vagus nerve to solitary nucleus of medulla (responds to ↑ and ↓ in BP).
- Carotid sinus (dilated region at carotid bifurcation) transmits via glossopharyngeal nerve to solitary nucleus of medulla (responds to ↓ and ↑ in BP).

- Hypotension:
- ↓ arterial pressure → ↓ stretch → ↓ afferent baroreceptor firing → ↑ efferent sympathetic firing and ↓ efferent parasympathetic stimulation → vasoconstriction, ↑ HR, ↑ contractility, ↑ BP.

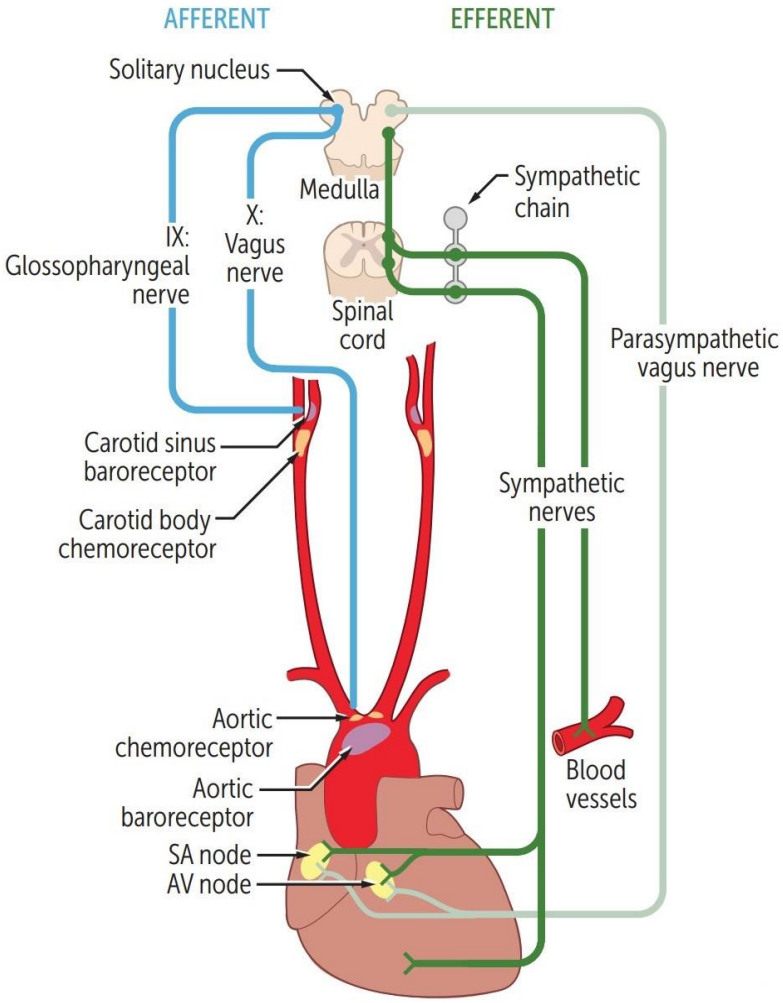
- Important in the response to severe hemorrhage.

- Carotid massage: ↑ pressure on carotid sinus →↑ stretch → ↑ afferent baroreceptor firing → ↑ AV node refractory period → ↓ HR.

- Contributes to Cushing reaction (triad of hypertension, bradycardia, and irregular respiration):
- ↑ intracranial pressure constricts arterioles → cerebral ischemia → central reflex sympathetic ↑ in perfusion pressure (hypertension is to maintain cerebral perfusion pressure) → ↑ stretch → peripheral reflex baroreceptor- induced bradycardia.

- Irregular respiration is caused by impaired brainstem function.

Cerebral perfusion pressure = Mean arterial pressure – intracranial pressure



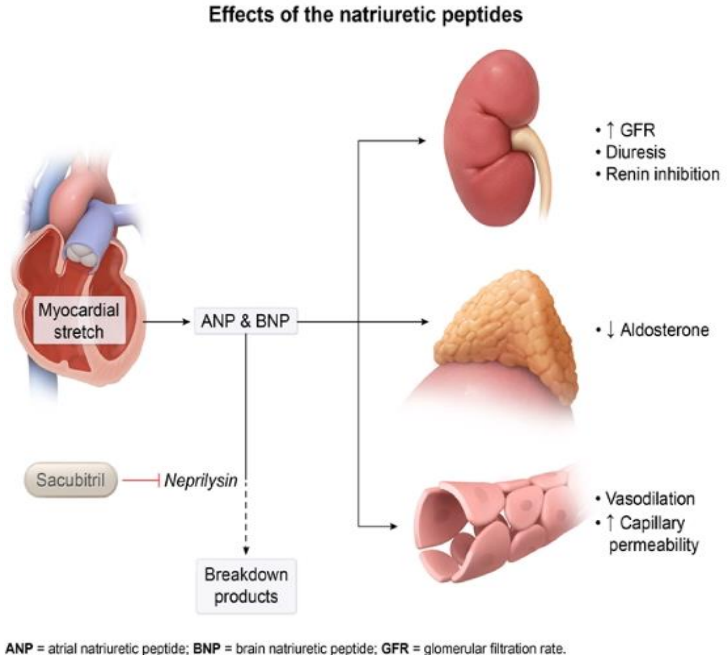
Natriuretic peptides

- Atrial natriuretic peptide is released from atrial myocytes in response to ↑ blood volume and atrial pressure.
- B type (brain) natriuretic peptide is released from ventricular myocytes in response to ↑ tension. Similar physiologic action to ANP, with longer half-life.
- BNP blood test used for diagnosing HF (very good negative predictive value). Available in recombinant form (nesiritide) for treatment of HF.
- The increase in myocardial wall stretch due to intravascular volume expansion leads to the release of endogenous natriuretic peptide hormones, including atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) from the atria and ventricles, respectively.
- Both ANP and BNP activate guanylate cyclase, which increases intracellular cyclic GMP, and leads to downstream physiologic effects in various tissues:

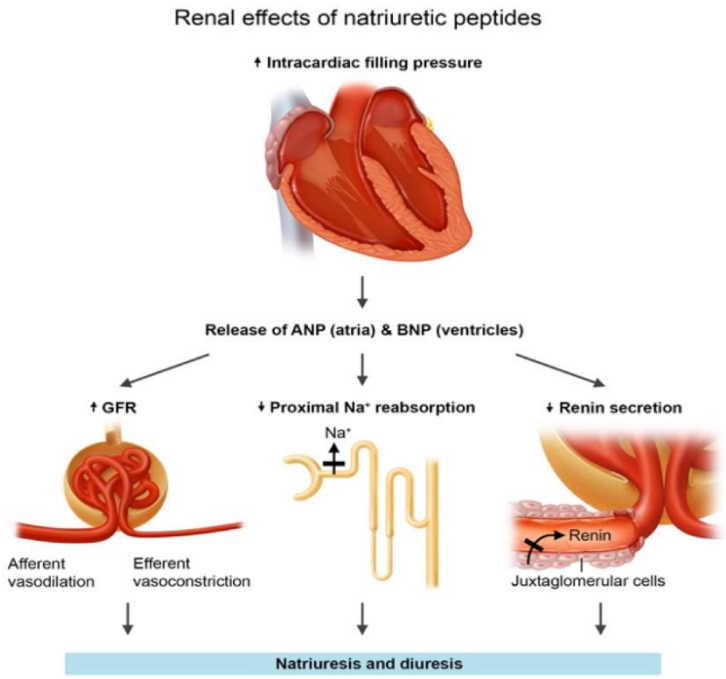
- In the kidney: natriuretic peptides promote afferent glomerular arteriolar vasodilation and efferent arteriolar constriction, causing increased glomerular filtration rate; this leads to increased natriuresis (sodium excretion) and diuresis (fluid excretion). Natriuretic peptides also directly inhibit proximal tubular sodium reabsorption and renin secretion. Decreased renin secretion results in reduced angiotensin II and aldosterone levels, further promoting natriuresis and diuresis.

- Adrenal glands: Secretion of aldosterone from the zona glomerulosa cells is inhibited, further counteracting RAAS activity and increase sodium and water excretion.

- Blood vessels: Arteriolar and venular smooth muscle relaxes, producing vasodilation. There is also increased capillary permeability, leading to fluid extravasation into the interstitium and a decrease in circulating blood volume.



ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; GFR = glomerular filtration rate.



Autoregulation of systemic blood

Organ	Factors determining autoregulation
Heart	Local metabolites (vasodilatory): adenosine, NO, CO_2, ↓ O_2
Brain	Local metabolites (vasodilatory): CO_2 (pH)
Kidneys	Myogenic and tubuloglomerular feedback
Lungs	Hypoxia causes vasoconstriction
Skeletal muscle	Local metabolites during exercise: CO_2, H, Adenosine, Lactate, K (CHALK) At rest: sympathetic tone
Skin	Sympathetic vasoconstriction most important mechanism for temperature control

❖ N.B:

1. The pulmonary vasculature is unique in that hypoxia causes vasoconstriction so that only well-ventilated areas are perfused.
   - In other organs, hypoxia causes vasodilation.

2. There are numerous local factors that are important in influencing coronary blood flow.
   - Of these, adenosine and nitric oxide (NO) are the most important factors involved in coronary blood flow autoregulation.
   - Adenosine, a product of ATP metabolism, acts as a vasodilatory element in the small coronary arterioles.
   - Nitric oxide is created by and released from endothelial cells in the coronary vasculature.
   - It is synthesized from arginine and oxygen by endothelial nitric oxide synthase (eNOS) and is released from the coronary endothelium in response to neurotransmitters.
   - Nitric oxide is also released in response to pulsatile stretch and flow shear stress in the coronary arteries.
   - It is the major regulator of flow-mediated vasodilation in large arteries and pre-arteriolar vessels.
   - Nitric oxide acts within the vascular smooth muscle cells via a soluble guanylate cyclase enzyme to increase production of cyclic GMP and cause smooth muscle relaxation.

Capillary fluid exchange

Starling forces determine fluid movement through capillary membranes:

- P_c = capillary hydrostatic pressure—pushes fluid out of capillary
- P_i = interstitial hydrostatic pressure—pushes fluid into capillary
- π_c = plasma colloid osmotic (oncotic) pressure—pulls fluid into capillary
- π_i = interstitial fluid colloid osmotic pressure—pulls fluid out of capillary

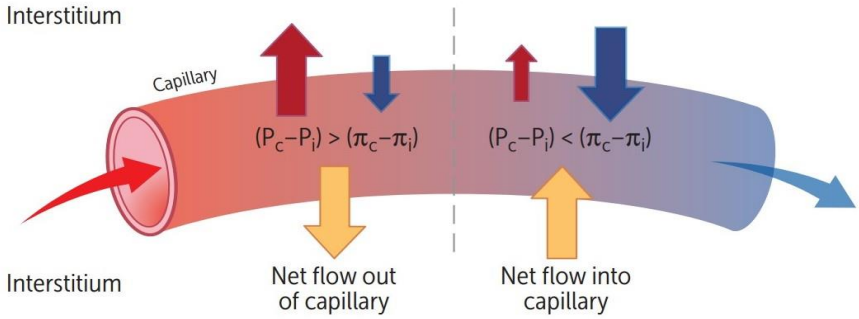
J_v = net fluid flow = $K_f [(P_c - P_i) - \sigma(\pi_c - \pi_i)]$

K_f = capillary permeability to fluid

σ = reflection coefficient (measure of capillary permeability to protein)

Edema—excess fluid outflow into interstitium commonly caused by:

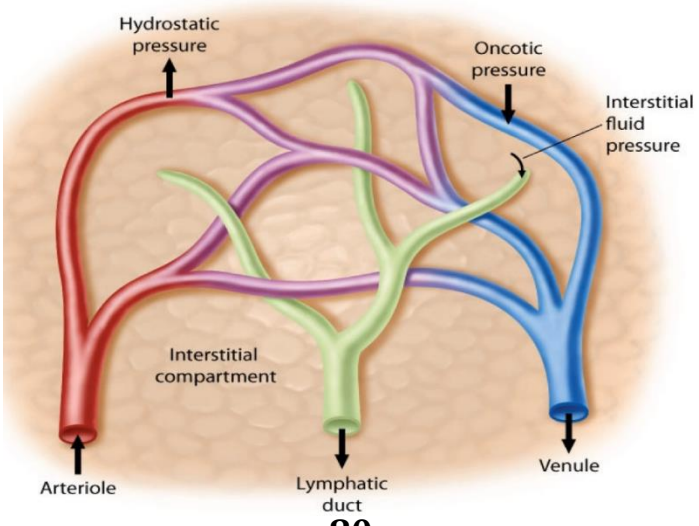
- ↑ capillary pressure (↑ P_c; eg, HF)
- ↑ capillary permeability (↑ K_f; eg, toxins, infections, burns)
- ↑ interstitial fluid colloid osmotic pressure (↑ π_i; eg, lymphatic blockage)
- ↓ plasma proteins (↓ π_c; eg, nephrotic syndrome, liver failure, protein malnutrition)



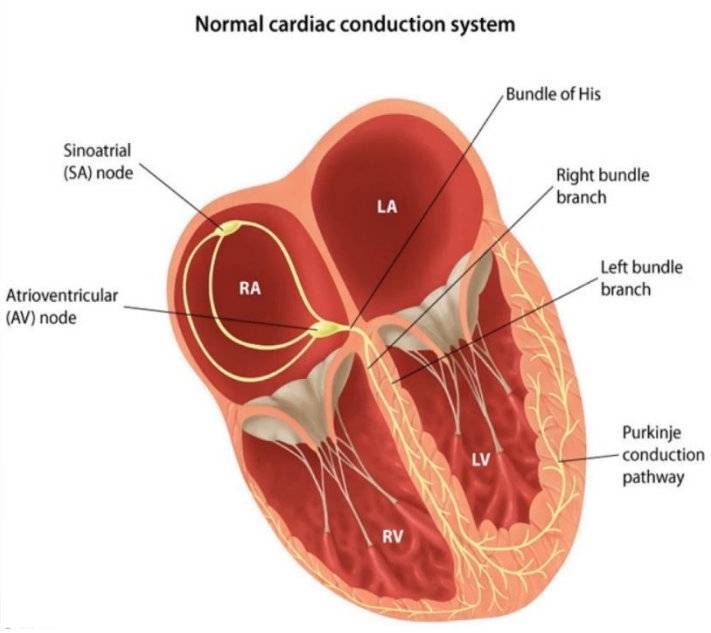
❖ N.B:

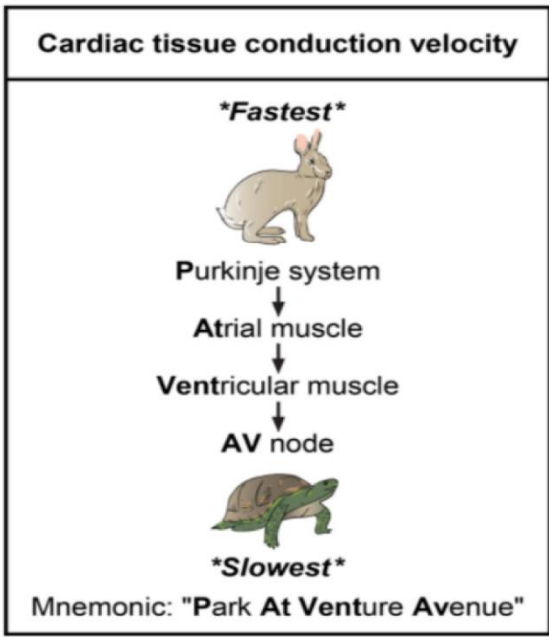
- Fluid movement across the capillary wall (filtration) into the interstitium is tightly balanced by lymphatic drainage, which returns interstitial fluid to the vasculature.
- Peripheral edema (accumulation of excess fluid in the interstitial space) develops when transcapillary plasma filtration exceeds the resorptive capacity of the lymphatics.
- Decreased lymphatic return impairs removal of excess interstitial fluid. Common causes of lymphatic obstruction include filariasis, invasive malignancies, and iatrogenic etiologies (surgical lymph node dissection and radiation therapy).

Factors affecting interstitial fluid volume



Cardiac conduction system





- Conduction pathway:

- SA node → atria → AV node → bundle of His → right and left bundle branches → Purkinje fibers → ventricles.
- left bundle branch divides into left anterior and posterior fascicles.

- AV node:

- located in posteroinferior part of interatrial septum.
- Blood supply usually from RCA.
- 100-msec delay allows time for ventricular filling.

- Cardiac pacemaker impulse generation normally occurs in the SA node, which has the fastest firing rate of all conductive cells.

- The sinoatrial node consists of specialized pacemaker cells located at the junction of the right atrium and superior vena cava.

- The cells in other areas of the conduction system (AV node, bundle of His, and Purkinje fibers) may serve as pacemakers if normal impulse conduction is impaired. AV nodal cells can become pacemakers when conduction between the SA and AV nodes is impaired. This can occur in complete (third-degree) atrioventricular (AV) block, in which SA node impulses cause atrial contraction while impulses generated by the AV node cause ventricular contraction.

- Normally, cardiac impulses originate in the sinoatrial (SA) node. The SA node cells have the property of automaticity, or pacemaker activity.

- SA node depolarization delivers an electrical impulse to the surrounding atrial myocardium, which carries the action potential to the atrioventricular (AV) node.
- The action potential is then delayed by the AV node in order to allow the ventricles to completely fill with blood during diastole.
- From the AV node, the action potential enters the His-Purkinje system.
- Impulses travel rapidly through the Purkinje fibers. Rapid transmission of electrical impulses during this phase of the cardiac cycle is essential to ensure contraction of the ventricles in a bottom-up fashion.
- Contraction of the ventricles from the apex of the heart toward the base is necessary to propel blood upward toward the pulmonary artery and aorta.
- From the Purkinje fibers, the action potential is transmitted to the ventricular myocardium where it travels.
- In summary, the slowest conduction velocity occurs in the AV node and the fastest conduction occurs in the Purkinje system.
- The conduction speed of the atrial muscle is higher than that of the ventricular muscle.
- Pacemaker firing rates:

  SA > AV > bundle of His/Purkinje/ventricles
- Velocity of conduction:

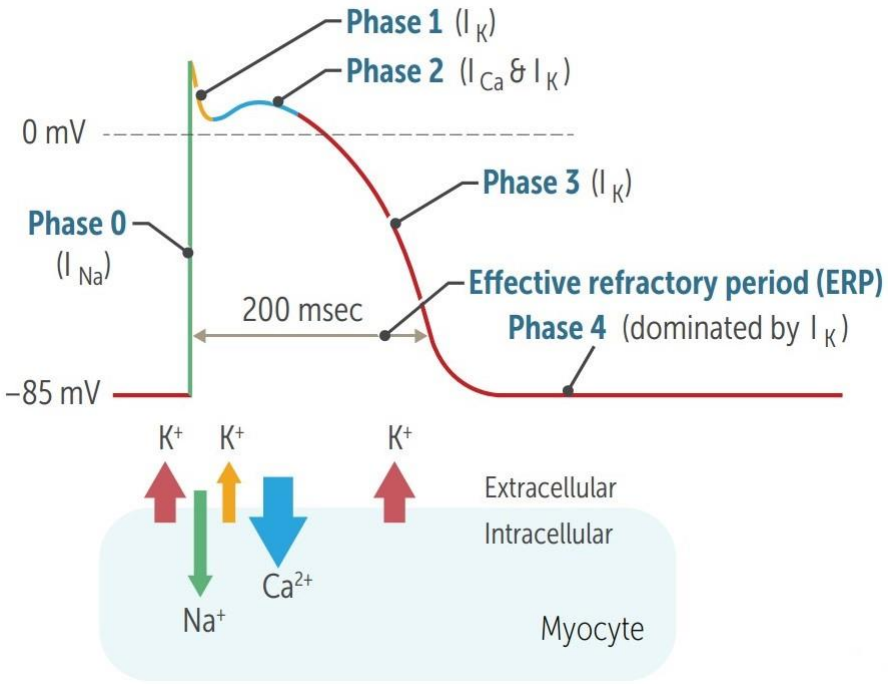
  Purkinje > atria> ventricles > AV node

❖ N.B:

- Radiofrequency ablation of the atrioventricular (AV) node is occasionally performed in patients with certain arrhythmias who do not respond or are intolerant to pharmacologic therapy.
- The AV node is located on the endocardial surface of the right atrium, near the insertion of the septal leaflet of the tricuspid valve and the orifice of the coronary sinus.

The Ventricular Action Potential

- Occurs in all cardiac myocytes except for those in the SA and AV nodes.



- Phase 0:

- Rapid upstroke and depolarization.

- Voltage-gated Na channels open.

- Phase 1:

- Initial repolarization.

- Inactivation of voltage-gated Na channels.

- Voltage-gated K channels begin to open.

- Phase 2:

- Plateau.

- Ca influx through voltage-gated Ca channels balances K efflux.

- Ca influx triggers Ca release from sarcoplasmic reticulum and myocyte contraction.

- Phase 3:

- Rapid repolarization.

- Massive K efflux due to opening of voltage-gated slow K channels and closure of voltage-gated Ca channels.

- Phase 4:

- Resting potential.

- High K permeability through leaky K channels.

- In contrast to skeletal muscle:

- Cardiac muscle action potential has a plateau, which is due to Ca influx and K efflux.

- Cardiac muscle contraction requires Ca influx from ECF to induce Ca release from sarcoplasmic reticulum (Ca-induced Ca release).

- Cardiac myocytes are electrically coupled to each other by gap junctions.

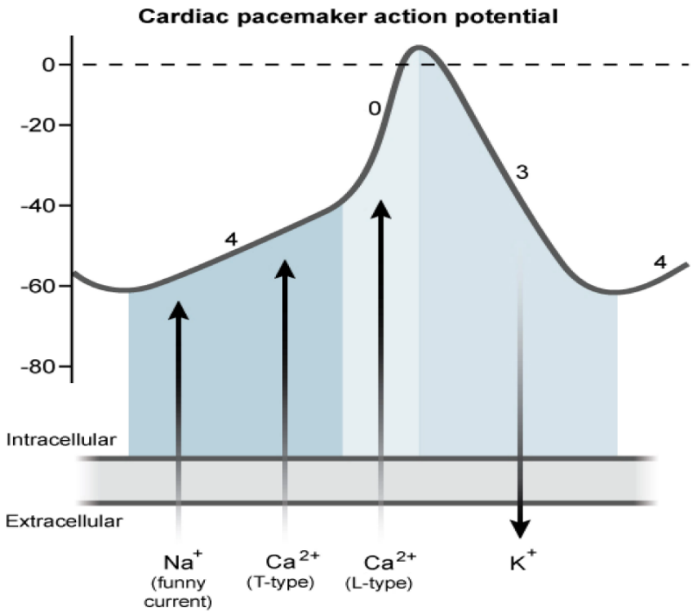
- Effective refractory period:

- During this period, a second action potential cannot be generated, no matter how strong the stimulus.

- It begins at threshold and continues until the cell has almost completely repolarized.

Pacemaker action potential

- Occurs in the SA and AV nodes.



- Key differences from the ventricular action potential include:

A. Phase 0:

- Upstroke depolarization.

- Opening of voltage-gated Ca channels.

- Fast voltage-gated Na channels are permanently inactivated because of the less negative resting potential of these cells.

- Results in a slow conduction velocity that is used by the AV node to prolong transmission from the atria to ventricles.

- Phase 0 of the non-pacemaker action potential is mediated by rapid sodium influx, in contrast to the slower calcium-mediated depolarization of pacemaker cells.

B. Phases 1 and 2 are absent.

C. Phase 3: Inactivation of the Ca channels and ↑ activation of K channels → ↑ K efflux.

D. Phase 4:

- Slow spontaneous diastolic depolarization due to I_f (funny current).

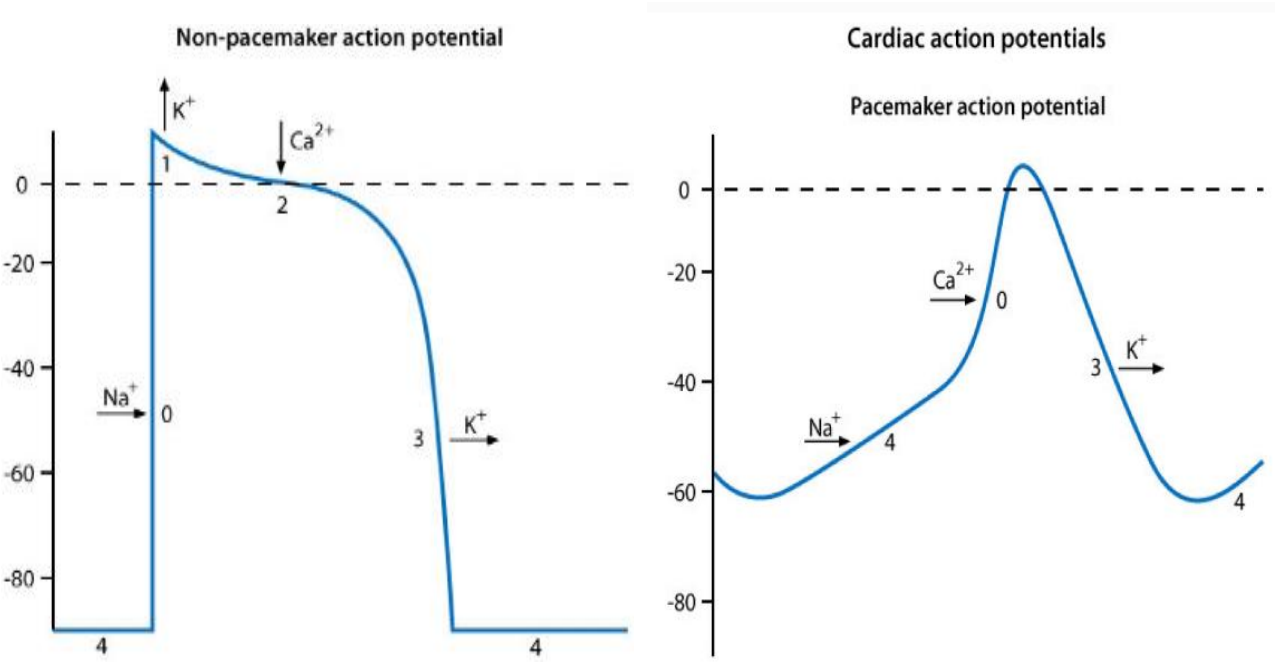
- I_f channels responsible for a slow, mixed Na/K inward current; different from I_{Na} in phase 0 of ventricular action potential.

- T-type (transient) Ca channels then open once the membrane potential becomes more positive, allowing Ca influx to contribute to depolarization. As the pacemaker cell approaches threshold, L-type (long-lasting) Ca channels begin to open, which further increases Ca influx.

- Accounts for automaticity of SA and AV nodes.

- The slope of phase 4 in the SA node determines HR.

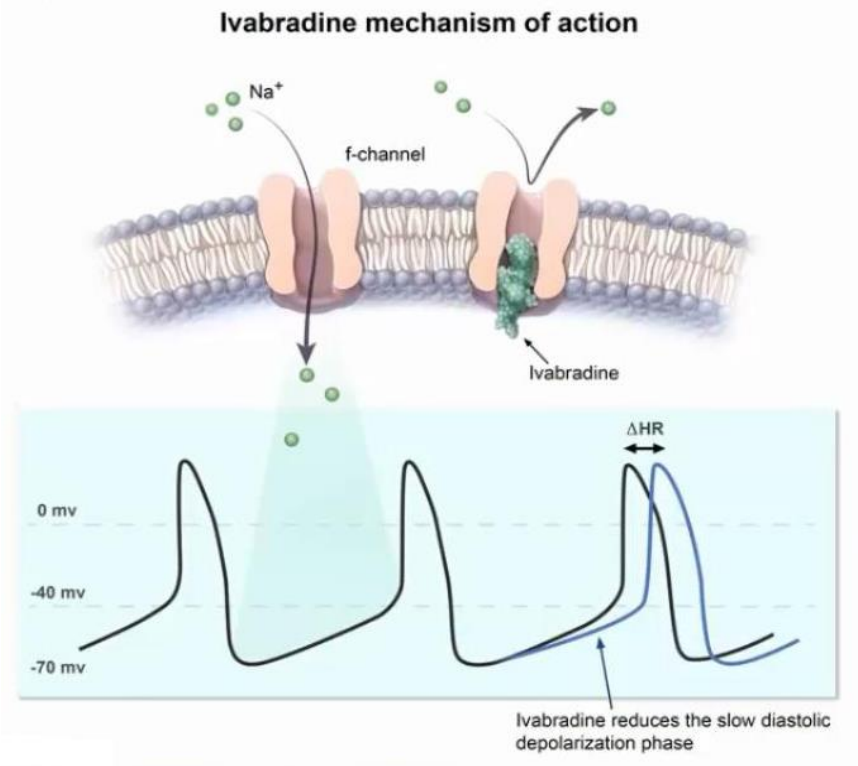
- ACh/adenosine ↓ the rate of diastolic depolarization and ↓ HR, while ↑ catecholamines ↑ depolarization and ↑ HR. Sympathetic stimulation ↑ the chance that I_f channels are open and thus ↑ HR.



❖ N.B:

1. Several classes of drugs, including beta blockers, non-dihydropyridine calcium channel blockers, digoxin, and ivabradine, can be used to modulate heart rate in patients with chronic heart failure (HF).

- Of these agents, ivabradine is the only drug that slows heart rate (negative chronotropic effect) with no effect on cardiac contractility (inotropy) and/or relaxation (lusitropy).
- It slows the rate of sinoatrial node firing by selective inhibition of funny sodium channels, thereby prolonging the slow depolarization phase (phase 4).
- Ivabradine is indicated in certain patients with chronic HF with reduced ejection fraction and persistent symptoms despite appropriate medical therapy. It has been shown to reduce the risk of hospitalization due to HF.

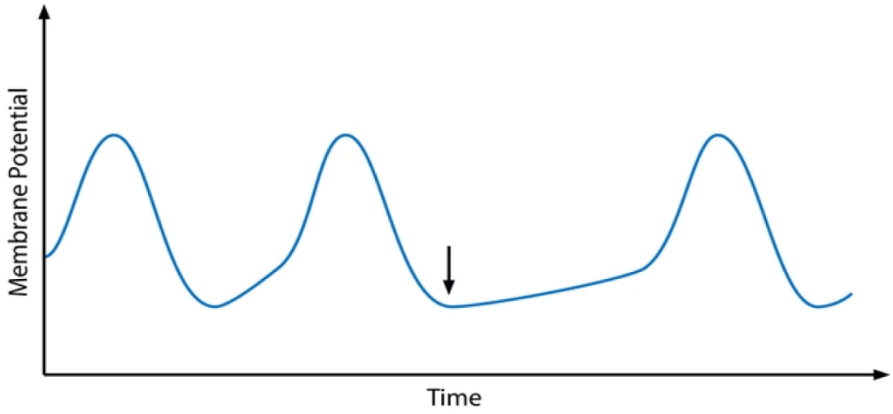


2. The below tracing demonstrates the typical action potential of cardiac pacemaker cells, which are found in cardiac slow-response tissues such as the sinoatrial (SA) and atrioventricular (AV) nodes.

- These tissues undergo diastolic depolarization during phase 4 due to a slow, inward sodium current.
- During the latter parts of phase 4, diastolic depolarization is augmented by transient inward calcium currents.
- Once the membrane potential reaches threshold, the opening of additional calcium channels is triggered and the resulting increase in calcium influx begins phase 0 depolarization.
- Verapamil is a calcium channel blocker and class IV antiarrhythmic drug that is useful in the treatment of angina, hypertension, and supraventricular tachyarrhythmias.
- By blocking SA and AV node calcium channels, verapamil slows the depolarization that occurs in phase 0 and the latter part of phase 4. This decreases the rate of SA node firing and slows AV node conduction.

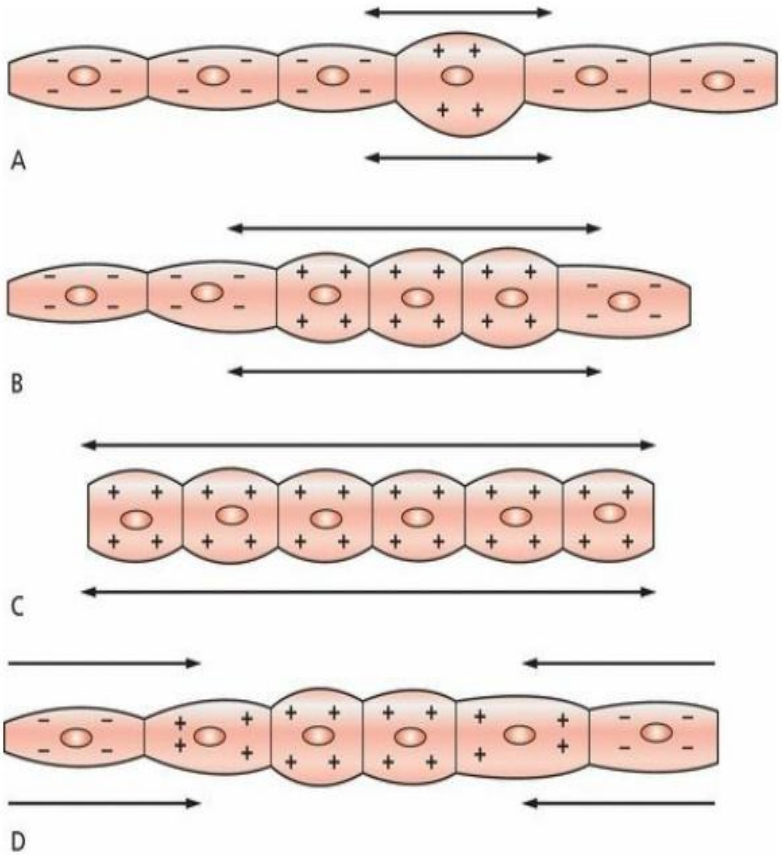
3. Adenosine and acetylcholine affect phase 4 of the action potential, reducing the rate of spontaneous depolarization in cardiac pacemaker cells.

- Adenosine interacts with receptors on the surface of cardiac cells, activating potassium channels and increasing potassium conductance, causing the membrane potential to remain negative for a longer period. Adenosine also inhibits L-type Ca channels, further prolonging the depolarization time.
- These actions result in a transient slowing of the sinus rate and an increase in atrioventricular (AV) nodal conduction delay.
- That's why adenosine is useful in the termination of paroxysmal supraventricular tachycardia.
- Acetylcholine behaves similarly by increasing outward K conductance while decreasing inward Ca and Na currents during phase 4.



Electrocardiography

- The EKG is nothing more than a recording of the heart's electrical activity.
- Cardiac cells, in their resting state, are electrically polarized; their insides are negatively charged with respect to their outsides.
- This electrical polarity is maintained by membrane pumps that ensure the appropriate distribution of ions (primarily potassium, sodium) necessary to keep the insides of these cells relatively electronegative.
- These ions pass into and out of the cell through special ion channels in the cell membrane.
- Cardiac cells can lose their internal negativity in a process called depolarization.
- Depolarization is the fundamental electrical event of the heart.
- In some cells, known as pacemaker cells, it occurs spontaneously. In others, it is initiated by the arrival of an electrical impulse that causes positively charged ions to cross the cell membrane.
- Depolarization is propagated from cell to cell, producing a wave of depolarization that can be transmitted across the entire heart.

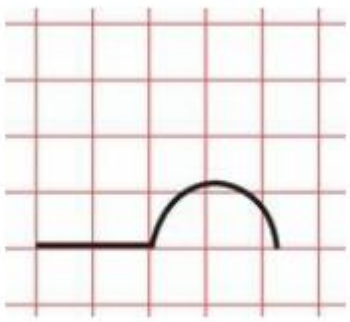


In *A*, a single cell has depolarized. A wave of depolarization then propagates from cell to cell (*B*) until all are depolarized (*C*). Repolarization (*D*) then restores each cell's resting polarity.

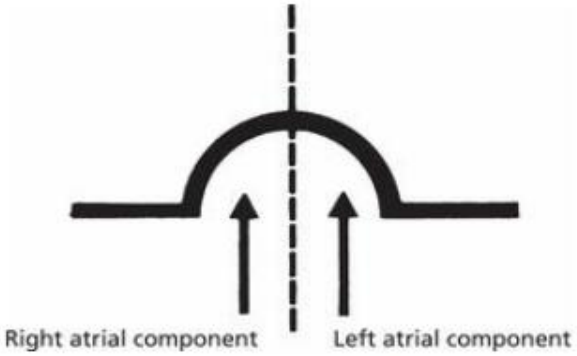
- This wave of depolarization represents a flow of electricity, an electrical current, that can be detected by electrodes placed on the surface of the body.
- After depolarization is complete, the cardiac cells restore their resting polarity through a process called repolarization.
- Repolarization is accomplished by the membrane pumps, which reverse the flow of ions. This process can also be detected by recording electrodes.
- All of the different waves that we see on an EKG are manifestations of these two processes: depolarization and repolarization.
- Let's follow one cycle of cardiac contraction (systole) and relaxation (diastole), focusing on the electrical events that produce the basic waves and lines of the standard EKG.

A. Atrial Depolarization:

- The sinus node fires spontaneously (an event not visible on the EKG), and a wave of depolarization begins to spread outward into the atrial myocardium.
- Depolarization of the atrial myocardial cells results in atrial contraction.
- During atrial depolarization and contraction, electrodes placed on the surface of the body record a small burst of electrical activity lasting a fraction of a second.
- This is the P wave. It is a recording of the spread of depolarization through the atrial myocardium from start to finish.



The EKG records a small deflection, the P wave.



The components of the P wave.

- Because the sinus node is located in the right atrium, the right atrium begins to depolarize before the left atrium and finishes earlier as well.
- Therefore, the first part of the P wave predominantly represents right atrial depolarization, and the second part left atrial depolarization.
- Once atrial depolarization is complete, the EKG again becomes electrically silent.

B. A Pause Separates Conduction from the Atria to the Ventricles:

- In healthy hearts, there is an electrical gate at the junction of the atria and the ventricles. The wave of depolarization, having completed its journey through the atria, is prevented from communicating with the ventricles by the heart valves that separate the atria and ventricles.

- Electrical conduction must be funneled along the interventricular septum, the wall that separates the right and left ventricles. Here, a structure called the atrioventricular (AV) node slows conduction to a crawl.

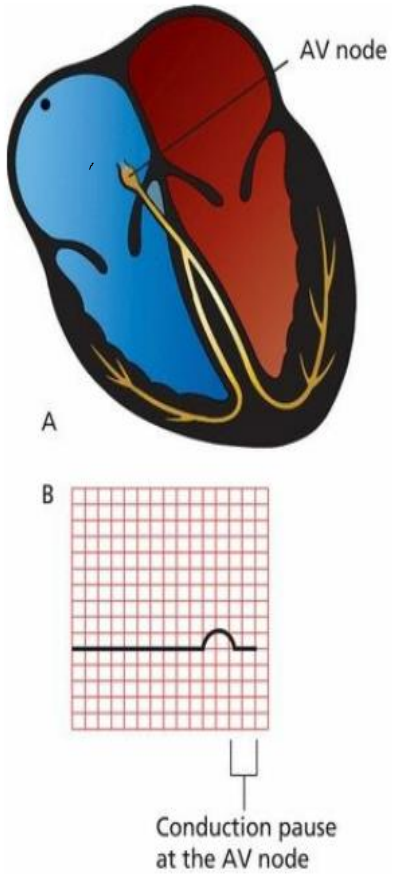
- This pause lasts only a fraction of a second.

- This physiologic delay in conduction is essential to allow the atria to finish contracting before the ventricles begin to contract.

- This clever electrical wiring of the heart permits the atria to empty their volume of blood completely into the ventricles before the ventricles contract.

- Like the sinus node, the AV node is also under the influence of the autonomic nervous system.

- Vagal stimulation slows the current even further, whereas sympathetic stimulation accelerates the current.



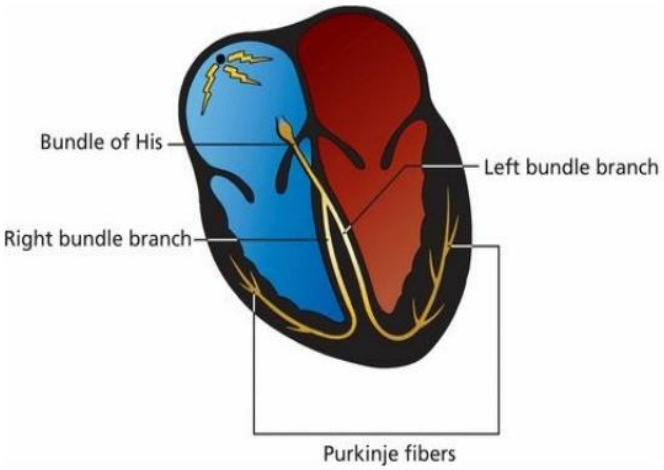
(*A*)The wave of depolarization is briefly held up at the AV node. (*B*)During this pause, the EKG falls silent; there is no detectable electrical activity.

C. Ventricular Depolarization:

- The depolarizing wave escapes the AV node and is swept rapidly down the ventricles along specialized electrical conducting cells.

- This ventricular conducting system has a complex anatomy but essentially consists of three parts:

1. Bundle of His.
2. Bundle branches.
3. Terminal Purkinje fibers.



- The bundle of His emerges from the AV node and almost immediately divides into right and left bundle branches.

- The right bundle branch and the left bundle branch terminate in countless tiny Purkinje fibers. These fibers deliver the electrical current into the ventricular myocardium.

- Ventricular myocardial depolarization causes ventricular contraction. It is marked by a large deflection on the EKG called the QRS complex.

- The amplitude of the QRS complex is much greater than that of the atrial P wave because the ventricles have so much more muscle mass than do the atria.

- The QRS complex consists of several distinct waves, each of which has a name.

- Because the precise configuration of the QRS complex can vary so greatly, a standard format for naming each component has been devised:

1. If the first deflection is downward, it is called a Q wave.

2. The first upward deflection is called an R wave.

3. If there is a second upward deflection, it is called R' ("R-prime").

4. The first downward deflection following an upward deflection is called an S wave.

- Therefore, if the first wave of the complex is an R wave, the ensuing downward deflection is called an S wave, not a Q wave. A downward deflection can only be called a Q wave if it is the first wave of the complex. Any other downward deflection is called an S wave.

- The earliest part of the QRS complex represents depolarization of the interventricular septum by the septal fascicle of the left bundle branch.

- The right and left ventricles then depolarize at about the same time, but most of what we see on the EKG represents left ventricular activation because the muscle mass of the left ventricle is about three times that of the right ventricle.

D. Repolarization:

- After myocardial cells depolarize, they pass through a brief refractory period during which they are resistant to further stimulation.

- They then repolarize; that is, they restore the electronegativity of their interiors so that they can be restimulated.

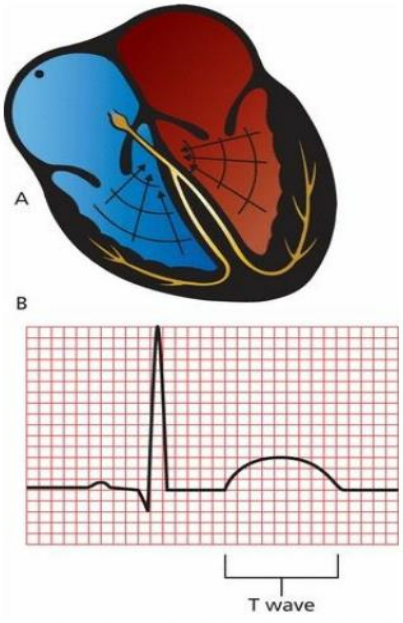
- Just as there is a wave of depolarization, there is also a wave of repolarization. This, too, can be seen on the EKG.

- Ventricular repolarization inscribes a third wave on the EKG, the T wave.

- Note: There is a wave of atrial repolarization as well, but it coincides with ventricular depolarization and is hidden by the much more prominent QRS complex.

- Ventricular repolarization is a much slower process than ventricular depolarization.

- Therefore, the T wave is broader than the QRS complex. Its configuration is also simpler and more rounded.



(*A*) Ventricular repolarization generates (*B*) a T wave on the EKG.

E. Naming the Straight Lines:

- The different straight lines connecting the various waves have also been given names. Thus, we speak of the PR interval, the ST segment, the QT interval, and so on.

- What differentiates a segment from an interval? A segment is a straight line connecting two waves, whereas an interval encompasses at least one wave plus the connecting straight line.

- The PR interval includes the P wave and the straight line connecting it to the QRS complex. It therefore measures the time from the start of atrial depolarization to the start of ventricular depolarization.

- The PR segment is the straight line running from the end of the P wave to the start of the QRS complex.

- It therefore measures the time from the end of atrial depolarization to the start of ventricular depolarization.

- The ST segment is the straight line connecting the end of the QRS complex with the beginning of the T wave. It measures the time from the end of ventricular depolarization to the start of ventricular repolarization.

- The QT interval includes the QRS complex, the ST segment, and the T wave. It therefore measures the time from the beginning of ventricular depolarization to the end of ventricular repolarization.

- The term QRS interval is used to describe the duration of the QRS complex alone without any connecting segments. Obviously, it measures the duration of ventricular depolarization.

Summary

1. Each cycle of cardiac contraction and relaxation is initiated by spontaneous depolarization of the sinus node. This event is not seen on the EKG.

2. The P wave records atrial depolarization and contraction. The first part of the P wave reflects right atrial activity; the second part reflects left atrial activity.

3. There is a brief pause when the electrical current reaches the AV node and the EKG falls silent (the PR segment).

4. The wave of depolarization then spreads along the ventricular conducting system (bundle of His, bundle branches, and Purkinje fibers) and out into the ventricular myocardium. The first part of the ventricles to be depolarized is the interventricular septum. Ventricular depolarization generates the QRS complex.

5. The T wave records ventricular repolarization. Atrial repolarization is not seen.

6. U wave: prominent in hypokalemia (think hyp"U"kalemia), bradycardia.

7. <u>Various segments and intervals describe the time between these events:</u>

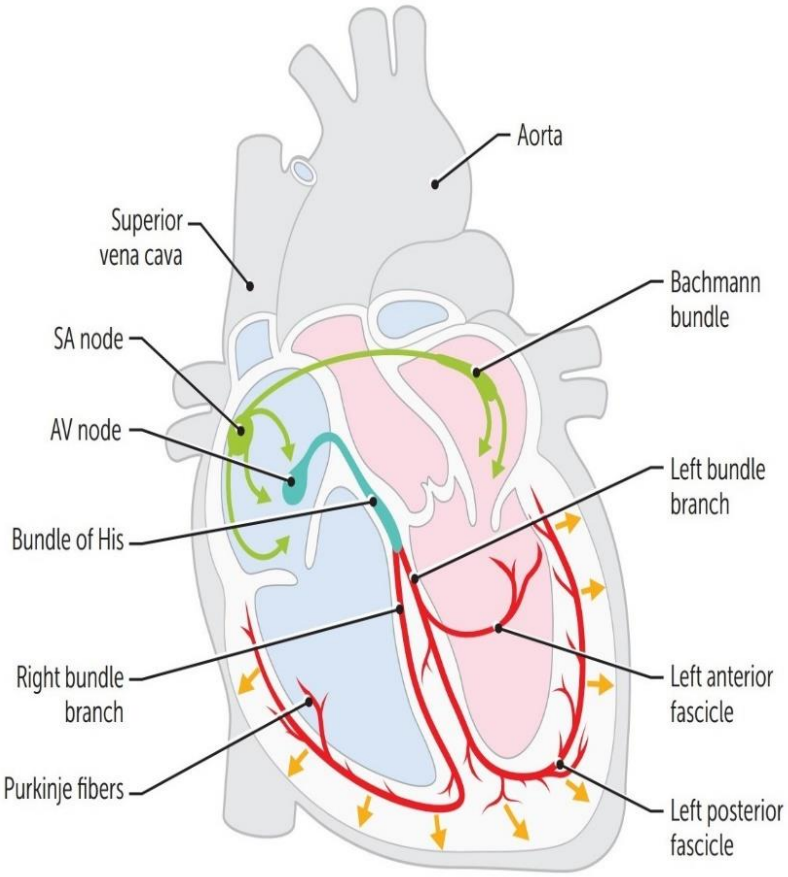
a. The PR interval measures the time from the start of atrial depolarization to the start of ventricular depolarization.

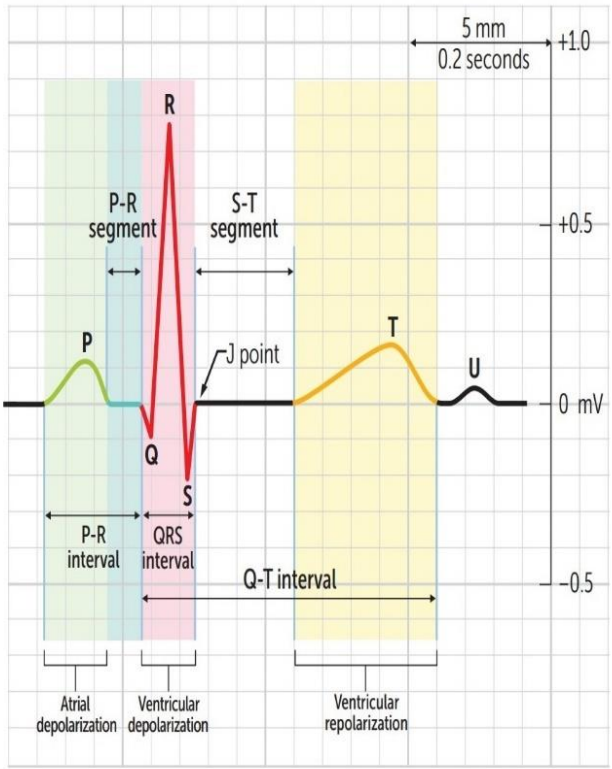
b. The PR segment measures the time from the end of atrial depolarization to the start of ventricular depolarization.

c. The ST segment records the time from the end of ventricular depolarization to the start of ventricular repolarization.

d. The QT interval measures the time from the start of ventricular depolarization to the end of ventricular repolarization.

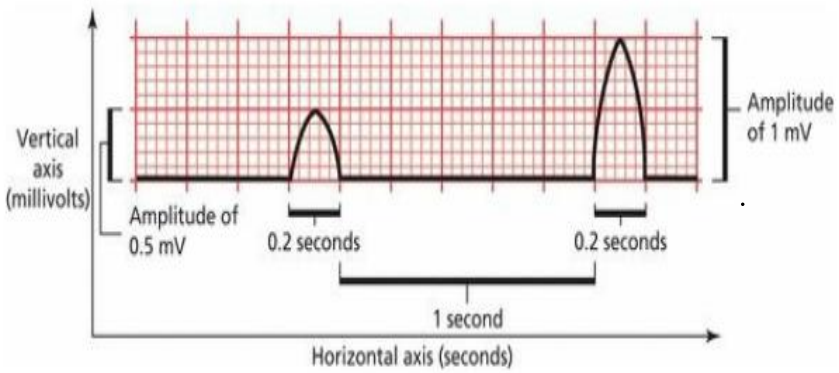
e. The QRS interval measures the time of ventricular depolarization





EKG Paper

- EKG paper is a long, continuous roll of graph paper, usually pink (but any color will do), with light and dark lines running vertically and horizontally.
- The light lines circumscribe small squares of 1 × 1 mm; the dark lines delineate large squares of 5 × 5 mm.
- The horizontal axis measures time. The distance across one small square represents 0.04 seconds.
- The distance across one large square is five times greater, or 0.2 seconds.
- The vertical axis measures voltage. The distance along one small square represents 0.1 mV, and along one large square represents 0.5 mV.

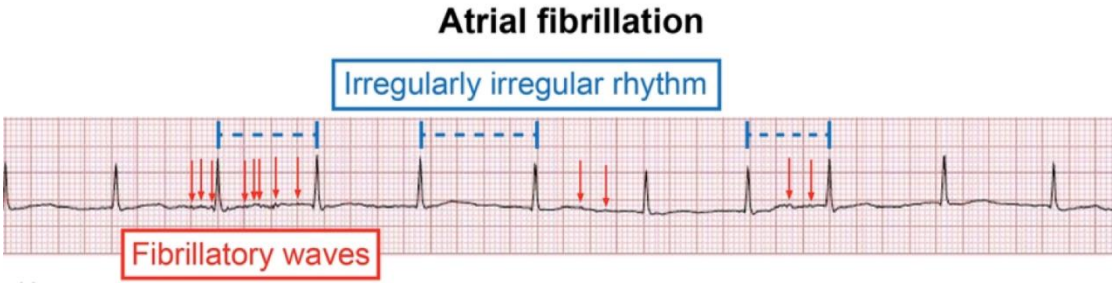


Both waves are one large square in duration (0.2 seconds), but the second wave is twice the voltage of the first (1 mV compared with 0.5 mV). The flat segment connecting the two waves is five large squares (5 × 0.2 seconds = 1 second) in duration.

ECG tracings

Atrial fibrillation

- Chaotic and erratic baseline with no discrete P waves in between irregularly spaced QRS complexes.
- Irregularly irregular heartbeat.
- Most common risk factors include hypertension and coronary artery disease (CAD).
- Can lead to thromboembolic events, particularly stroke.
- Treatment includes anticoagulation, rate control, rhythm control, and/or cardioversion.



- The most common trigger is aberrant electrical foci in the pulmonary veins near their ostia into the left atrium; therefore, catheter ablation of pulmonary vein trigger sites (pulmonary vein isolation) is used for the treatment of symptomatic, paroxysmal AF.

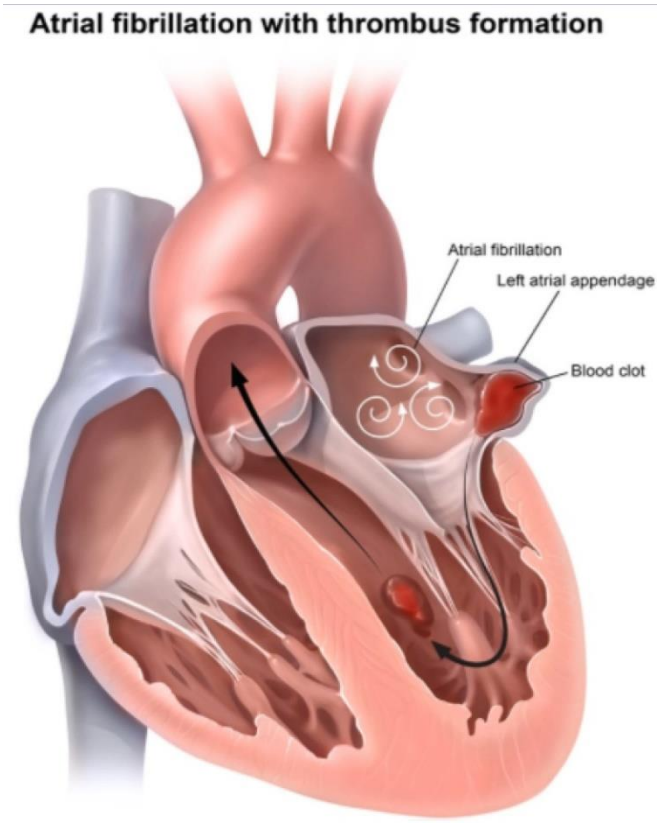
❖ N.B:

1. The ECG in patients with AF typically shows an absence of P waves and irregularly irregular rhythm with varying R-R intervals.

- Some patients have irregular, low-amplitude, fine fibrillatory waves (f waves) between the QRS complexes that represent the chaotic atrial activation.
- AF is the most common tachyarrhythmia and is often precipitated by acute systemic illness or increased sympathetic tone.
- It is occasionally seen in patients after excessive alcohol consumption ("holiday heart syndrome").
- Systemic illnesses that can precipitate AF include long-standing hypertension, heart failure, and hyperthyroidism.
- Palpitations refer to a subjective sensation/awareness of the heartbeat due to rapid arrhythmias or forceful ventricular contractions.
- Ventricular response in AF is dependent on the transmission of abnormal atrial impulses through the atrioventricular (AV) node.
- Each time the AV node is excited, it enters a refractory period during which additional atrial impulses cannot be transmitted to the ventricles; consequently, the majority of atrial impulses never reach the ventricles.
- The average ventricular rate in AF usually ranges between 90-170 beats per minute.

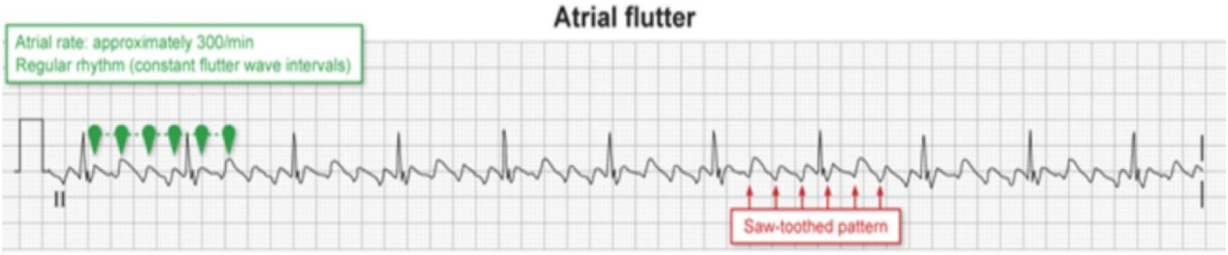
2. Several factors contribute to thrombus development in atrial fibrillation, including left atrial enlargement, stasis of blood due to ineffective atrial contraction, and atrial inflammation and fibrosis (exerts a procoagulant effect).

- The left atrial appendage (LAA) is a small saclike structure in the left atrium that is particularly susceptible to thrombus formation. Approximately 90% of left atrial thrombi are found within the LAA in patients with nonvalvular atrial fibrillation.
- These clots can then systemically embolize and lead to stroke.



Atrial flutter

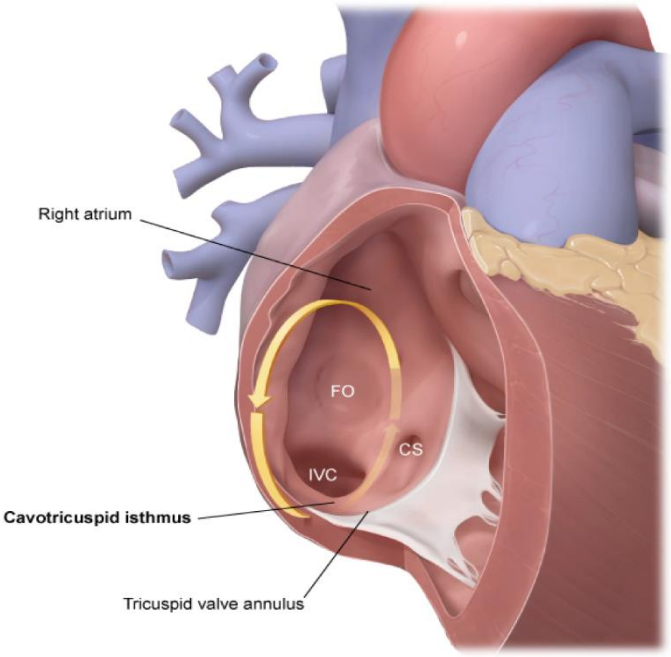
- A rapid succession of identical, back-to-back atrial depolarization waves.
- The identical appearance accounts for the "sawtooth" appearance of the flutter waves.
- Treat like atrial fibrillation.
- Definitive treatment is catheter ablation.



❖ N.B:

- Atrial flutter shares many of the same triggers as atrial fibrillation; underlying comorbidities that cause atrial dilation (heart failure) are often present and alcohol intake may contribute.
- Typical atrial flutter is caused by a large reentrant circuit that traverses the cavotricuspid isthmus, the region of right atrial tissue between the inferior vena cava and the tricuspid valve annulus.
- This region is identified during electrophysiologic study and is the target for radiofrequency ablation to interrupt the reentrant circuit and abolish atrial flutter.

Reentrant circuit in atrial flutter



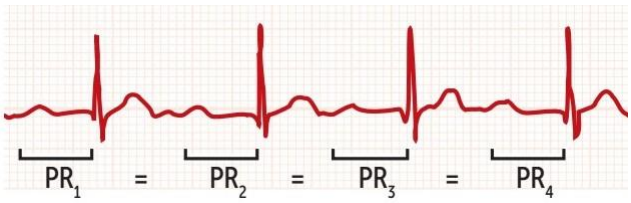
Ventricular fibrillation

- A completely erratic rhythm with no identifiable waves.
- Fatal arrhythmia without immediate CPR and defibrillation.

AV block

1st degree

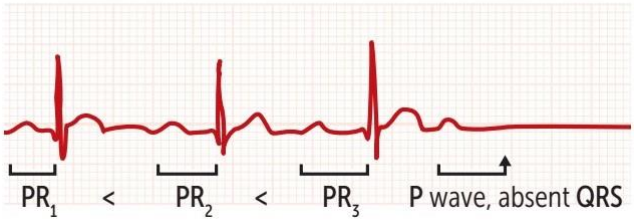
- The PR interval is prolonged (> 200 msec).
- Benign and asymptomatic.
- No treatment required.



2nd degree

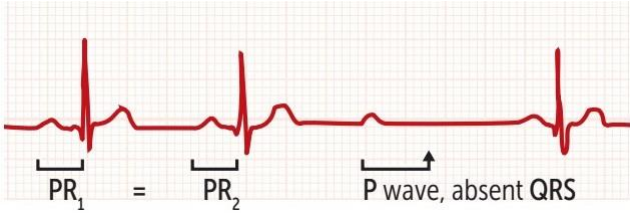
A. Mobitz type I (Wenckebach):

- Progressive lengthening of PR interval until a beat is dropped (a P wave not followed by a QRS complex).
- Usually asymptomatic.
- Variable RR interval with a pattern (regularly irregular).



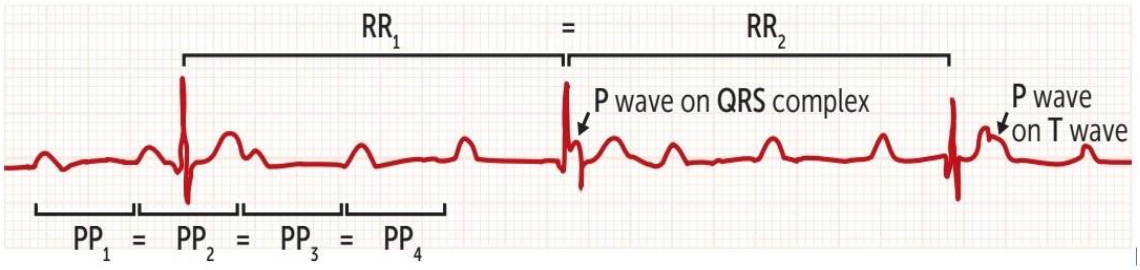
B. Mobitz type II:

- Dropped beats that are not preceded by a change in the length of the PR interval (as in type I).
- May progress to 3rd-degree block.
- Often treated with pacemaker.



3rd degree (complete)

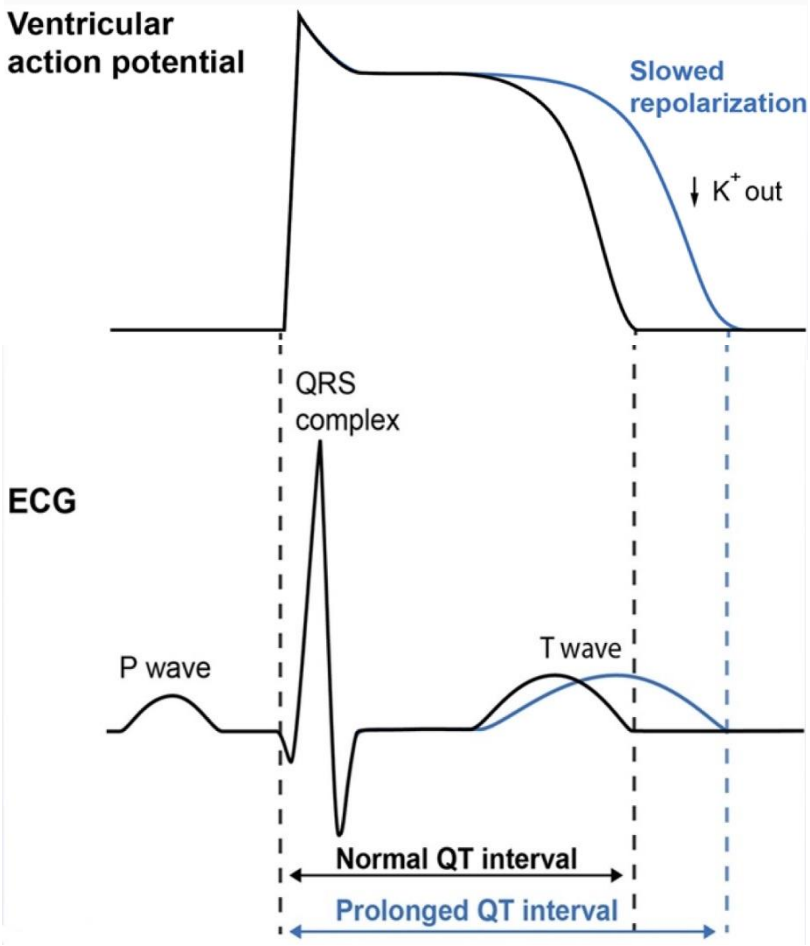
- The atria and ventricles beat independently of each other.
- P waves and QRS complexes not rhythmically associated.
- Atrial rate > ventricular rate. Usually treated with pacemaker.
- Can be caused by Lyme disease.



Congenital long QT syndrome

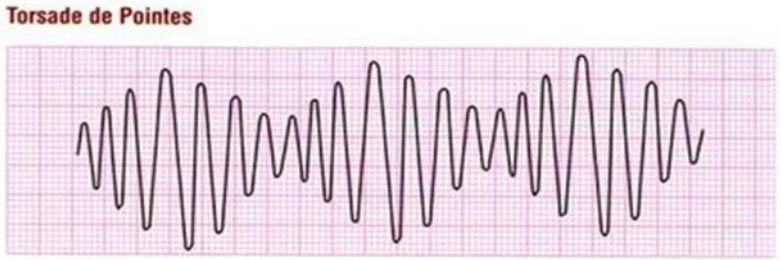
- Inherited disorder of myocardial repolarization, typically due to ion channel defects; ↑ risk of sudden cardiac death (SCD) due to torsades de pointes.
- These syndromes result from mutations in a K channel protein that contributes to the delayed rectifier current.
- Decreased outward K current during the repolarization phase of the cardiac action potential results in QT prolongation.
- The major cardiac pathophysiological consequence of QT prolongation is an increased risk of episodic polymorphic ventricular tachycardia, including torsades de pointes.
- Includes:

- Romano-Ward syndrome: Autosomal dominant, pure cardiac phenotype (no deafness).
- Jervell and Lange-Nielsen syndrome: autosomal recessive, sensorineural deafness.



Torsades de pointes

- Torsades de pointes = twisting of the points.
- Polymorphic ventricular tachycardia characterized by shifting sinusoidal waveforms on ECG; can progress to ventricular fibrillation (VF).
- Long QT interval predisposes to torsades de pointes.
- Caused by drugs, ↓ K+, ↓ Mg2+, congenital abnormalities.
- Treatment includes magnesium sulfate.



- Drug-induced long QT (ABCDE):

- AntiArrhythmics (class IA, III).
- AntiBiotics (macrolides).
- Anti"C"ychotics (haloperidol).
- AntiDepressants (TCAs).
- AntiEmetics (ondansetron).

Causes of QT prolongation	
Acquired	Medications • Macrolides & fluoroquinolones • Antiemetics (eg, ondansetron) • Azoles (eg, fluconazole) • Antipsychotics & tricyclic antidepressants • Class IA antiarrhythmics (eg, quinidine) • Class III antiarrhythmics (eg, dofetilide) Electrolyte abnormalities (eg, hypomagnesemia)
Congenital	• Romano-Ward syndrome • Jervell & Lange-Nielson syndrome (associated with deafness)

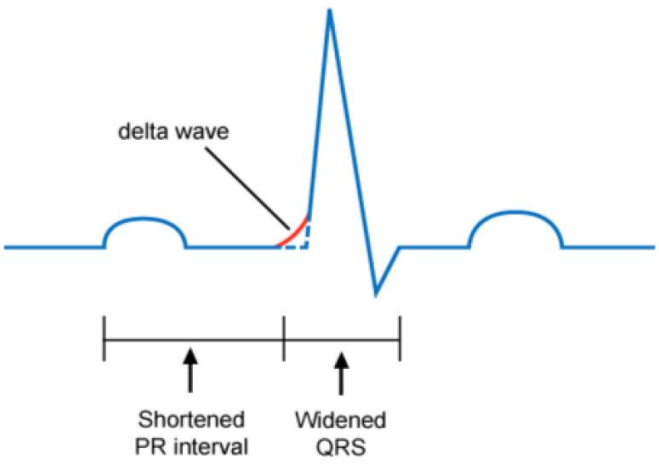
Brugada syndrome

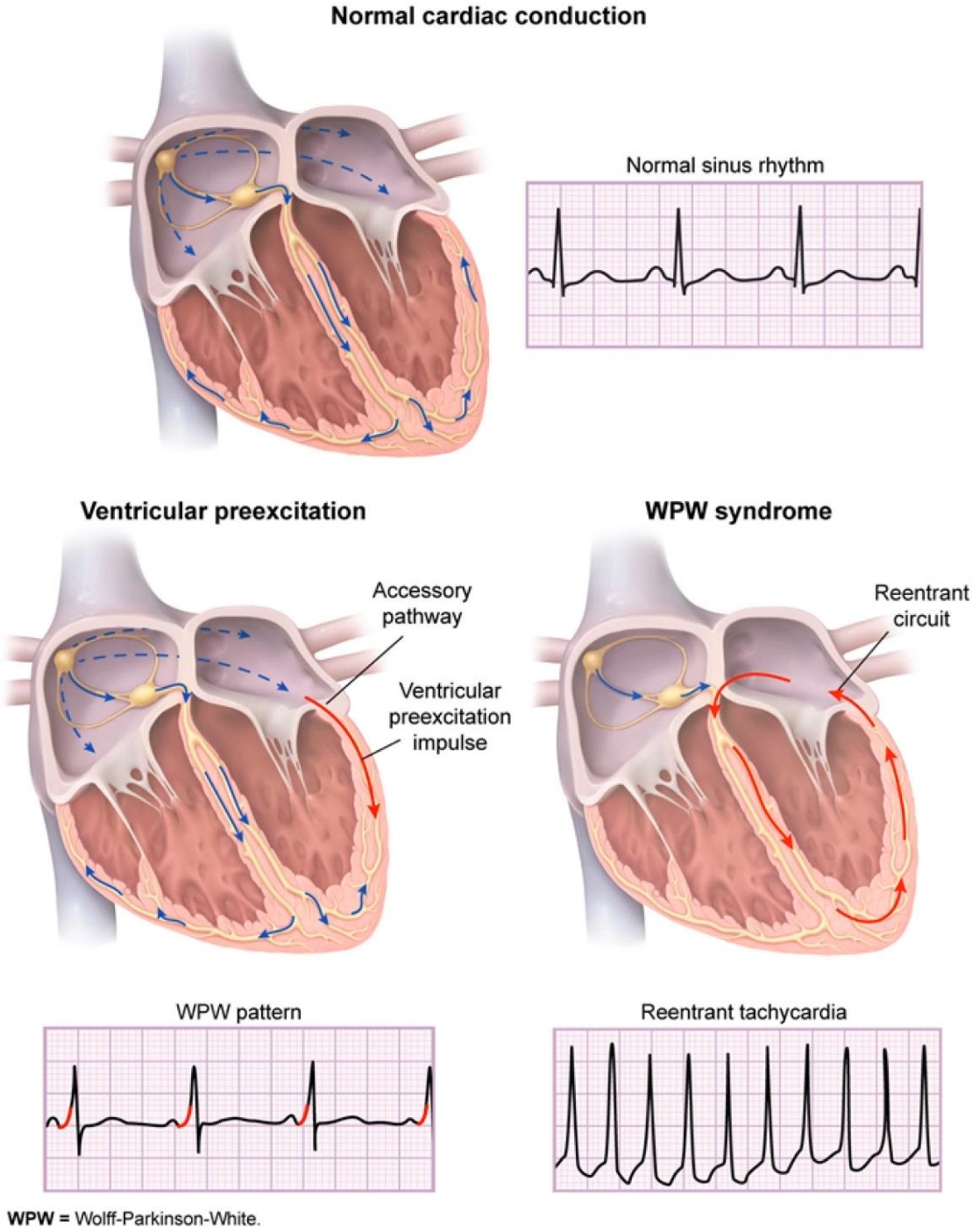
- Autosomal dominant disorder most common in Asian males.
- ECG pattern of pseudo-right bundle branch block and ST elevations in V1-V3.
- ↑ risk of ventricular tachyarrhythmias and SCD.
- Prevent SCD with implantable cardioverter-defibrillator (ICD).

Wolff-Parkinson-White syndrome

- Most common type of ventricular preexcitation syndrome.
- Abnormal fast accessory conduction pathway from atria to ventricle (bundle of Kent) bypasses the rate-slowing AV node → ventricles begin to partially depolarize earlier → characteristic delta wave with widened QRS complex and shortened PR interval on ECG.
- May result in re-entry circuit → supraventricular tachycardia.
- In patients with this anatomical abnormality, when there is no re-entrant tachycardia, normal sinus impulses reach the ventricles first via the accessory pathway and shortly thereafter via the AV node.
- The accessory pathway "pre-excites" the ventricles ahead of the normal conduction pathway, hence the term "pre-excitation syndrome."
- The result is a shortened PR interval (often <0.12 seconds) with an early upslope (delta wave) at the start of each QRS complex. The QRS complex is wider than normal as a result of the delta wave.
- Note that the widened QRS complex converts to a narrow QRS during tachyarrhythmia because the accessory pathway no longer pre-excites the ventricles but instead forms a re-entrant circuit back to the atria.
- An accessory AV conduction pathway (Wolff-Parkinson-White syndrome) can manifest clinically as recurrent paroxysmal supraventricular tachycardia in an otherwise healthy individual.
- The baseline ECG generally shows a triad of abnormalities corresponding to ventricular pre-excitation: a shortened PR-interval, a delta wave at the start of the QRS complex, and a wide ned QRS interval.
- In Wolff-Parkinson-White syndrome, Block accessory pathway with IA or III. Don't slow AV conduction (avoid digoxin, β-blocker, Ca-channel blocker, adenosine) because this can enhance the arrhythmia.

Wolff-Parkinson-White triad





WPW = Wolff-Parkinson-White.

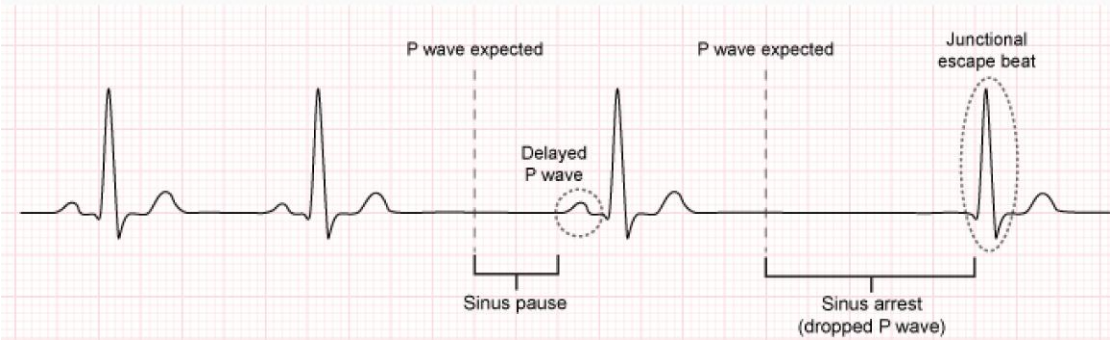
❖ N.B:

1. Paroxysmal supraventricular tachycardia (PSVT) is the most common paroxysmal tachycardia.

- PSVT typically results from a re-entrant impulse traveling through slowly and rapidly conducting segments of the AV node.
- Simple treatments for this condition include maneuvers that increase cardiac parasympathetic tone, such as carotid sinus massage and the Valsalva maneuver.
- The parasympathetic nervous system primarily functions to slow the heart rate by slowing conduction through the AV node.
- Slowed conduction in the AV node is specifically beneficial for this arrhythmia because it abolishes the re-entrant circuit.

2. Although lightning injuries are rare, they are associated with a 25% fatality rate.
- Two-thirds of lightning-related deaths occur within the first hour after injury, with fatal arrhythmias and respiratory failure as the most common causes.
- Patients with minor cutaneous involvement may still have major internal injury after lightning strikes and high-voltage electrical contact.

3. Sick sinus syndrome most commonly results from age-related degeneration of the sinoatrial node, which is located on the right atrial wall and is responsible for initiating normal cardiac conduction.
- Impaired signaling from the sinoatrial node can markedly slow the rate of ventricular contraction, leading to reduced cardiac output and symptoms of dyspnea, fatigue, lightheadedness, presyncope, and syncope.
- Typical ECG findings include bradycardia, sinus pauses (delayed P waves), and sinus arrest (prolonged delay of a P wave such that the P wave is dropped). Because the atrioventricular node triggers conduction based on its own pacemaker if it does not receive a timely signal from the sinoatrial node, sinus arrest will lead to a junctional escape beat (narrow QRS complex preceded by a long pause and no P wave). Sick sinus syndrome can also cause brief periods of atrial tachycardia (atrial fibrillation) alternating with bradycardia



CHAPTER 4

Pathology

Congenital heart diseases

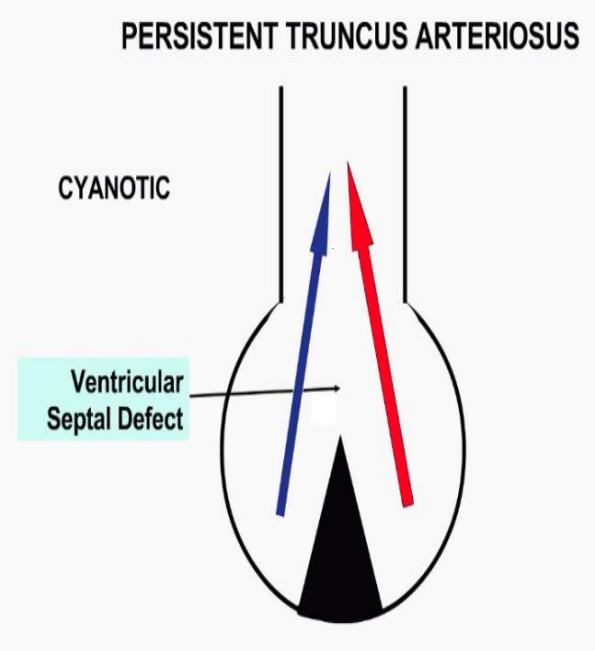
Right to left shunts

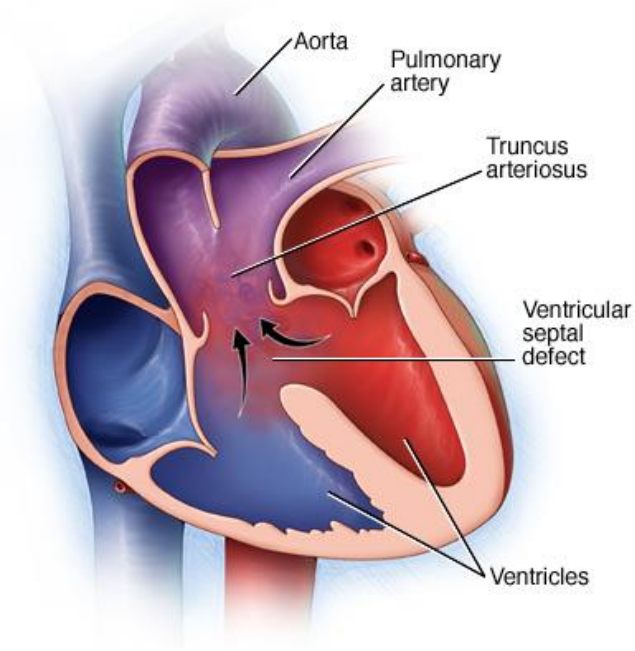
- Early cyanosis "blue babies".
- Often diagnosed prenatally or become evident immediately after birth.
- Usually require urgent surgical treatment and/or maintenance of a PDA.
- The 5 Ts:

1. Truncus arteriosus (1 vessel)
2. Transposition (2 switched vessels)
3. Tricuspid atresia (3 = Tri)
4. Tetralogy of Fallot (4 = Tetra)
5. TAPVR (5 letters in the name)

1. Persistent truncus arteriosus:

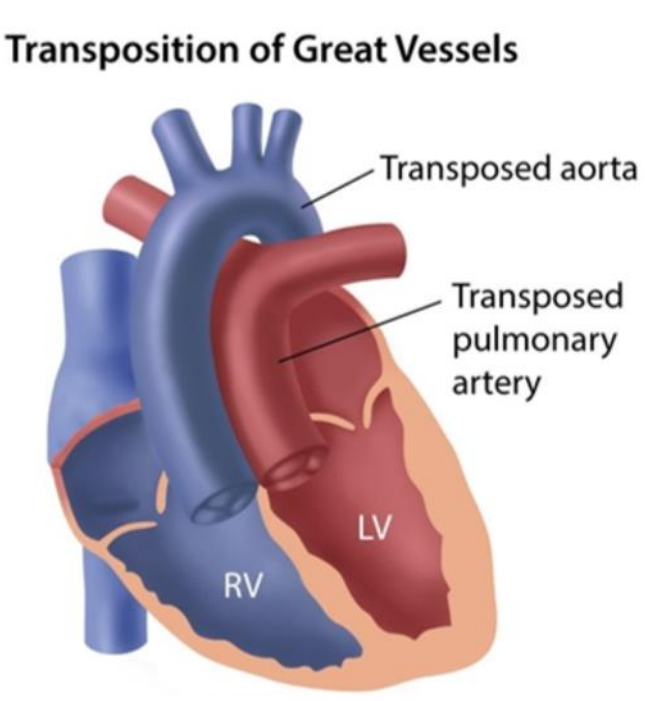
- Truncus arteriosus fails to divide into pulmonary trunk and aorta due to lack of aorticopulmonary septum formation.
- Presents with early cyanosis; deoxygenated blood from right ventricle mixes with oxygenated blood from left ventricle before pulmonary and aortic circulations separate.
- Most patients have accompanying VSD.

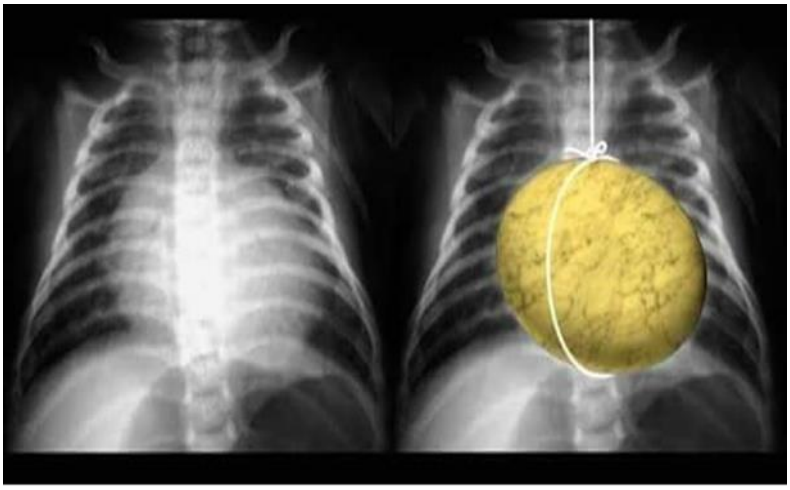




2. D-transposition of great vessels:

- Results from failure of the fetal aorticopulmonary septum to spiral normally during septation of the truncus arteriosus.
- Aorta leaves RV (anterior) and pulmonary trunk leaves LV (posterior) → separation of systemic and pulmonary circulations ("arterial switch").
- Associated with maternal diabetes.
- Thus, there is separation of the pulmonary and systemic circulations. As a result, deoxygenated blood coming from the body goes to the right atrium and ventricle and is cycled back to the body through the aorta. Oxygenated blood from the lungs is returned to the lungs by the left side of the heart through the pulmonary artery.
- Incompatible with life in the absence of an accompanying connection (patent foramen ovale, septal defect, or patent ductus arteriosus) to allow mixing of oxygenated pulmonary circulation blood with the systemic circulation.
- An echocardiogram showing an aorta lying anterior to and to the right of the pulmonary artery is diagnostic of transposition of the great arteries (TGA).
- Chest x-ray will show an "egg on a string" due to narrow mediastinum.
- PGE can be administered to maintain a PDA until definitive surgical repair is performed.
- Without surgical intervention, most infants die within the first few months of life.





Transposition Of Great Arteries.

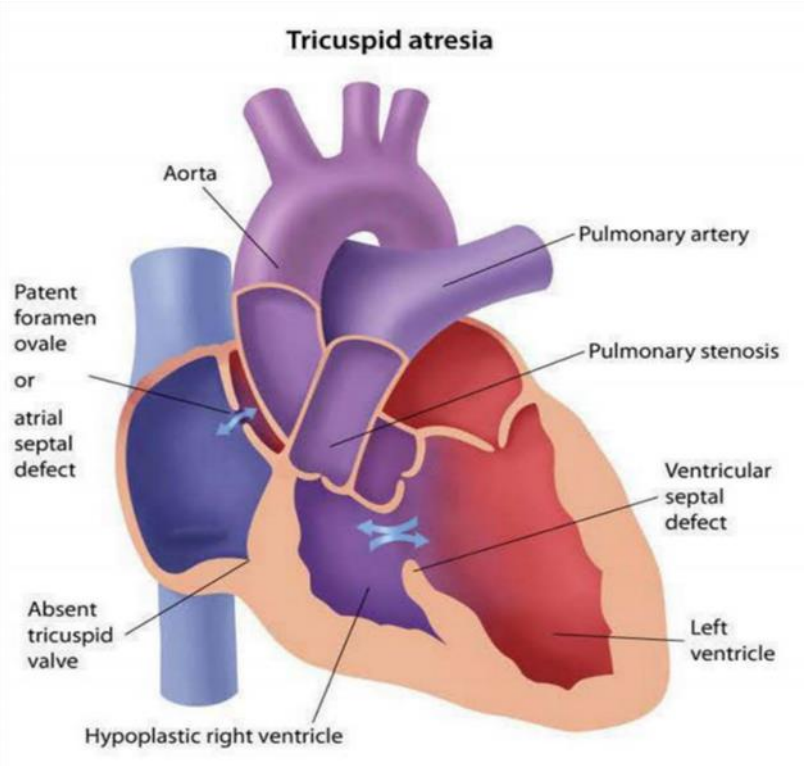
(Egg on String Appearance)

3. Tricuspid atresia:

- No outlet from the right atrium to the right ventricle; entire venous (systemic) return enters the left atrium from a foramen ovale or ASD (there must be an atrial communication); left ventricular blood to right ventricle (atretic) via a VSD and is augmented by PDA; therefore, pulmonary blood flow depends on presence (and size) of VSD.

- Associated atrial and ventricular septal defects are necessary for survival, allowing for mixing of oxygenated and deoxygenated blood to provide some oxygenated blood for the systemic circulation.

- Will present at birth with severe cyanosis.



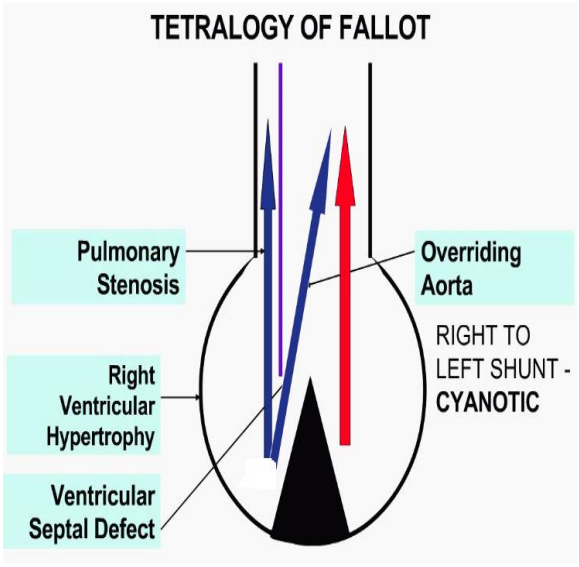
4. Tetralogy of Fallot:

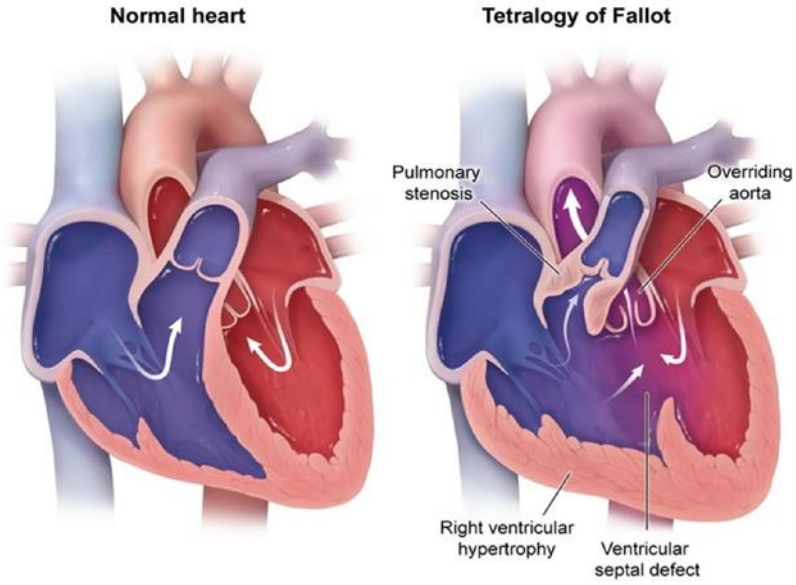
- Tetralogy of Fallot is the most common cyanotic heart defect in children.

- Associated with 22q11 syndromes.

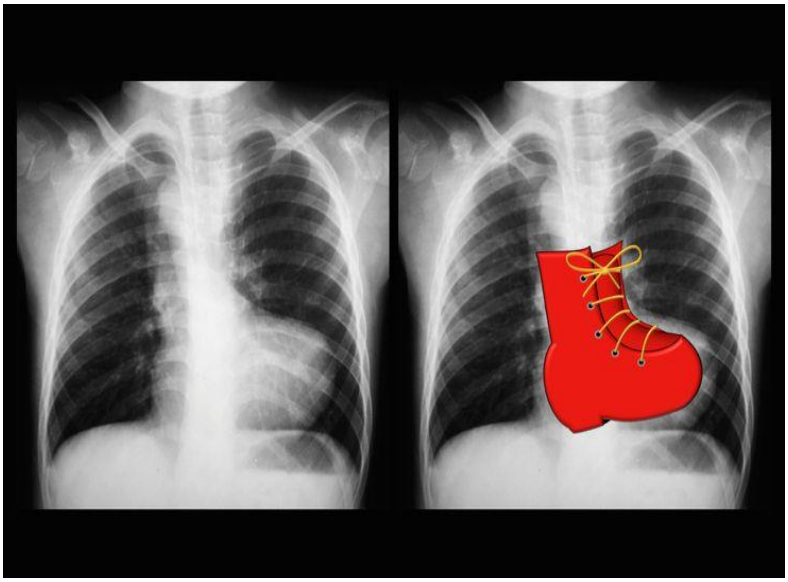
- TOF is characterized by 4 anomalies that result from deviation of the infundibular septum in utero:

- Pulmonary stenosis.
- Right ventricular hypertrophy.
- Ventricular septal defect (VSD).
- Overriding aorta.





- Tetralogy of Fallot presents with varying degrees of cyanosis depending on the severity of right ventricular outflow tract obstruction.
- "Tet" spells result from sudden spasm of the right ventricular outflow tract during exertion.
- Placement of patients in a knee-chest position (Squatting) during a cyanotic spell increases systemic vascular resistance, increases pulmonary blood flow, and improves symptoms and cyanosis.
- Squatting → ↑ SVR, ↓ right-to-left shunt, improves cyanosis.
- Chest x-ray showing a boot-shaped heart due to right ventricular hypertrophy.
- Treatment: early surgical correction.



❖ N.B:

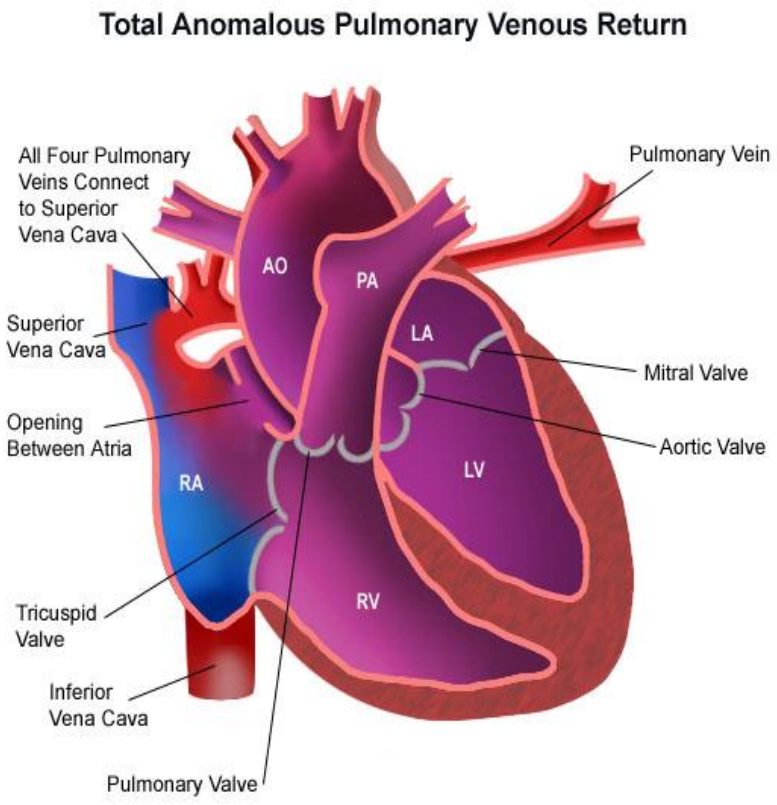
- Tetralogy of Fallot is the most common cause of cyanotic congenital heart disease, although it does not always present with cyanosis in the immediate newborn period, especially when the pulmonary stenosis component is only mild.
- Mild pulmonary stenosis allows the ventricular septal defect (VSD) to act mainly as a left-to-right shunt early in childhood, resulting in relatively infrequent cyanotic episodes.

5. Total anomalous pulmonary venous return:

- Pulmonary veins drain into right heart circulation (SVC, coronary sinus).

- It is a rare cyanotic congenital heart defect in which all four pulmonary veins are malpositioned and make anomalous connections to the systemic venous circulation. (Normally, pulmonary veins return oxygenated blood from the lungs to the left atrium where it can then be pumped to the rest of the body).

- Associated with ASD and sometimes PDA to allow for right-to-left shunting to maintain CO.



Left to right shunts

- Late cyanosis (2° to Eisenmenger syndrome) "blue kids".

- Frequency: VSD > ASD > PDA.

- Eisenmenger syndrome:

- Uncorrected left-to-right shunt (VSD, ASD, PDA) → ↑ pulmonary blood flow → pathologic remodeling of vasculature → pulmonary arterial hypertension.
- RVH occurs to compensate → shunt becomes right to left.
- Causes leading to late cyanosis (Eisenmenger syndrome) with right ventricular hypertrophy, polycythemia (due to hypoxemia → increase secretion of erythropoietin from the kidney), and clubbing (due to cyanosis).

- Right-to-Left shunts: eaRLy cyanosis. Left-to-Right shunts: "LateR" cyanosis.

1. Ventricular septal defect:

- Most common congenital cardiac defect.

- Asymptomatic at birth, may manifest weeks later or remain asymptomatic throughout life.

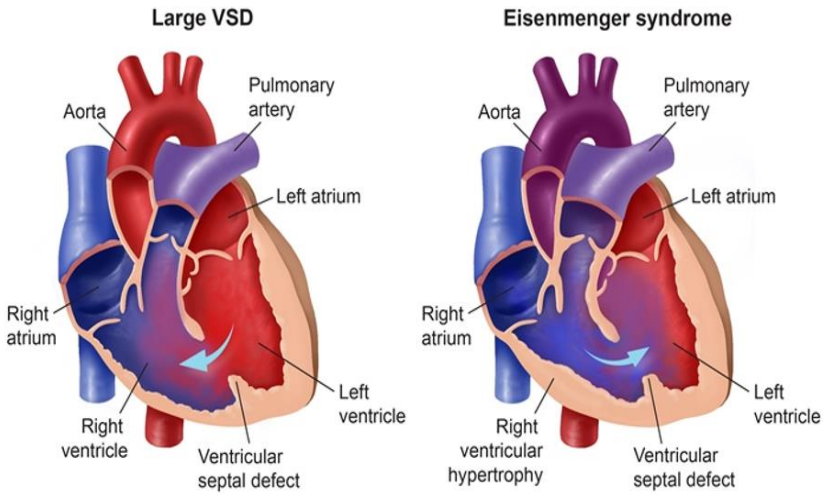
- Size of defect determines extent of shunting and age at presentation. Small defects are often asymptomatic; large defects can lead to Eisenmenger syndrome.

- Large ventricular septal defects can cause failure to thrive, easy fatigability, and heart failure.

- Harsh, holosystolic murmur best heard at the left lower sternal border.

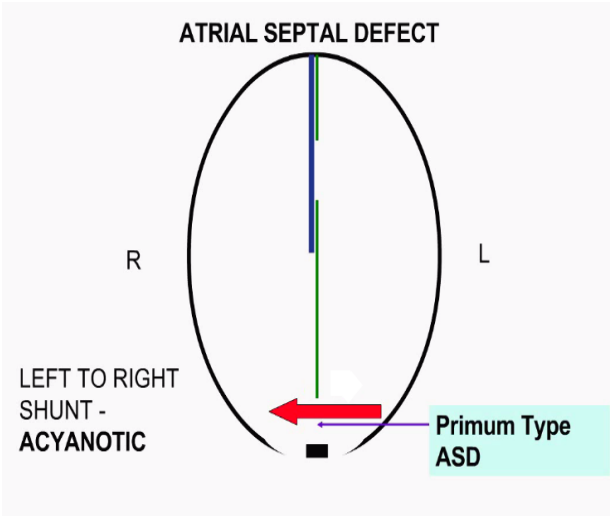
- Treatment involves surgical closure; small defects may close spontaneously.

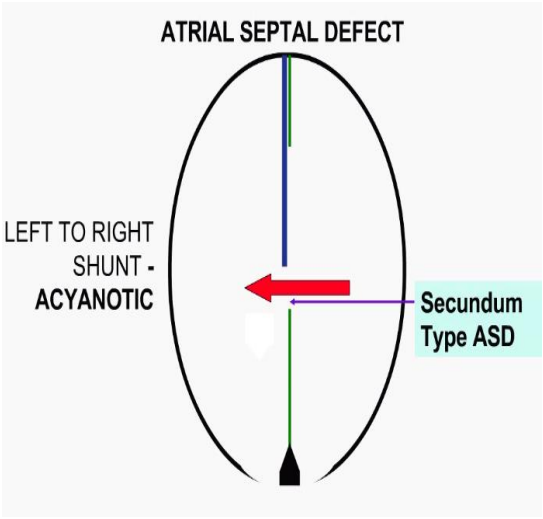
- O_2 saturation ↑ in RV and pulmonary artery.

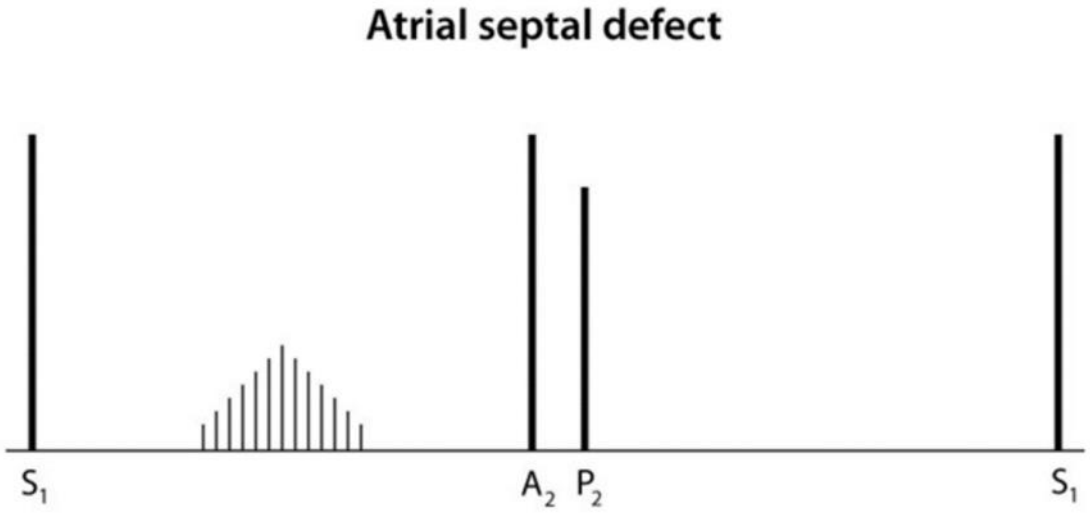


2. Atrial septal defect:

- Defect in interatrial septum; loud S1; wide, fixed split S2 (increased blood in right heart delays closure of pulmonary valve).
- Ostium secundum defects most common (90% of cases) and usually occur as isolated findings; ostium primum defects rarer yet usually occur with other cardiac anomalies.
- Ostium primum type is associated with Down syndrome.
- Symptoms range from none to HF.
- Distinct from patent foramen ovale in that septa are missing tissue rather than unfused.
- O_2 saturation ↑ in RA, RV, and pulmonary artery.
- Paradoxical emboli are an important complication.

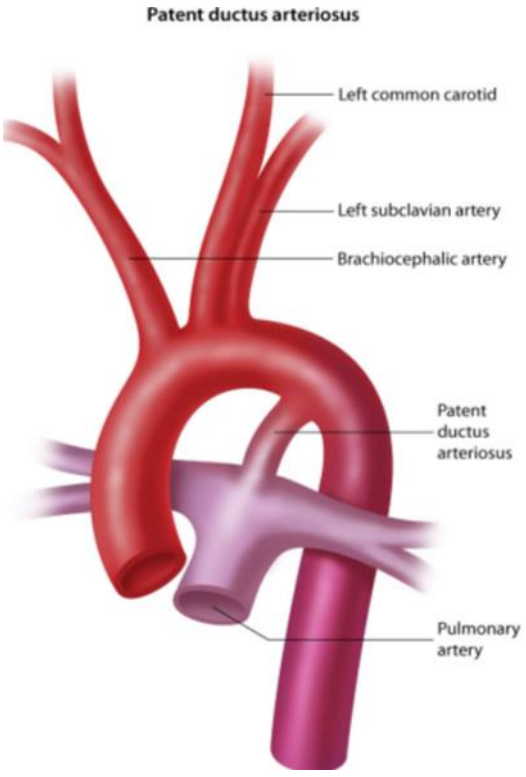


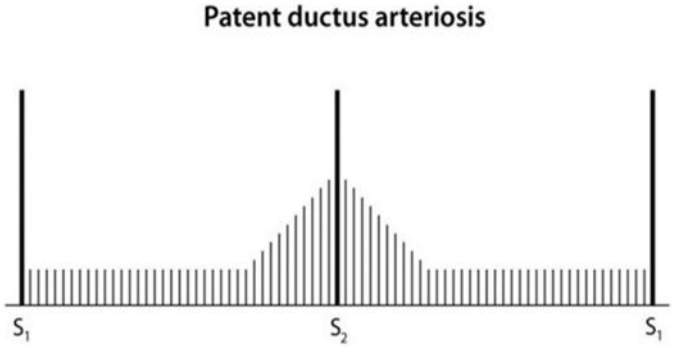




3. Patent ductus arteriosus:

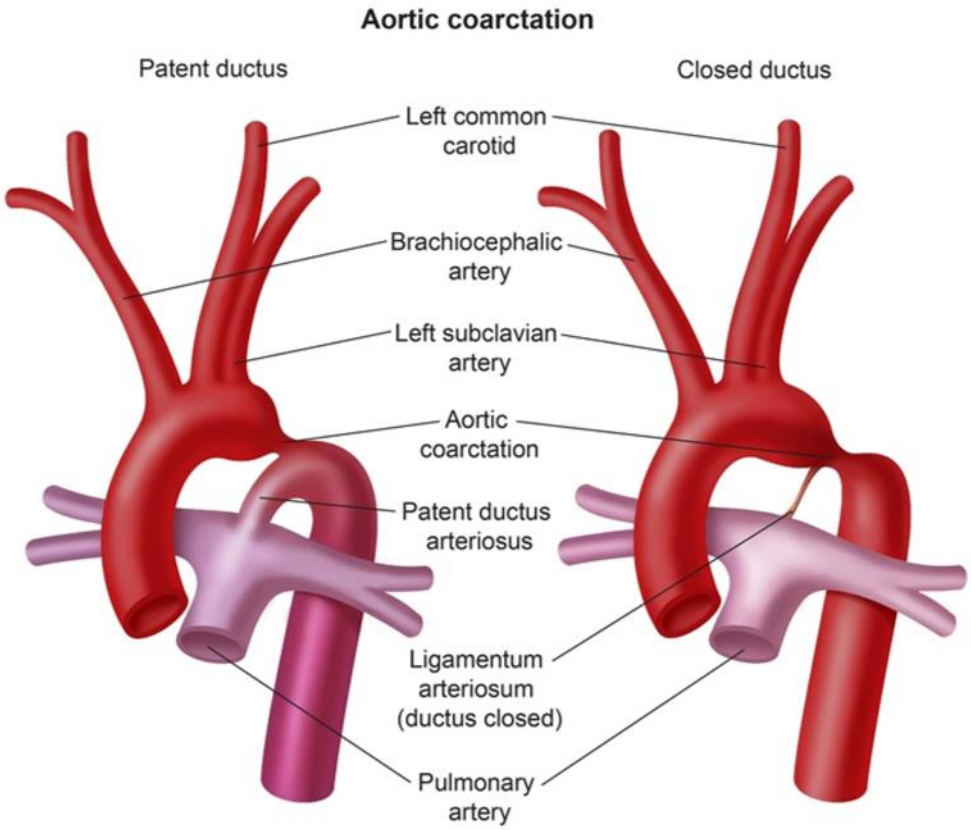
- Failure of ductus arteriosus to close; associated with prematurity and congenital rubella.
- In fetal period, shunt is right to left (normal).
- In neonatal period, ↓ pulmonary vascular resistance → shunt becomes left to right → progressive RVH and/or LVH and HF.
- "Continuous machinery-like" murmur. A patent ductus arteriosus (PDA) is associated with a continuous flow murmur due to constant movement of blood from the high-pressure aorta to the low-pressure pulmonary artery. Small PDAs are often asymptomatic and detected incidentally on routine cardiac auscultation.
- Differential cyanosis is a cyanosis of the lower extremities but not of the upper body.
- Differential cyanosis is the result of reduced arterial oxygen saturation in the distal aorta compared to that in the aorta proximal to the left subclavian artery. The most likely cause is right-to-left shunting of blood through a patent ductus arteriosus (PDA) into the junction between the aortic arch and the descending aorta.
- Therapy with indomethacin successfully closes this defect in the majority of patients.
- "Endomethacin" (indomethacin) ends patency of PDA; PGE keeps ductus Going (may be necessary to sustain life in conditions such as transposition of the great vessels).





Coarctation of the aorta

- Narrowing of the aorta; classically divided into infantile and adult forms:



A. Infantile form (Preductal):

- Coarctation of the aorta results from thickening of the tunica media near the junction of ductus arteriosus and the aortic arch. Luminal narrowing causes a mechanical obstruction to aortic blood flow.

- It is associated with a PDA; coarctation lies after (distal to) the aortic arch, but before (proximal to) the PDA.

- It has a frequent association with Turner syndrome. If the exam question mentions a short girl with webbed neck, shield chest, streak gonads, horseshoe kidneys, or shortened fourth metacarpal, think coarctation of the aorta.

- Presents as lower extremity exercise intolerance in infants.

- Severe aortic narrowing makes systemic blood flow dependent on the ductus arteriosus. As the ductus begins to close (normally around day 3 of life), infants may develop heart failure with tachypnea, poor feeding, fussiness, and lethargy. Patients are also at significant risk of shock, metabolic acidosis, and decreased renal perfusion (decreased urine output).

- Uncorrected cases often don't survive post-neonatal period.

B. Adult form (Postductal):

- Not associated with a PDA; coarctation lies after (distal to) the aortic arch and ligamentum arteriosum.

- Presents as hypertension in the upper extremities and hypotension with weak pulses in the lower extremities (brachial-femoral delay); classically discovered in adulthood.

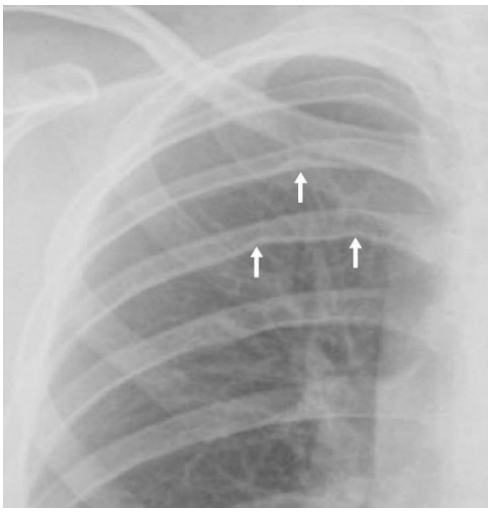
- Headaches and epistaxis may be caused by hypertension in the arteries supplying the head and neck.

- Chest x-ray usually demonstrates inferior notching of the third to eighth ribs. With age, Collateral circulation develops across the intercostal arteries; engorged arteries cause 'notching' of ribs on x-ray.

- The triad of upper body hypertension, diminished lower extremity pulses, and enlarged intercostal artery collaterals is typical of adult-type coarctation and is not seen in other congenital cardiovascular malformations.

- Patients with adult-type coarctation of the aorta commonly die of hypertension-associated complications, including left ventricular failure, ruptured dissecting aortic aneurysm, and intracranial hemorrhage.

- These patients are at increased risk for ruptured intracranial aneurysms because of the increased incidence of congenital berry aneurysms of the Circle of Willis as well as aortic arch hypertension.

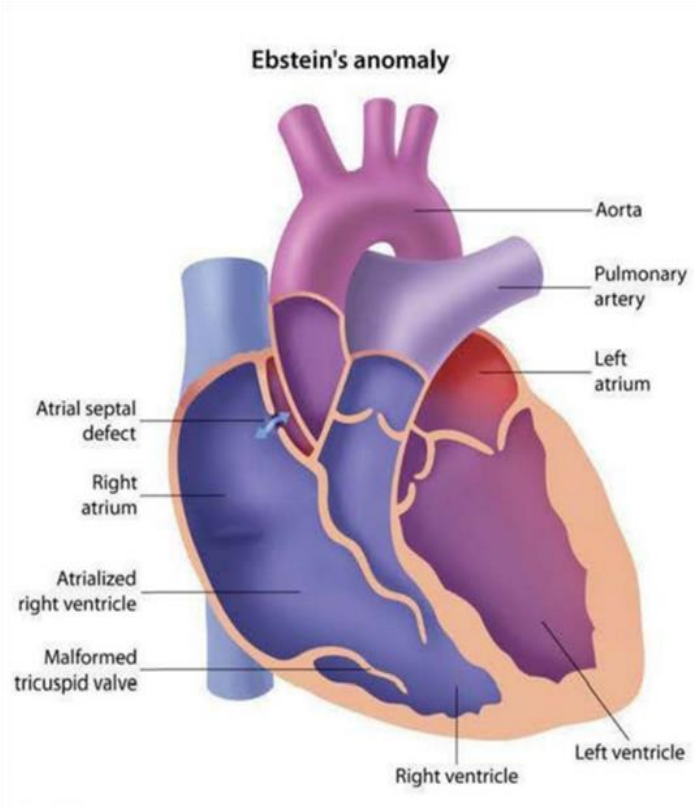


❖ N.B:

- Differential cyanosis is a cyanosis of the lower extremities but not of the upper body.
- Differential cyanosis is the result of reduced arterial oxygen saturation in the distal aorta compared to that in the aorta proximal to the left subclavian artery.
- The most likely cause is right-to-left shunting of blood through a patent ductus arteriosus (PDA) into the junction between the aortic arch and the descending aorta.
- Differential clubbing and cyanosis without blood pressure or pulse discrepancy are pathognomonic for a large patent ductus arteriosus complicated by Eisenmenger syndrome (reversal of shunt flow from left-to-right to right-to-left).
- Severe coarctation of the aorta can cause lower extremity cyanosis.

Ebstein anomaly

- Characterized by displacement of tricuspid valve leaflets downward into RV, artificially "atrializing" the ventricle.
- Associated with tricuspid regurgitation and right HF.
- Can be caused by lithium exposure in utero.



Congenital cardiac defect associations

Disorder	Defect
Alcohol exposure in utero (fetal alcohol syndrome)	VSD, PDA, ASD, tetralogy of Fallot
Congenital rubella	PDA, pulmonary artery stenosis, septal defects
Down syndrome	AV septal defect (endocardial cushion defect), VSD, ASD
Infant of diabetic mother	Transposition of great vessels, VSD
Marfan syndrome	MVP, thoracic aortic aneurysm and dissection, aortic regurgitation
Prenatal lithium exposure	Ebstein anomaly
Turner syndrome	Bicuspid aortic valve, coarctation of aorta
Williams syndrome	Supravalvular aortic stenosis
22q11 syndromes	Truncus arteriosus, tetralogy of Fallot

Hypertension

- Increased blood pressure; may involve pulmonary or systemic circulation
- Systemic HTN is defined as persistent systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 80 mm Hg.

A. Primary HTN:

- HTN of unknown etiology.
- 90% of hypertension is 1° (essential) and related to ↑ CO or ↑ TPR.
- Risk factors are ↑ age, obesity, diabetes, physical inactivity, excess salt intake, excess alcohol intake, family history; African American > Caucasian > Asian.

B. Secondary hypertension:

- Secondary hypertension is hypertension in the presence of an identifiable underlying cause (<5% cases of hypertension):
  - Renal artery stenosis.
  - Primary hyperaldosteronism (Conn Syndrome).
  - Pheochromocytoma.
  - Cushing disease
  - Coarctation of the aorta.
  - Other causes of secondary hypertension are the use of oral contraceptives, acromegaly, congenital adrenal enzyme deficiencies, and virtually any cause of chronic renal disease such as glomerulonephritis, polycystic disease, diabetic nephropathy, or chronic pyelonephritis.

Renal artery stenosis

- Marked narrowing of the renal artery prevents enough blood from reaching the kidney to maintain normal glomerular filtration rates.
- This is sensed by the juxtaglomerular (JG) apparatus, which consists of macula densa and JG cells.
- Significant renal hypoperfusion leads to a compensatory increase in renin synthesis and secretion by JG cells.
- Increased renin stimulates the cleavage of angiotensinogen to angiotensin I, which is then converted to angiotensin II by angiotensin-converting enzyme.
- Angiotensin II causes systemic vasoconstriction and aldosterone release.

- In addition, aldosterone and angiotensin II act on the kidney to enhance sodium and water retention, increasing extracellular fluid volume.

- Severe, long-term renal artery stenosis (RAS) causes the JG cells of the affected kidney(s) to undergo hypertrophy and hyperplasia.

- Hypertension can occur in both unilateral and bilateral RAS.

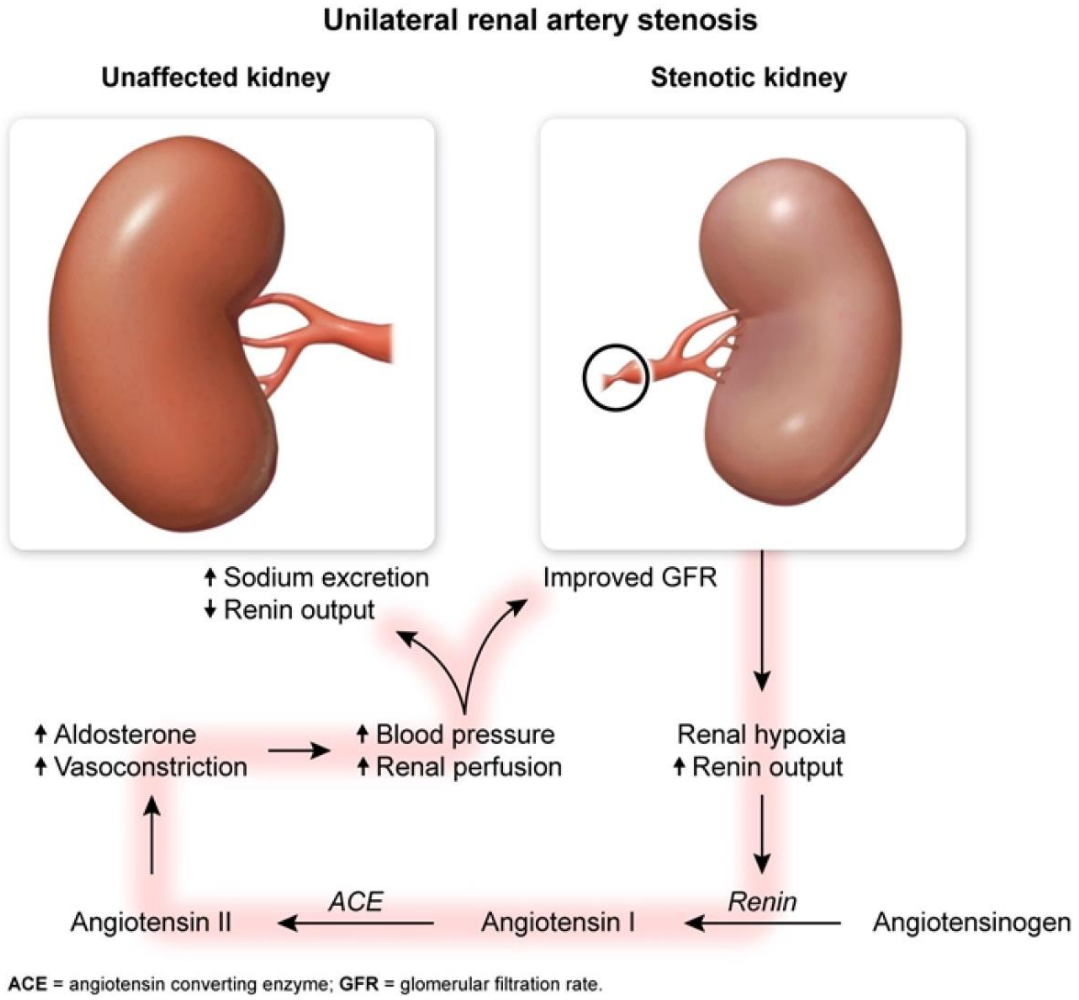
- Although the contralateral kidney can be functionally normal in unilateral RAS, secretion of renin by the stenotic kidney will cause increased aldosterone and angiotensin II, leading to systemic vasoconstriction and retention of salt and water by both kidneys.

- Bilateral RAS can result in chronic kidney disease, which does not occur with unilateral RAS as the normal kidney is still able to efficiently filter and excrete waste products (creatinine, urea, etc.).

- <u>Main causes of renal artery stenosis:</u>

- Atherosclerotic plaques: proximal 1/3 of renal artery, usually in older males, smokers.

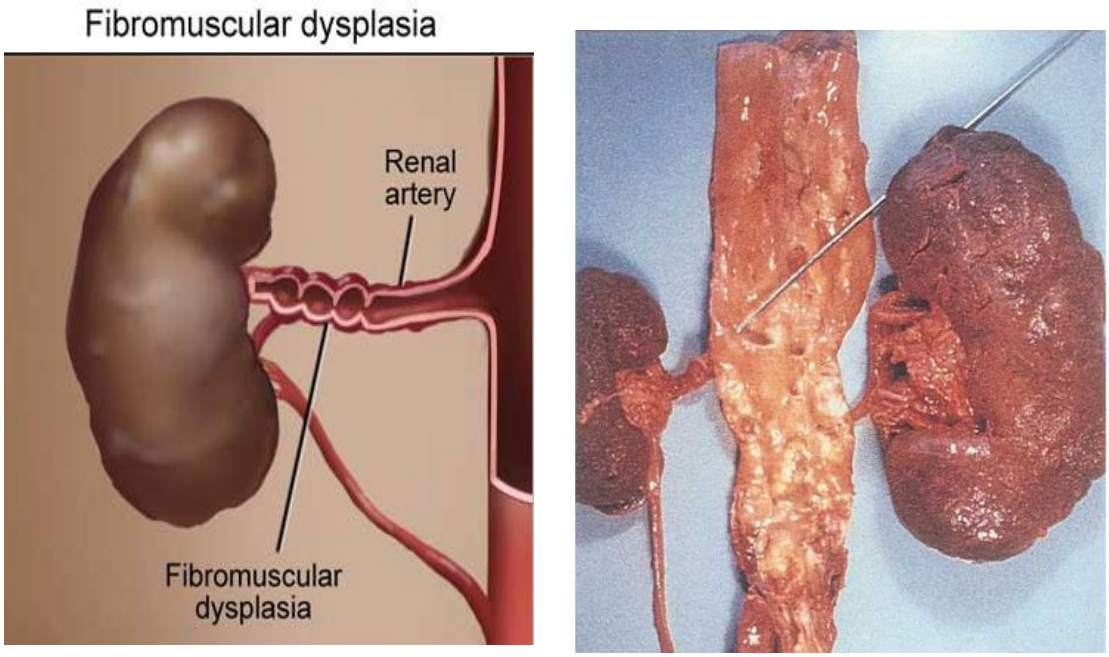
- Fibromuscular dysplasia: distal 2/3 of renal artery or segmental branches ("string of beads"), usually young or middle-aged females.



- Finding:

- Most common cause of 2° HTN in adults.

- Clinically, patients can have refractory HTN with negative family history of HTN, asymmetric renal size, epigastric/flank bruits.

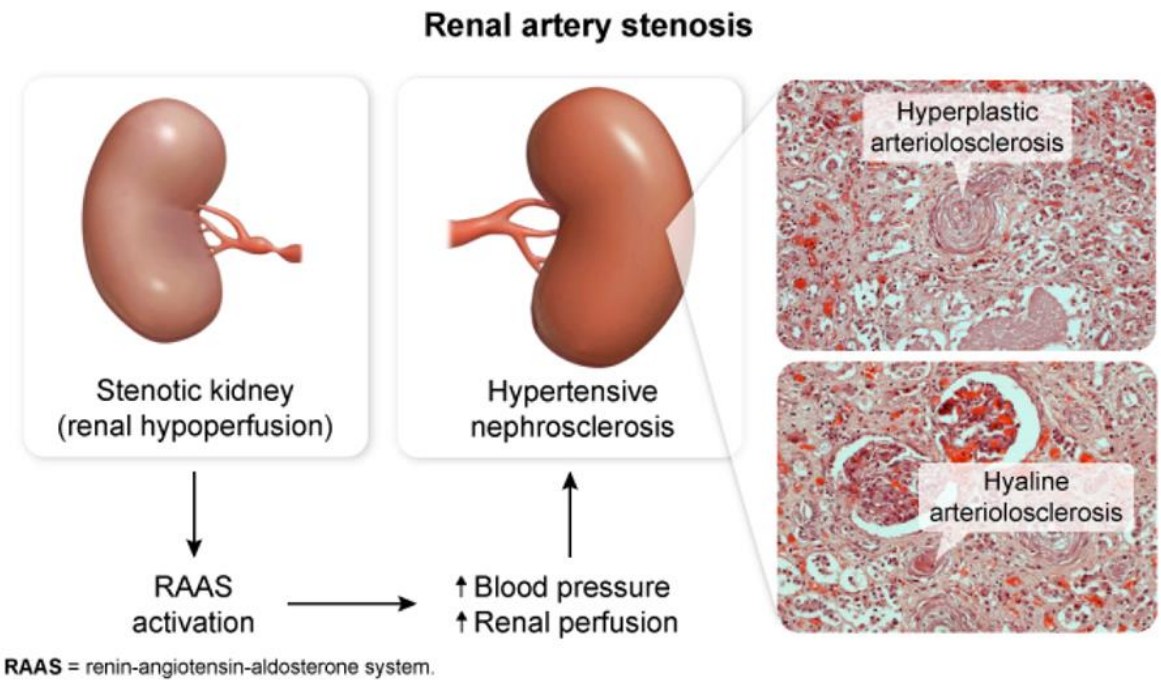


- If you give ACEI in bilateral renal stenosis, you will further compromise the already poor blood flow to the kidneys, causing acute renal failure, thats why they are not given in BILATERAL kidney disease.

- RAS causes morphologic changes that markedly differ in the affected kidney and the contralateral kidney:

A. The narrowing of the renal artery to the affected kidney protects the organ parenchyma from high systemic pressure. Morphologic changes in the affected kidney are instead related to hypoperfusion and include diffuse cortical thinning and atrophy (due to oxygen and nutrient deprivation).

B. In contrast, the contralateral nonstenotic kidney is exposed to high blood pressure and therefore demonstrates typical signs of hypertensive nephrosclerosis, including arterial intimal fibroplasia and hyalinization of the arterioles (hyaline arteriolosclerosis). In cases of severe hypertension, hyperplastic arteriosclerosis (onion-skinning) may occur.



- Hypertension Predispose to:

- Coronary Artery Diseases, Left Ventricular Concentric Hypertrophy, Heart Failure, Atrial Fibrillation; aortic dissection, aortic aneurysm; stroke; chronic kidney disease (hypertensive nephropathy); retinopathy.

- Hypertensive urgency: severe (≥ 180/≥ 120 mm Hg) hypertension without acute end-organ damage.

- Hypertensive emergency: severe hypertension with evidence of acute end-organ damage (encephalopathy, stroke, retinal hemorrhages and exudates, papilledema, MI, HF, aortic dissection, kidney injury, microangiopathic hemolytic anemia, eclampsia).

- Isolated systolic hypertension (ISH):

- If the systolic blood pressure is elevated (>130) with a normal (<80) diastolic blood pressure (DBP), it is called isolated systolic hypertension.

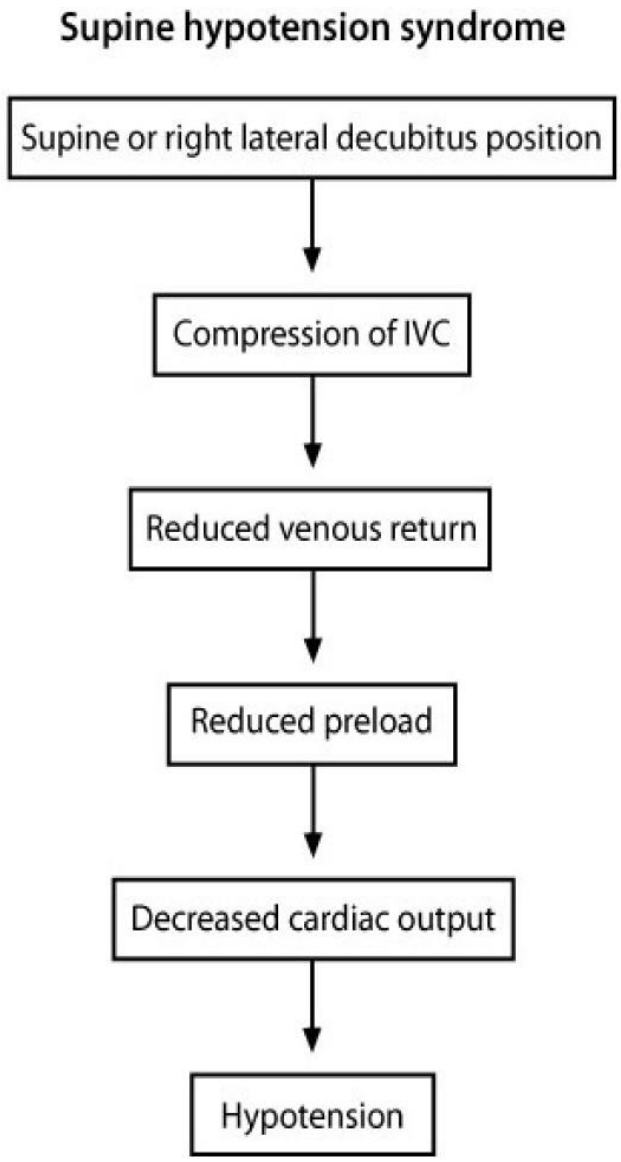
- After age 50, the pattern of isolated systolic hypertension (ISH) becomes quite common.

- ISH is caused by age-related decreases in the compliance of the aorta and its proximal major branches (aortic stiffening).

- Numerous alterations in vessel wall structure and function, including atherosclerotic changes, have been proposed to explain this stiffening.

❖ N.B:

- Supine hypotension syndrome (or aortocaval compression syndrome) is characterized by hypotension, pallor, sweating, nausea, and dizziness that occur when a pregnant woman lies supine (on her back).
- Symptoms resolve with sitting, standing up, or when assuming a left lateral decubitus position. It occurs predominantly in women > 20 weeks gestation, and is due to the gravid uterus compressing and obstructing the inferior vena cava.
- This reduces the venous return (preload), which subsequently lowers the cardiac output leading to hypotension.
- In severe cases, it can result in loss of consciousness and even fetal demise.



Arteriosclerosis

- Literally, "hard arteries;" due to thickening of the blood vessel wall.

- Three pathologic patterns:

A. Atherosclerosis.
B. Arteriolosclerosis.
C. Monckeberg medial calcific sclerosis.

A. Atherosclerosis:

- Intimal plaque that obstructs blood flow.

- Involves large- and medium-sized arteries.

Abdominal aorta > coronary artery > popliteal artery > carotid artery

- Consists of a necrotic lipid core (mostly cholesterol) with a fibromuscular cap; often undergoes dystrophic calcification.

- Risk factors:

- Risk factors for atherosclerosis are divided into modifiable and non-modifiable:
  - Modifiable risk factors: include hypertension, hypercholesterolemia (LDL increases risk; HDL decreases risk), smoking, and diabetes.
  - Nonmodifiable risk factors: include age (number and severity of lesions increase with age), gender (increased risk in males and postmenopausal females; estrogen is protective), and genetics (multifactorial, but family history is highly predictive of risk).

- Pathogenesis:

- The pathogenesis of atherosclerotic plaques (atheromas) is thought to begin with endothelial cell injury, which results in increased endothelial permeability and enhanced leukocyte adhesion.

- Chronic endothelial cell injury may result from hypertension (and related hemodynamic factors), hyperlipidemia, smoking, and diabetes mellitus.

- Such injury leads to endothelial cell dysfunction and/or exposure of subendothelial collagen.

- Endothelial cell dysfunction results in monocyte and lymphocyte adhesion and migration into the intima, while exposure of subendothelial collagen promotes platelet adhesion.

- At the same time, increased vascular permeability allows LDL cholesterol into the intima, where it is phagocytosed by the accumulating macrophages to produce lipid-laden foam cells (fatty streak).

- Platelet-derived growth factor (PDGF) released by locally adherent platelets, dysfunctional endothelial cells, and infiltrating macrophages promotes migration of smooth muscle cells (SMCs) from the media into the intima and increases SMC proliferation.

- Platelets also release transforming growth factor beta (TGF-β), which is chemotactic for SMCs. Vascular smooth muscle cells (VSMCs) are the only cells within the atherosclerotic plaque capable of synthesizing structurally important collagen and extracellular matrix.

- The lesion eventually organizes into a core of lipid debris surrounded by monocytes and lymphocytes covered by a fibrous cap with intermixed SMCs (fibrofatty atheroma).

▪ Morphologic stages:

- Begins as fatty streaks; arise early in life (present in most teenagers).

- Fatty streaks are composed of intimal lipid-filled foam cells, derived from macrophages and smooth muscle cells (SMC) that have engulfed lipoprotein (predominantly LDL), which has entered the intima through an injured, leaky endothelium.

- Progresses to atherosclerotic plaque.

▪ Complications:

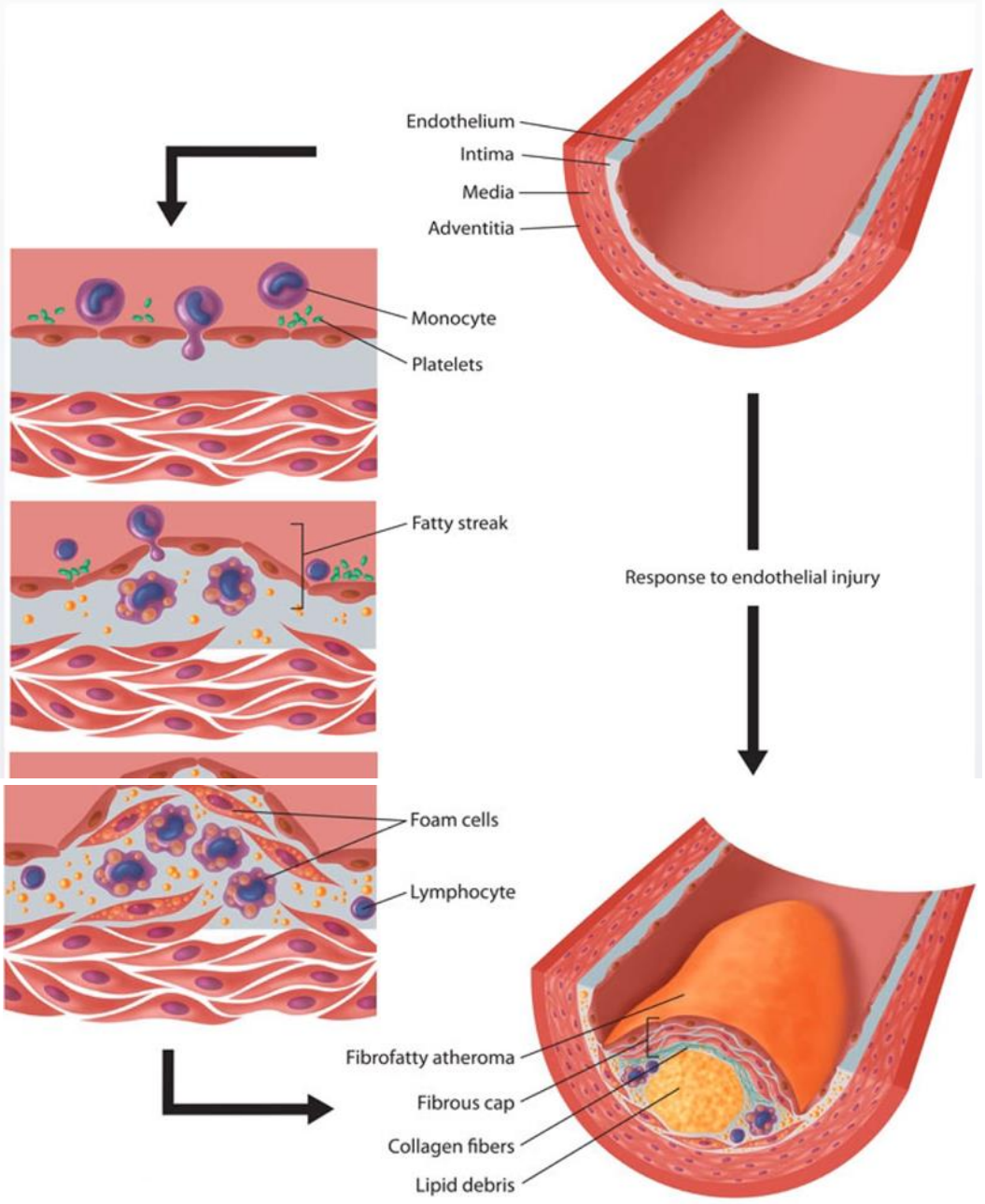
- Complications of atherosclerosis account for > 50% of disease in Western countries.

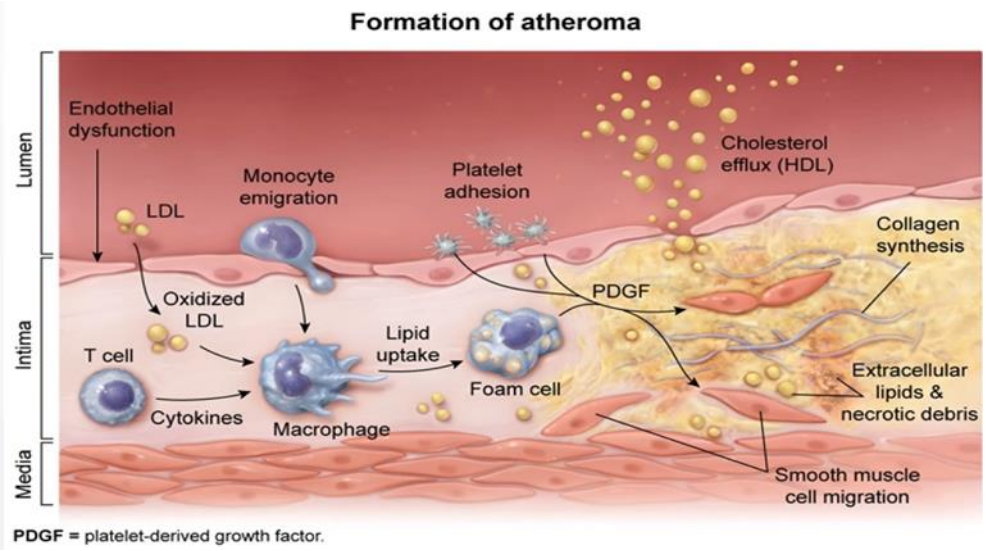
- Stenosis of medium-sized vessels results in impaired blood flow and ischemia leading to:
  - Peripheral vascular disease (lower extremity arteries; popliteal artery).
  - Angina (coronary arteries).
  - Ischemic bowel disease (mesenteric arteries).

- Plaque rupture with thrombosis results in myocardial infarction (coronary arteries) and stroke (middle cerebral artery).

- Plaque rupture with embolization results in atherosclerotic emboli, characterized by cholesterol crystals within the embolus.

- Weakening of vessel wall results in aneurysm (abdominal aorta).

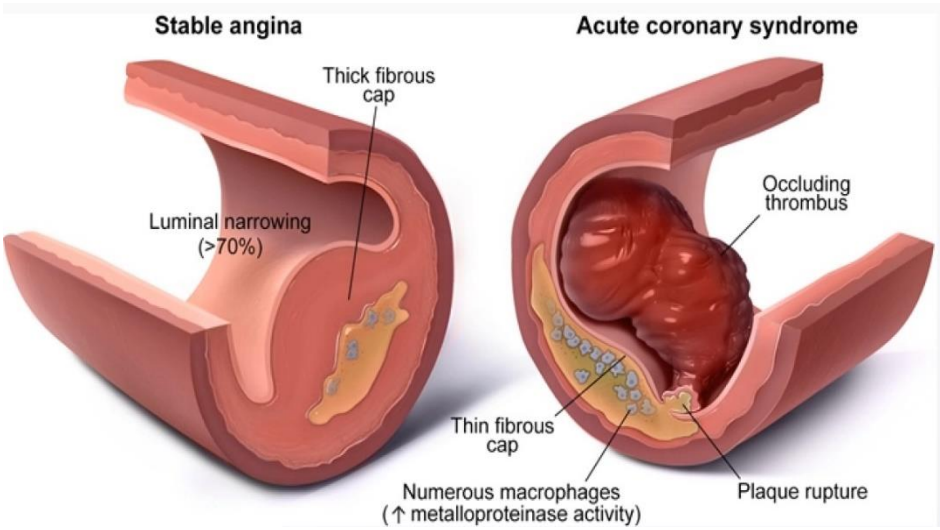

Endothelium
Intima
Media
Adventitia
Monocyte
Platelets
Fatty streak
Response to endothelial injury
Foam cells
Lymphocyte
Fibrofatty atheroma
Fibrous cap
Collagen fibers
Lipid debris


Formation of atheroma
Lumen
Intima
Media
Endothelial dysfunction
LDL
Monocyte emigration
Platelet adhesion
Cholesterol efflux (HDL)
Collagen synthesis
Oxidized LDL
PDGF
T cell
Lipid uptake
Foam cell
Cytokines
Macrophage
Extracellular lipids & necrotic debris
Smooth muscle cell migration
PDGF = platelet-derived growth factor.

❖ N.B:

1. Plaque rupture can produce an acute coronary syndrome via superimposed thrombosis and/or thromboembolism.

- The likelihood of plaque rupture or other acute plaque change has more to do with plaque stability than plaque size.
- Plaque stability depends upon the mechanical strength of the overlying fibrous cap.
- A weak fibrous cap increases the probability of plaque rupture.
- During the chronic inflammatory progression of an atheroma, the fibrous cap is continually being remodeled.
- The balance of collagen synthesis and degradation determines the mechanical strength of the cap.
- Activated macrophages in the atheroma contribute to collagen degradation by secreting metalloproteinases.
- Thus, a high degree of ongoing intimal inflammation can destabilize the mechanical integrity of plaques through release of these metalloproteinases.
- High intraplaque activity of such enzymes predisposes the patient to plaque rupture and a consequent acute coronary syndrome, including myocardial infarction.



2. Intermittent claudication is a muscle pain with exercise that remits with rest.

- Claudication is almost always the result of atherosclerosis of larger named arteries.
- The obstruction of blood flow in these arteries results from fixed stenotic atheromatous lesions.
- These stenoses prevent sufficient increase in blood flow to muscles during exercise, resulting in ischemic muscle pain.
- This pain is rapidly relieved by rest because the residual blood flow is adequate to meet the metabolic demands of resting, but not exercising muscle.

B. Arteriolosclerosis:

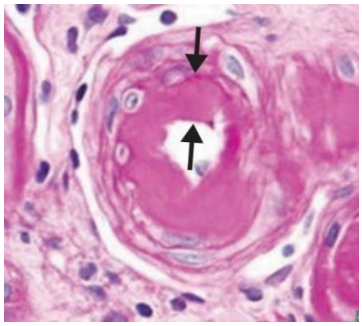
- Narrowing of small arterioles; divided into hyaline and hyperplastic types:

1. Hyaline arteriolosclerosis:

- It is caused by proteins leaking into the vessel wall, producing vascular thickening; proteins are seen as pink hyaline on microscopy.

- Homogeneous deposition of eosinophilic hyaline material in the intima and media of small arteries and arterioles characterizes hyaline arteriolosclerosis, which is typically produced by long-standing nonmalignant hypertension and/or diabetes.

- Results in reduced vessel caliber with end-organ ischemia; classically produces glomerular scarring (arteriolonephrosclerosis) that slowly progresses to chronic renal failure.



2. Hyperplastic arteriolosclerosis:

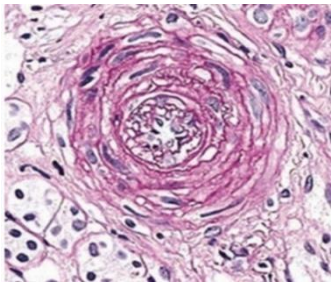
- It involves thickening of vessel wall by hyperplasia of smooth muscle.

- Presents as onion-like concentric thickening of the walls of arterioles as a result of laminated smooth muscle cells (SMC) and reduplicated basement membranes.

- Consequence of malignant hypertension.

- Results in reduced vessel caliber with end-organ ischemia.

- May lead to fibrinoid necrosis of the vessel wall with hemorrhage; classically causes acute renal failure with a characteristic 'flea-bitten' appearance.

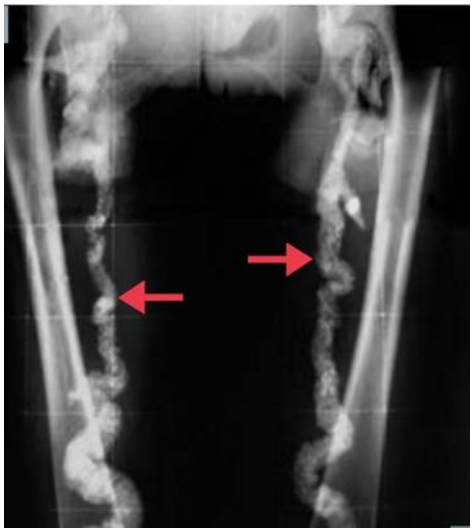


C. Monckeberg medial calcific sclerosis:

- Calcification of the media of muscular (medium-sized) arteries; nonobstructive.

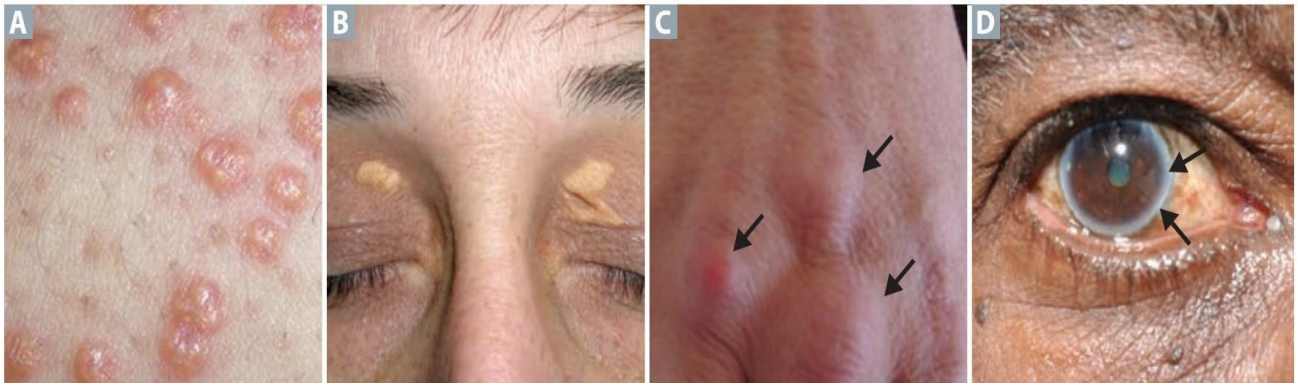
- Not clinically significant; seen as an incidental finding on x-ray or mammography.

- "Pipestem" appearance on x-ray.



Hyperlipidemia signs

- Xanthomas: Plaques or nodules composed of lipid-laden histiocytes in skin (A), especially the eyelids (xanthelasma B).
- Tendinous xanthoma: Lipid deposit in tendon (C), especially Achilles.
- Corneal arcus: Lipid deposit in cornea. Common in elderly (arcus senilis D) but appears earlier in life in hypercholesterolemia.



Aortic dissection

- Pathophysiology:

- It is initiated by a tear in the aortic intima forming a false lumen.

- Occurs in the proximal 10 cm of the aorta (high stress region) with preexisting weakness of the media.

- This condition develops when overwhelming hemodynamic stress leads to tearing of the aortic intima with blood subsequently dissecting through the aortic media.

- The resulting intramural hematoma can extend both proximally and distally and can compress major arterial branches and impair blood flow.

- Risk Factors:

- Associated with hypertension, bicuspid aortic valve, inherited connective tissue disorders (Marfan syndrome).

- Hypertension is the single most important risk factor for the development of intimal tears leading to aortic dissection.

- Cystic medial degeneration, which may be seen in connective tissue diseases such as Marfan syndrome, also predisposes patients (especially younger ones) to aortic dissection.

- Presentation:

- Can present with tearing chest pain, of sudden onset, radiating to the back +/− markedly unequal BP in arms.

- CXR shows mediastinal widening.

- Two types:

A. Stanford type A (proximal):

- Involves Ascending aorta.

- May extend to aortic arch or descending aorta.

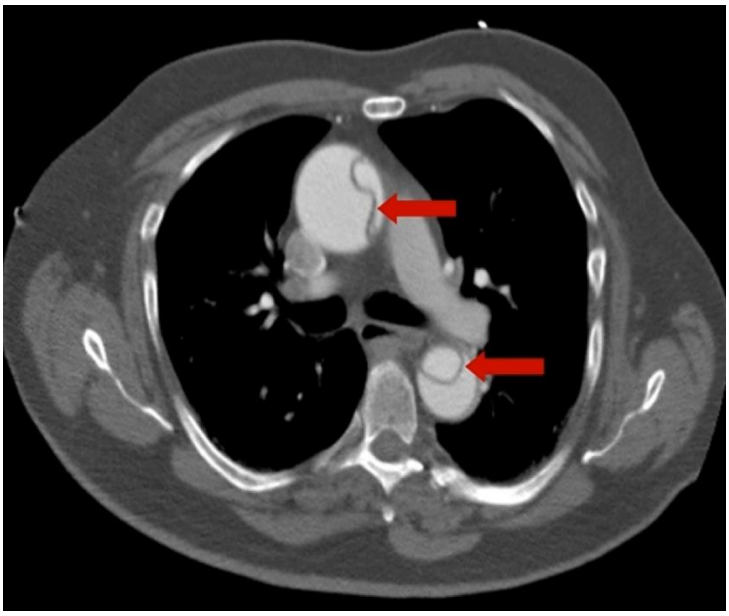
- The intimal tear usually originates in the sinotubular junction.

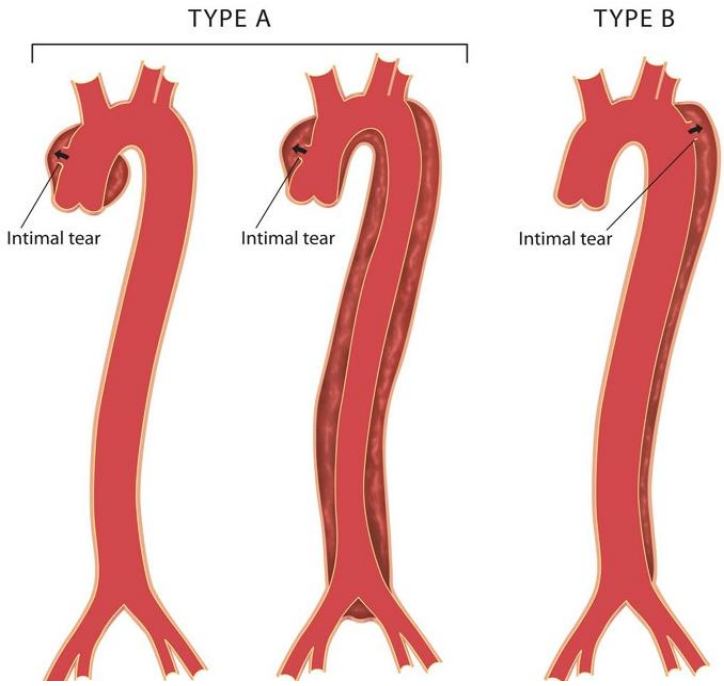
- May result in acute aortic regurgitation or cardiac tamponade.

- Treatment: surgery.

B. Stanford type B (distal):

- Involves only descending aorta (Below left subclavian artery).
- No ascending aorta involvement.
- The intimal tear usually originates below the origin of the left subclavian artery.
- Treat medically with β-blockers, then vasodilators.





- Complication of aortic dissection:

- If an ascending dissection extends proximally to the aortic root, it can affect the coronary ostia or aortic valve, resulting in myocardial ischemia or aortic regurgitation, respectively.
- In addition, a dissection may extend proximally into the pericardium, leading to life-threatening acute tamponade (most common cause of death).
- As blood accumulates in the pericardial sac, the rising pressure can rapidly supersede right sided filling pressure and restrict venous return, resulting in a precipitous drop in cardiac output and hemodynamic collapse (obstructive shock).
- Other signs and symptoms include blood pressure asymmetry, stroke, or paraplegia, depending on the vessels and structures involved (subclavian artery, carotid artery, spinal arteries).
- Aortic rupture with fatal hemorrhage.

Acute aortic dissection	
Clinical features	• History of HTN, Marfan syndrome, or cocaine use • Severe, sharp, tearing chest or back pain • >20 mm Hg variation in SBP between arms
Complications due to extension (involved structure)	• Stroke (carotid artery) • Acute aortic regurgitation (aortic valve) • Myocardial ischemia/infarction (coronary artery ostia) • Pericardial effusion/tamponade (pericardium) • Renal injury, abdominal pain (renal, mesenteric arteries) • Lower-extremity paraplegia (spinal arteries)

HTN = hypertension; **SBP** = systolic blood pressure.

Aortic aneurysm

- Localized pathologic dilatation of the aorta.

Thoracic aortic aneurysm

- Balloon-like dilation of the thoracic aorta due to weakness in the aortic wall.

- Risk Factors:

- Risk factors include hypertension, bicuspid aortic valve, connective tissue disease (Marfan syndrome).

- Associated with cystic medial degeneration.

- Also associated with tertiary syphilis. The pathogenesis of such an aneurysm begins with vasa vasorum endarteritis and obliteration, resulting in inflammation, ischemia, and weakening of the aortic adventitia. FTA-ABS is a test specific for syphilis.

- Presentation:

- The most common symptomatic presentation of TAA is pain, which is typically localized to the chest and back.

- Chest x-ray may suggest the diagnosis of TAA, demonstrating a widened mediastinum, enlarged aortic knob, and tracheal deviation.

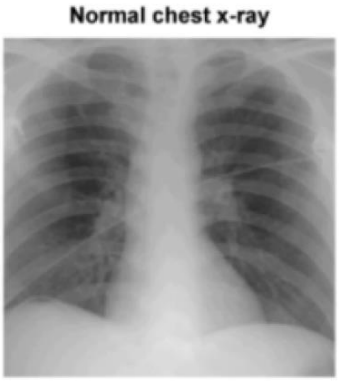
- Complication:

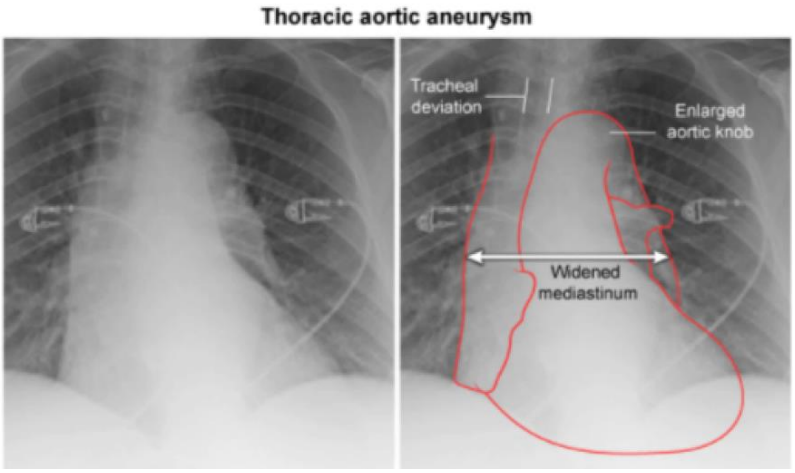
- Major complication is dilation of the aortic valve root, resulting in aortic valve regurgitation.

- Other complications include compression of mediastinal structures (airway or esophagus) and thrombosis/embolism.

- If the TAA impinges upon the esophagus, it can also cause dysphagia. Similarly, compression of the left recurrent laryngeal nerve or left vagus nerve results in hoarseness, whereas compression of the phrenic nerve can cause hemidiaphragmatic paralysis.

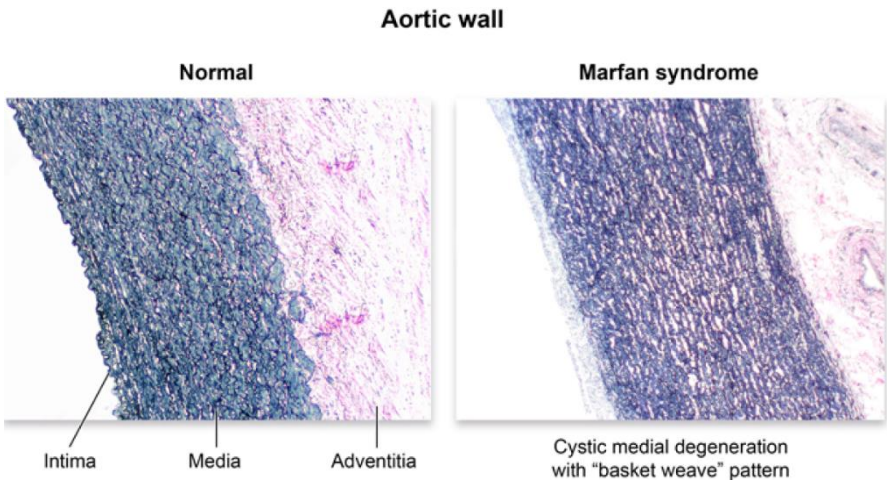
- Respiratory manifestations, including wheeze, cough, hemoptysis, and dyspnea may occur due to tracheobronchial obstruction.





❖ N.B:

- Myxomatous changes with pooling of proteoglycans in the media layer of large arteries are found in cystic medial degeneration, which predisposes to the development of aortic dissections and aortic aneurysms.
- Medial degeneration is frequently seen in younger individuals with Marfan syndrome.
- Medial degeneration is characterized by the fragmentation of elastic tissue ("basket weave" pattern, compared to normal) and separation of the elastic and fibromuscular components of the tunica media by small, cleft-like spaces that become filled with amorphous extracellular matrix (white arrow).
- β-aminopropionitrile (a chemical found in certain kinds of sweet peas) causes inhibition of lysyl oxidase, an enzyme responsible for cross-linking elastin fibers and collagen fibers.
- Ingestion of this compound can cause a change in the elasticity of the aorta that mimics the myxomatous degeneration seen in patients with Marfan syndrome.



Abdominal aortic aneurysm

- Balloon-like dilation of the abdominal aorta; usually arises below the renal arteries, but above the aortic bifurcation.

- Risk Factors:

- Primarily due to atherosclerosis; classically seen in male smokers > 60 years old with hypertension.

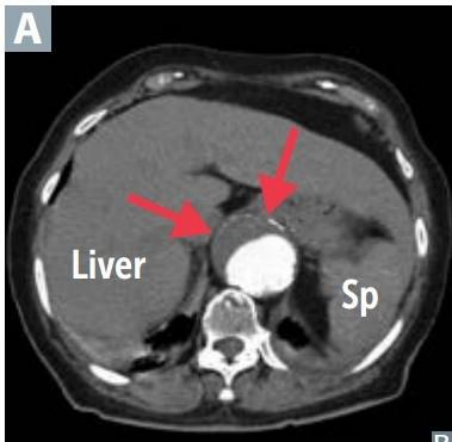
- Atherosclerosis increases the diffusion barrier to the media, resulting in atrophy and weakness of the vessel wall.

- AAAs are characterized by chronic transmural inflammation of the aortic wall.

- Presentation:

- Presents as a pulsatile abdominal mass that grows with time.

- Arrows in A point to outer dilated calcified aortic wall, with partial crescent-shaped non-opacification of aorta due to flap/clot



- Major complication is rupture, especially when > 5 cm in diameter; presents with triad of hypotension, pulsatile abdominal mass, and flank pain

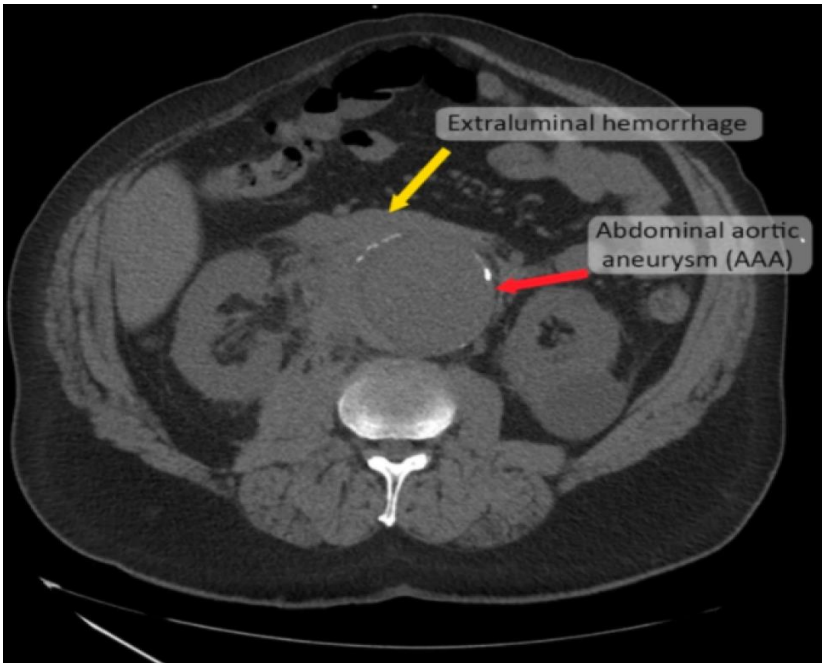
- Other complications include compression of local structures (ureter) and thrombosis/embolism.

❖ N.B:

- Early detection of AAA can be difficult because patients frequently have few symptoms until the AAA either ruptures or markedly expands. Therefore, ruptured AAA should be suspected in patients with consistent symptoms and known risk factors, which include advanced age (>60), smoking, male sex, and a history of atherosclerosis or connective tissue disease.
- Ruptured abdominal aortic aneurysm (AAA) is a surgical emergency involving full-thickness compromise of the aortic wall with extravasation of blood into surrounding tissues and spaces.
- The acute onset of severe abdominal and back pain is the most common presenting symptom. In general, anterior rupture into the peritoneal cavity is quickly accompanied by syncope, hypotension,

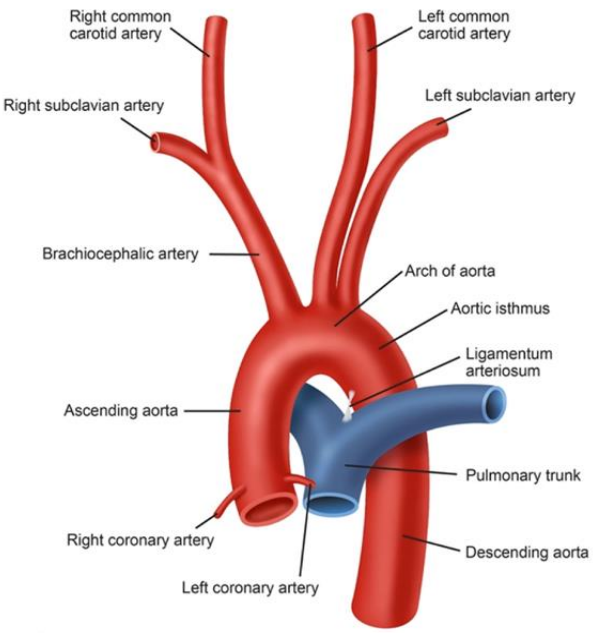
and shock, whereas posterior rupture into the retroperitoneum may be temporarily contained, resulting in delayed onset of hemodynamic instability.

- Other signs suggesting AAA rupture include abdominal distension, a pulsatile abdominal mass, and umbilical or flank hematoma (indicators of retroperitoneal hemorrhage).
- CT imaging can confirm the diagnosis, but hemodynamically unstable patients with suspected ruptured AAA should go straight to emergent surgical repair.



Traumatic aortic rupture

- Due to trauma and/or deceleration injury, most commonly at aortic isthmus (proximal descending aorta just distal to origin of left subclavian artery).



Subclavian steal syndrome

- Stenosis of subclavian artery proximal to origin of vertebral artery due to arteriosclerosis, Takayasu arteritis, heart surgery.

- An arteriosclerotic stenotic plaque at the origin of the subclavian (proximal to the take-off of the vertebral arteries) allows enough blood supply to reach the arm for normal activity but does not allow enough to meet higher demands when the arm is exercised.

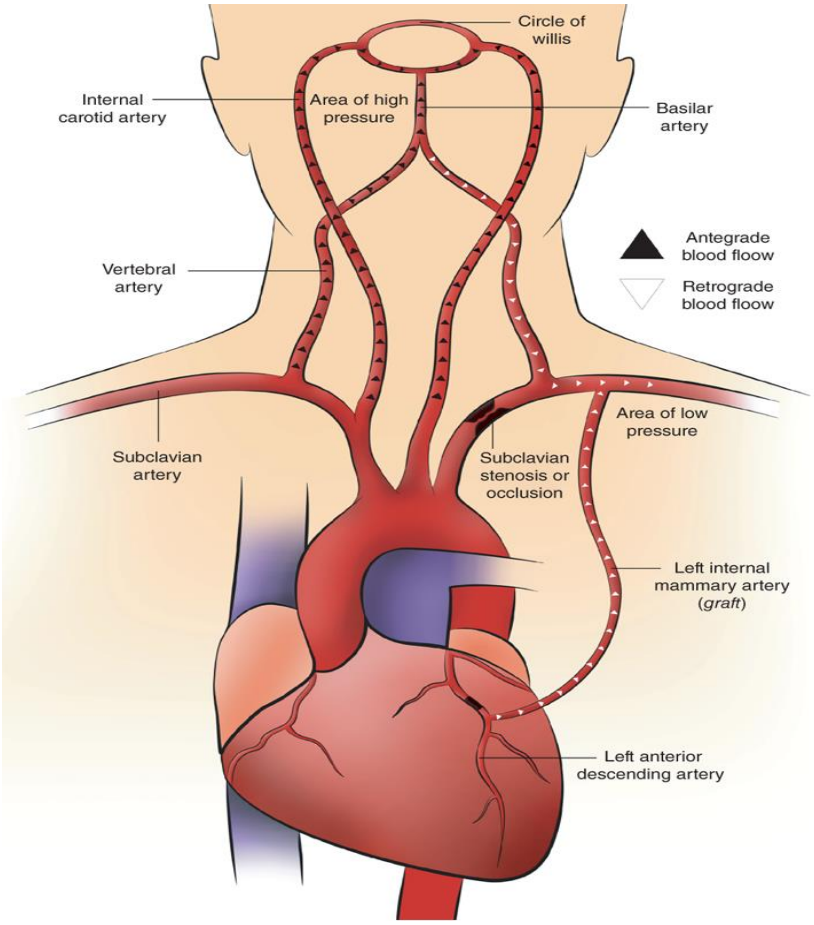
- When that happens, the arm sucks blood away from the brain by reversing the flow in the vertebral.

- Clinically the patient describes claudication of the arm (coldness, tingling, muscle pain) and posterior neurologic signs (visual symptoms, equilibrium problems) when the arm is exercised. >15 mmHg difference in systolic BP between arms.

- Vascular symptoms alone would suggest thoracic outlet syndrome, but the combination with neurologic symptoms identifies the subclavian steal.

- Duplex scanning is diagnostic when it shows reversal of flow.

- Bypass surgery is curative.



Ischemic heart disease (IHD)

- Group of syndromes related to myocardial ischemia; IHD is the leading cause of death in the US.
- Usually due to atherosclerosis of coronary arteries, which decreases blood flow to the myocardium.
- Risk factors for IHD are similar to those of atherosclerosis; incidence increases with age.

Angina

A. Stable angina:

- Chest pain that arises with exertion or emotional stress.
- Due to atherosclerosis of coronary arteries with > 70% stenosis; decreased blood flow is not able to meet the metabolic demands of the myocardium during exertion.
- Represents reversible injury to myocytes (no necrosis).
- Presents as chest pain (lasting < 20 minutes) that radiates to the left arm or jaw, diaphoresis, and shortness of breath.
- EKG shows ST-segment depression due to subendocardial ischemia.
- Relieved by rest or nitroglycerin.

B. Unstable angina:

- Chest pain that occurs at rest.
- Usually due to rupture of an atherosclerotic plaque with thrombosis and incomplete occlusion of a coronary artery.
- Represents reversible injury to myocytes (no necrosis).
- EKG shows ST-segment depression due to subendocardial ischemia but no cardiac biomarker elevation (unlike NSTEMI).
- Relieved by nitroglycerin.
- High risk of progression to myocardial infarction.

C. Variant (Prinzmetal) angina:

- Episodic chest pain unrelated to exertion.
- It is caused by temporary spasm of the coronary arteries, as opposed to atherosclerotic narrowing which is seen in myocardial infarction.
- Young women are classically affected, and the greatest risk factor for variant angina is smoking. Aside from smoking, there is often an absence of cardiovascular risk factors.
- Represents reversible injury to myocytes (no necrosis).
- Known triggers include tobacco, cocaine, and triptans, but trigger is often unknown.
- EKG shows ST-segment elevation due to transmural ischemia.
- Relieved by nitroglycerin or calcium channel blockers and smoking cessation (if applicable). These medications work in variant angina by promoting vasodilation and preventing vasoconstriction.
- In prinzmetal angina there is coronary vasospasm which further can be aggravated by beta blockers because by blocking beta receptors, alpha receptors on the vasculature are left unopposed → aggravating the vasospasm.
- The ergonovine test is the most sensitive provocative diagnostic test for coronary vasospasm.
- Ergonovine is an ergot alkaloid that constricts vascular smooth muscle by stimulating both alpha adrenergic and serotonergic receptors.
- In patients with hypercontractile coronary artery segments (as in Prinzmetal's angina), low doses of ergonovine induce coronary spasm, chest pain, and ST-segment elevation.

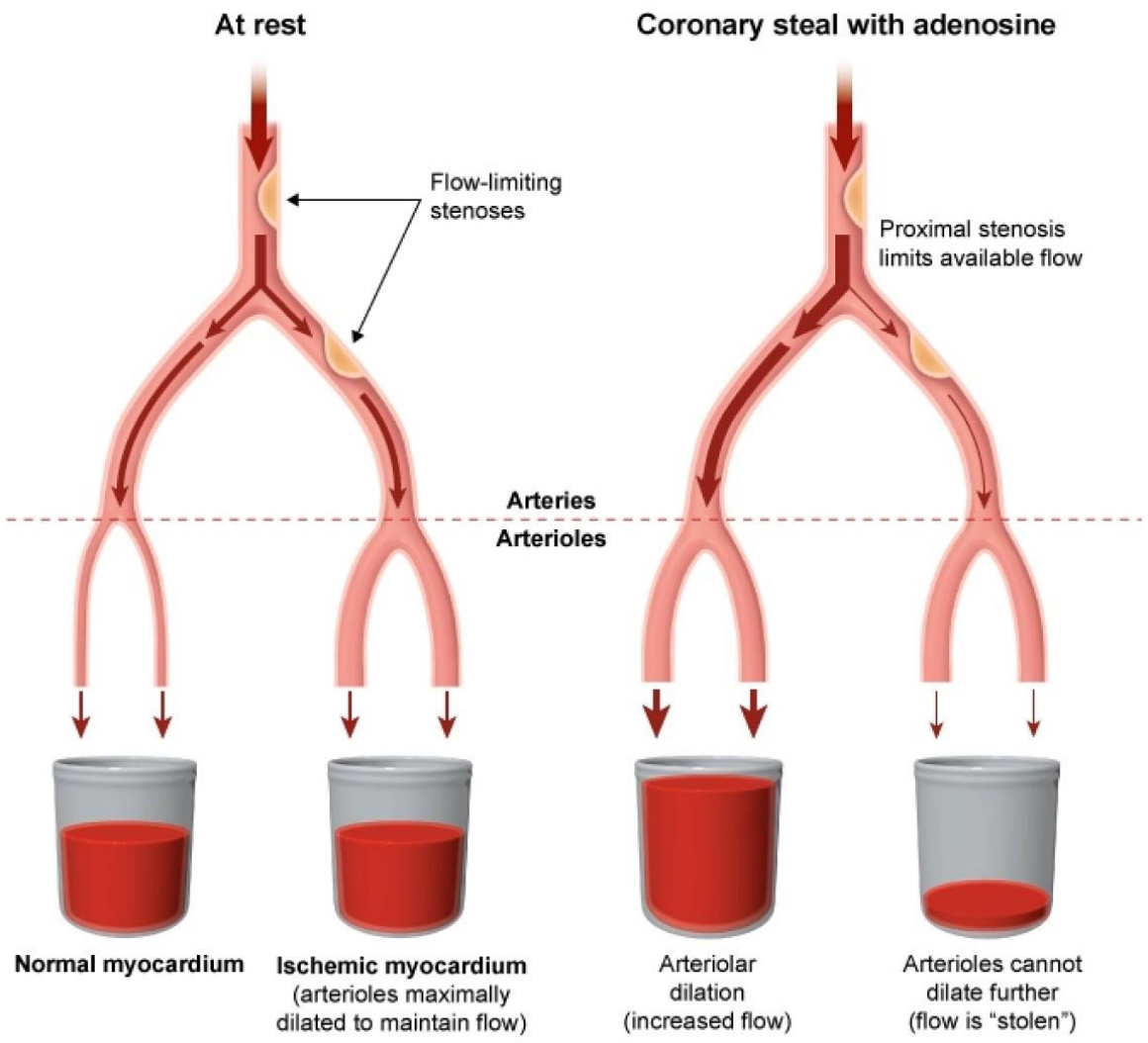
Coronary steal syndrome

- In coronary artery disease, coronary vessel occlusion can be bypassed by the natural existence and compensatory recruitment of collateral vessels that help support blood flow.
- These collateral microvessels from a network of passageways between major vessels allowing supplemental blood flow to myocardium distal to an occluded vessel.
- In the presence of myocardial ischemia, coronary arterioles vasodilate in response to local mediators, diverting collateral blood flow to ischemic areas. Thus, collateral circulation helps to alleviate ischemia and preserve myocardial function.
- Drugs such as adenosine and dipyridamole are selective vasodilators of coronary vessels.

- Use of these drugs causes vasodilation of coronary arterioles in nonischemic regions. This leads to decreased perfusion pressure within the collateral microvessels supplying the ischemic myocardium, diverting blood flow from ischemic areas to nonischemic areas.

- This phenomenon, known as coronary steal, may lead to hypoperfusion and potential worsening of existing ischemia.

- Principle behind pharmacologic stress tests with coronary vasodilators.



Myocardial infarction

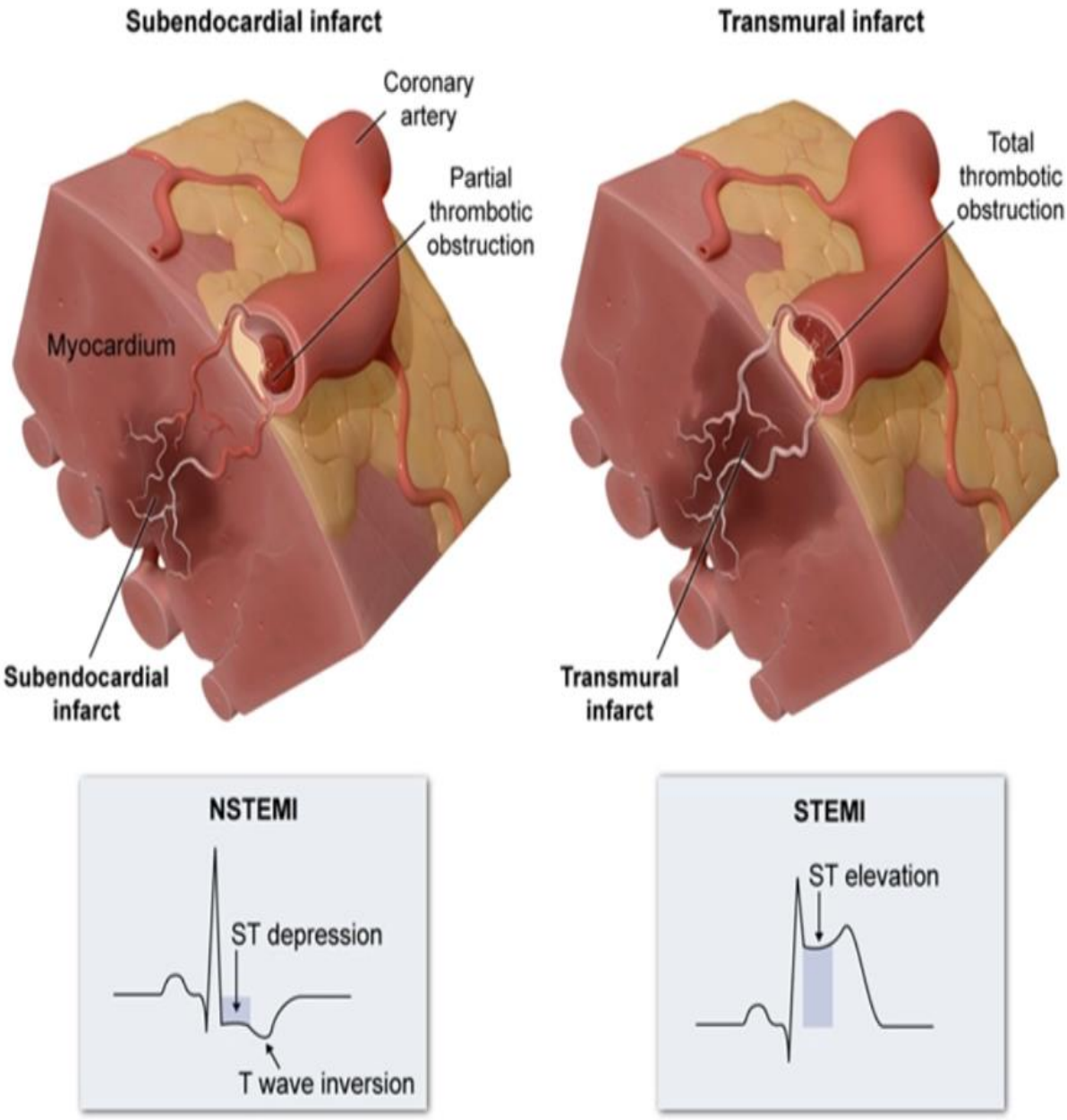
- Necrosis of cardiac myocytes.
- Usually due to rupture of an atherosclerotic plaque with thrombosis and complete occlusion of a coronary artery.
- Other causes include coronary artery vasospasm (due to Prinzmetal angina or cocaine use), emboli, and vasculitis (Kawasaki disease).
- Clinical features include severe, crushing chest pain (lasting > 20 minutes) that radiates to the left arm or jaw, diaphoresis, and dyspnea; symptoms are not relieved by nitroglycerin.
- Infarction usually involves the left ventricle (LV); right ventricle (RV) and both atria are generally spared.
- Occlusion of left anterior descending artery (LAD) leads to infarction of the anterior wall and anterior septum of the LV; LAD is the most commonly involved artery in MI (45% of cases).
- Occlusion of right coronary artery (RCA) leads to infarction of the posterior wall, posterior septum; RCA is the 2nd most commonly involved artery in MI.
- Occlusion of left circumflex artery leads to infarction of lateral wall of the LV.
- Laboratory tests detect elevated cardiac enzymes.

A. ST-segment elevation MI (STEMI):

- Transmural infarcts.
- Full thickness of myocardial wall involved.
- ST elevation on ECG, Q waves.

B. Non-ST segment elevation MI (NSTEMI):

- Subendocardial infarcts.
- Subendocardium (inner 1⁄3) especially vulnerable to ischemia.
- ST depression on ECG.



- Treatment includes:

- Antiplatelet therapy (aspirin + ADP receptor inhibitors; clopidogrel) or heparin: limits thrombosis.
- Supplemental O_2 minimizes ischemia.
- Nitrates: vasodilate coronary arteries.
- β-blocker: slows heart rate, decreasing O_2 demand and risk tor arrhythmia.
- ACE inhibitor: decreases LV dilation.

- Fibrinolysis or angioplasty → opens blocked vessel:
  - Reperfusion of irreversibly damaged cells results in calcium influx, leading to hypercontraction of myofibrils (contraction band necrosis).
  - Return of oxygen and inflammatory cells may lead to free radical generation, further damaging myocytes (reperfusion injury).

❖ N.B:

1. Ischemia is characterized by the reduction of blood flow, usually as a result of mechanical obstruction within the arterial system (thrombus).
   - If the flow of blood to the ischemic tissue is restored in a timely manner, those cells that were reversibly injured will typically recover.
   - Sometimes, however, the cells within the damaged tissue will paradoxically die at an accelerated pace through apoptosis or necrosis after resumption of blood flow.
   - This process is termed reperfusion injury, and is thought to occur secondary to oxygen free radical generation, mitochondrial damage, and inflammation.
   - When the cells within heart, brain, or skeletal muscle are injured, the enzyme creatine kinase leaks across the damaged cell membrane and into circulation.

2. A stable atheromatous lesion without an overlying thrombus, but obstructing greater than 70% of the coronary artery lumen, would likely cause only stable angina.
   - A lesser degree of occlusion by a thrombus superimposed on an acute plaque change would more likely cause unstable angina.
   - An acute transmural myocardial infarction marked by ST-elevation and subsequent Q-wave formation is most likely the result of a fully obstructive thrombus superimposed on a ruptured atherosclerotic coronary artery plaque.

3. Costosternal syndrome (also known as costochondritis or anterior chest wall syndrome) usually occurs after repetitive activity and involves the upper costal cartilage at the costochondral or costosternal junctions.
   - The pain is typically reproduced with palpation and worsened with movement or changes in position.

Evolution of myocardial infarction

- Commonly occluded coronary arteries: LAD > RCA > circumflex.

- Symptoms: diaphoresis, nausea, vomiting, severe retrosternal pain, pain in left arm and/or jaw, shortness of breath, fatigue.

A. < 4 hours:

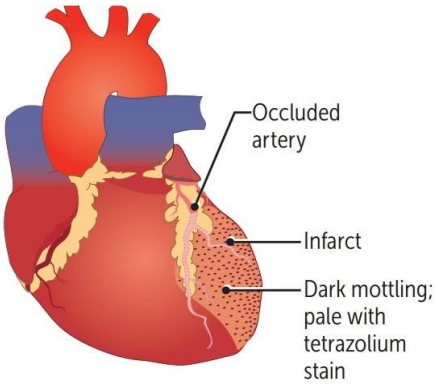
- Gross changes: None.

- Microscopic changes: None (Normal myocardium).

- Complications: Cardiogenic shock (massive infarction), congestive heart failure, and arrhythmia.

B. 4-24 hours:

- Gross changes:

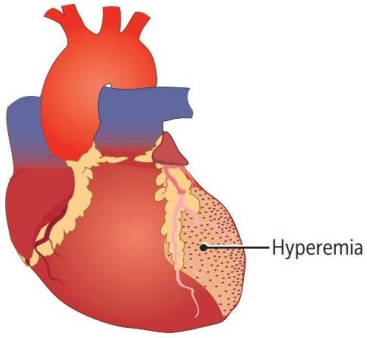


- Microscopic changes:
  - Early coagulative necrosis, release of necrotic cell contents into blood; edema, hemorrhage, wavy fibers.
  - Early signs of coagulative necrosis do not become apparent on light microscopy until 4 hours after the onset of MI.
  - Reperfusion injury, associated with generation of free radicals, leads to hypercontraction of myofibrils through ↑ free calcium influx.

- Complications: Arrhythmia is an important cause of death before reaching the hospital and within the first 24 hours post-MI.

C. 1-3 Days:

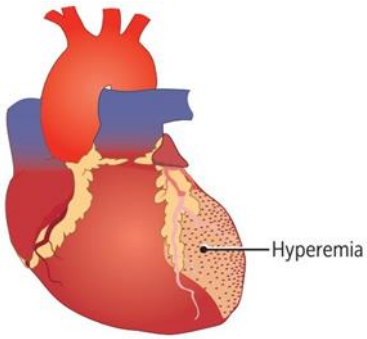
- Gross changes:



- Microscopic changes:
  - Extensive coagulative necrosis.
  - Tissue surrounding infarct shows acute inflammation with neutrophils.
- Complications: Postinfarction fibrinous pericarditis (transmural infarction).

D. 4-7 Days:

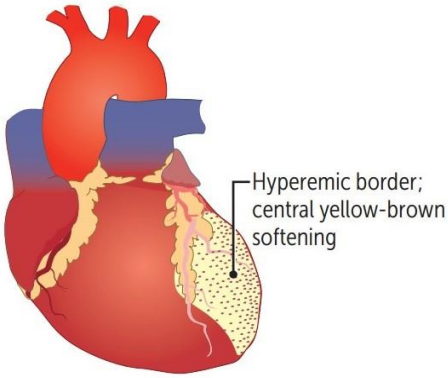
- Gross changes:



- Microscopic changes: robust phagocytosis of dead cells by macrophages.
- Complications:
  - Free wall rupture → cardiac tamponade. Ventricular free wall rupture is a complication of transmural (ST-elevation) myocardial infarction (MI) that generally occurs 3 to 7 days after the onset of total ischemia, when coagulative necrosis, neutrophil infiltration, and enzymatic lysis of connective tissue have substantially weakened the infarcted myocardium. Free wall rupture causes cardiac tamponade, which greatly limits ventricular filling during diastole.
  - Papillary muscle rupture → mitral regurgitation.
  - Interventricular septal rupture due to macrophage-mediated structural degradation → VSD.

E. 1-2 Weeks:

- Gross changes:

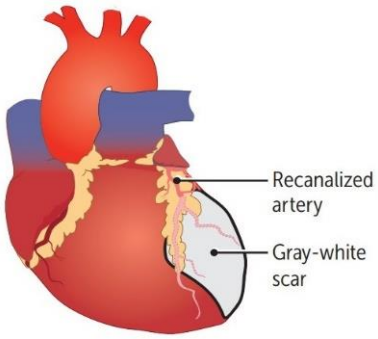


- Microscopic changes:
  - Well-developed granulation tissue with neovascularization.
  - During the second week after MI, the damaged tissue is replaced by granulation tissue and neovascularization is found in the infarct zone.

- Complcations:
  - Free wall rupture → cardiac tamponade; papillary muscle rupture → mitral regurgitation; interventricular septal rupture due to macrophage-mediated structural degradation → VSD.

F. 2 Weeks to several months:

- Gross changes:



- Microscopic changes: progressive collagen deposition and scar formation.

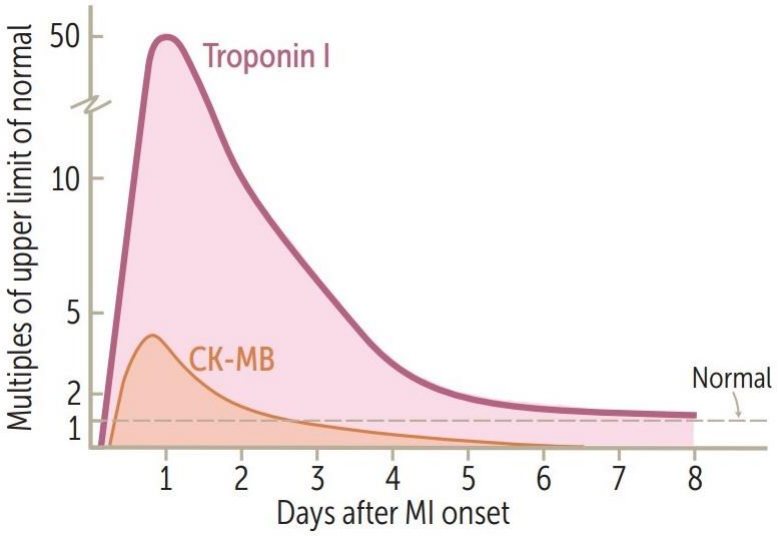
- Complications:
  - Aneurysm [Outward bulge with contraction ("dyskinesia"), associated with fibrosis].
  - Mural thrombus.
  - Dressler syndrome (autoimmune inflammatory reaction to myocardial neo-antigens formed as a result of the MI → autoimmune pericarditis; it takes weeks for antibodies to develop Vs. post-infarction fibrinous pericarditis).

❖ N.B:

- In contrast to angina, the chest pain of pericarditis is sharp and pleuritic, and may be exacerbated by inspiration and swallowing or relieved by leaning forward.
- Early-onset pericarditis develops in about 10-20% of patients between days 2 and 4 following a transmural myocardial infarction.
- It represents an inflammatory reaction to cardiac muscle necrosis that occurs in the adjacent visceral and parietal pericardium.
- Late-onset post-myocardial infarction (MI) pericarditis (Dressler's syndrome) begins one week to a few months following the MI, and affects less than 4% of cases. Dressler's syndrome is thought to be an autoimmune polyserositis.

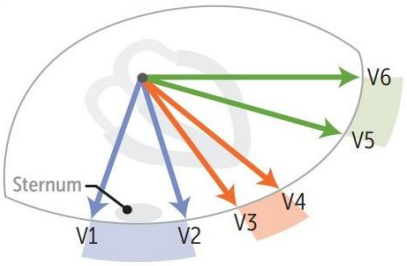
Diagnosis of myocardial infarction

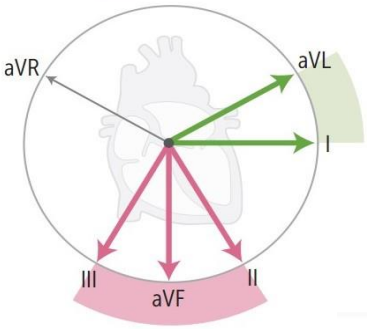
- In the first 6 hours, ECG is the gold standard.
- Cardiac troponin I rises after 4 hours (peaks at 24 hr) and is ↑ for 7–10 days; more specific than other protein markers.
- CK-MB rises after 6-12 hours (peaks at 16–24 hr) and is predominantly found in myocardium but can also be released from skeletal muscle. Useful in diagnosing reinfarction following acute MI because levels return to normal after 48 hours.
- Large MIs lead to greater elevations in troponin I and CK-MB.
- ECG changes can include ST elevation (STEMI, transmural infarct), ST depression (NSTEMI, subendocardial infarct), hyperacute (peaked) T waves, T-wave inversion, new left bundle branch block, and pathologic Q waves or poor R wave progression (evolving or old transmural infarct).

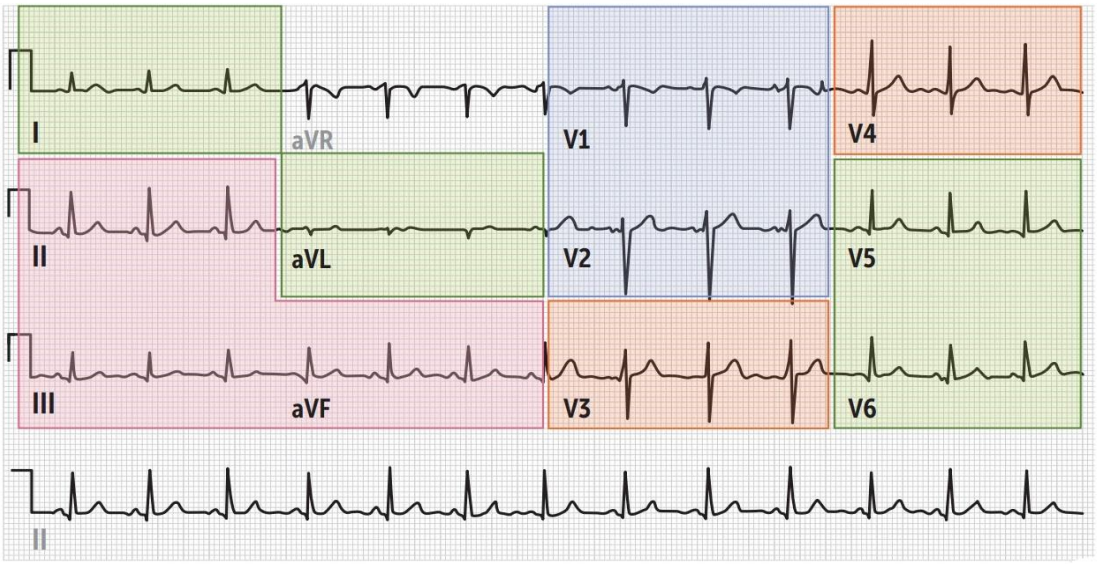


ECG localization of STEMI

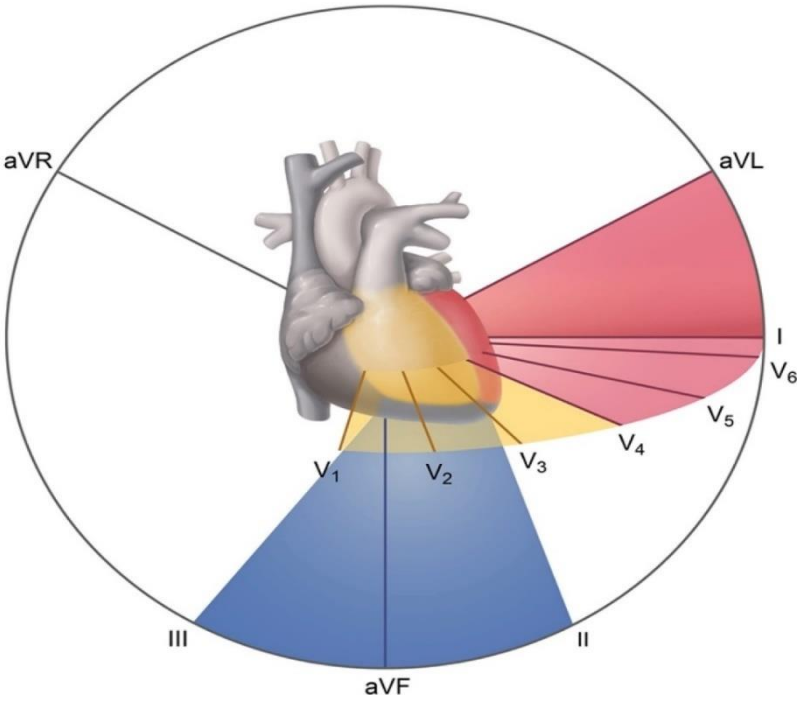
INFARCT LOCATION	LEADS WITH ST-SEGMENT ELEVATIONS OR Q WAVES
Anteroseptal (LAD)	V_1–V_2
Anteroapical (distal LAD)	V_3–V_4
Anterolateral (LAD or LCX)	V_5–V_6
Lateral (LCX)	I, aVL
InFerior (RCA)	II, III, aVF
Posterior (PDA)	V_7–V_9, ST depression in V_1–V_3 with tall R waves







ECG infarct localization



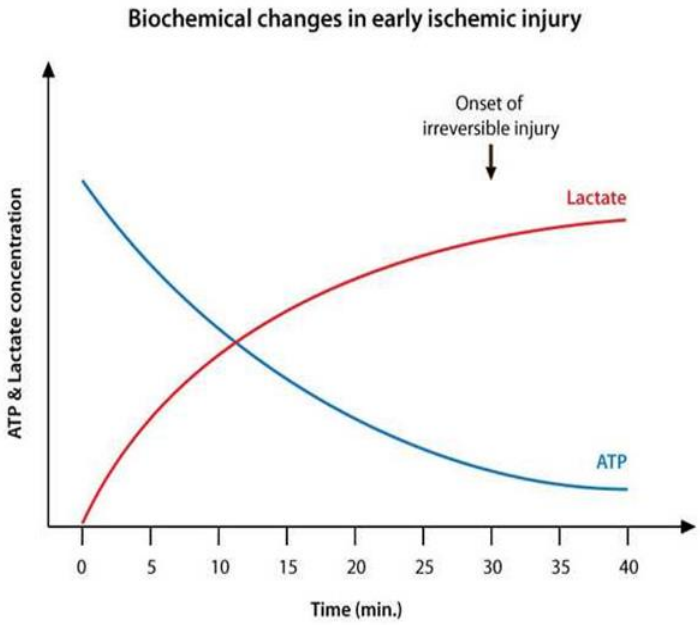
❖ N.B:

1. Repetitive ischemia of cardiac myocytes or persistent hypoperfusion of myocytes can result in a chronic but reversible loss of contractile function, referred to as "hibernation."

- In hibernating myocardium, myocardial energy metabolism is reduced but there is sufficient ATP to prevent contracture.
- The syndrome of cardiac muscle hibernation can be reversed by revascularization with CABG surgery or balloon angioplasty.
- Myocardial stunning is a less severe form of ischemia-induced reversible loss of contractile function.
- Repetitive stunning can result in hibernation.

2. Loss of cardiomyocyte contractility occurs within 60 seconds after the onset of total ischemia.

- When ischemia lasts less than 30 minutes, restoration of blood flow leads to reversible contractile dysfunction (myocardial stunning), with contractility gradually returning to normal over the next several hours to days.
- However, after about 30 minutes of total ischemia, ischemic injury becomes irreversible.



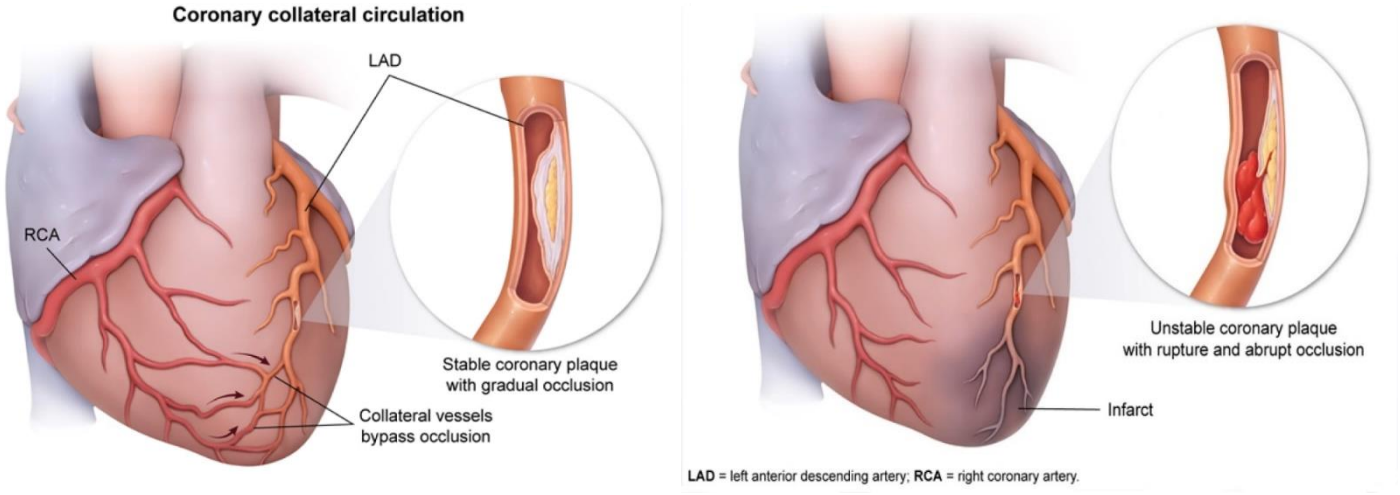
3. When blood flow cannot meet myocardial demands, cardiac myocytes transition from aerobic to anaerobic metabolism.

- However, anaerobic metabolism cannot maintain proper intracellular ATP levels, and ADP, AMP and adenosine accumulate.
- Without ATP, the membrane Na-K-ATPases and the sarcoplasmic reticulum Ca-ATPases fail, leading to increased intracellular Na and Ca and increased intramitochondrial Ca concentrations.
- The increased intracellular solute concentration draws free water into the cell, causing the cellular and mitochondrial swelling that is observed histologically in cases of cardiac ischemia.
- Simple mitochondrial swelling is associated with reversible cellular injury, however. Mitochondrial vacuolization is typically a sign of irreversible cell injury, signifying that the involved mitochondria are permanently unable to generate ATP.
- When the mitochondria are injured irreversibly, the cell cannot recover.

4. The major determinant of whether or not a coronary artery plaque will cause ischemic myocardial injury is the rate of growth at which it occludes the involved artery.
- A slowly developing occlusion would allow for formation of collaterals that could prevent myocardial necrosis.
- A thin fibrous cap, a rich lipid core, and active inflammation in the atheroma would all decrease plaque stability and thus potentially promote rapid coronary occlusion via superimposed thrombosis if the plaque were to rupture.

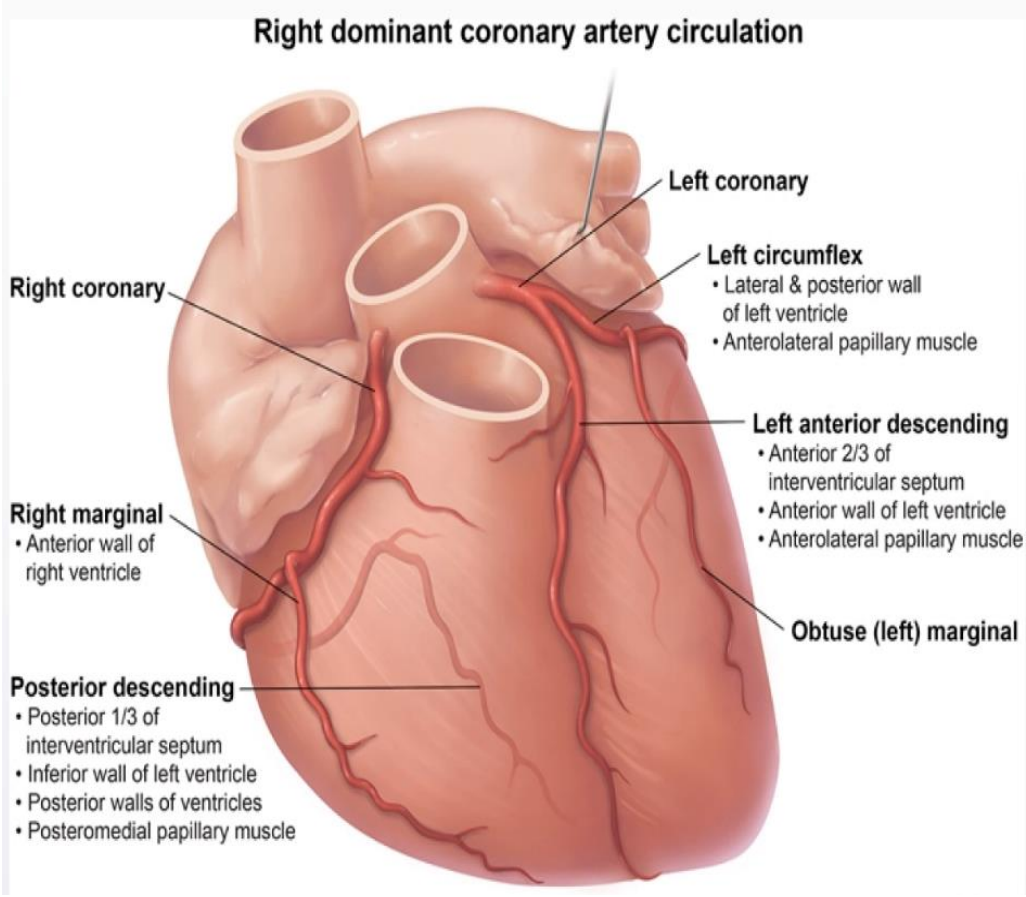
5. In 90% of individuals occlusion of the right coronary artery can result in transmural ischemia of the inferior wall of the left ventricle, producing ST elevation in leads II, III, and aVF as well as possible sinus node dysfunction → Bradycardia.

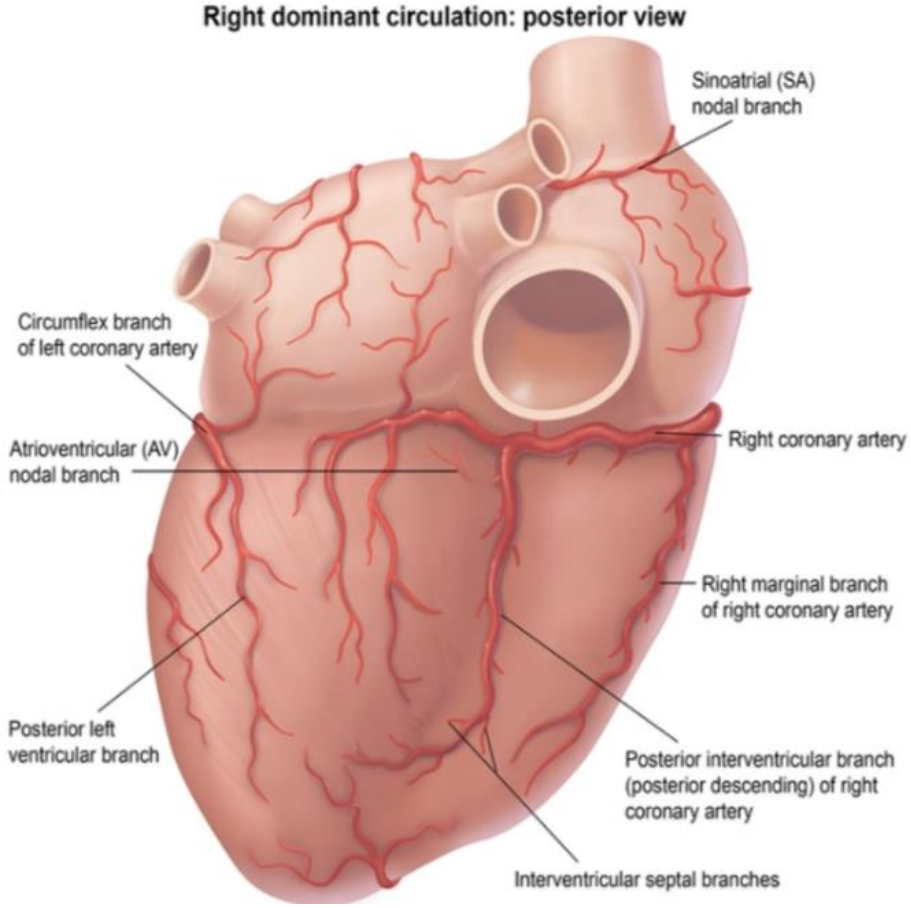
6. Leads I and aVL corresponds to the lateral limb leads on ECG. Therefor, ST elevation or Q waves in these leads are indicative of infarction involving the lateral aspect of the left ventricle, which is supplied by the left circumflex artery.



7. Papillary muscle rupture is a life-threatening complication that typically occurs 3-5 days after myocardial infarction and presents with acute mitral regurgitation and pulmonary edema. The posteromedial papillary muscle is supplied solely by the posterior descending artery, making it susceptible to ischemic rupture.

8. The inferior wall of the left ventricle (LV) is supplied by the posterior descending artery, which arises off the dominant right coronary artery.
- Because the right coronary artery also gives off marginal branches that supply most of the right ventricle (RV), inferior wall myocardial infarction is often associated with right ventricular infarction.
- Right-sided heart failure typically presents with hypotension and distended jugular veins, but the lungs are clear unless significant left-sided heart failure is also present.
- Right ventricular infarction decreases RV stroke volume, which in turn leads to diminished LV filling and cardiac output despite preserved LV systolic function, resulting in hypotension and shock.
- Because left¬sided filling pressures are reduced, pulmonary capillary wedge pressure (PCWP) also decreases as it reflects left atrial pressure.
- In addition, patients have elevated central venous pressure due to impaired forward flow and backup of blood into the systemic venous system.


Right dominant coronary artery circulation
Left coronary
Left circumflex
• Lateral & posterior wall of left ventricle
• Anterolateral papillary muscle
Right coronary
Left anterior descending
• Anterior 2/3 of interventricular septum
• Anterior wall of left ventricle
• Anterolateral papillary muscle
Right marginal
• Anterior wall of right ventricle
Obtuse (left) marginal
Posterior descending
• Posterior 1/3 of interventricular septum
• Inferior wall of left ventricle
• Posterior walls of ventricles
• Posteromedial papillary muscle


Right dominant circulation: posterior view
Sinoatrial (SA) nodal branch
Circumflex branch of left coronary artery
Atrioventricular (AV) nodal branch
Right coronary artery
Right marginal branch of right coronary artery
Posterior left ventricular branch
Posterior interventricular branch (posterior descending) of right coronary artery
Interventricular septal branches

Sudden cardiac death (SCD)

- Unexpected death due to cardiac disease; occurs without symptoms or < 1 hour after symptoms arise.
- Usually due to fatal ventricular arrhythmia.
- Associated with Coronary Artey Diseases (up to 70% of cases), cardiomyopathy (hypertrophic, dilated), and hereditary ion channelopathies (long QT syndrome, Brugada syndrome).
- In the majority of CAD-related SCD, the pathogenesis involves an acute plaque change resulting in acute myocardial ischemia. Ischemia then induces electrical instability in the heart, which can generate a potentially lethal arrhythmia.
- Ventricular fibrillation is usually the first arrhythmia to appear as the result of acute myocardial ischemia and is the most common cause of lethal cardiac arrest in CAD-related SCD.
- Prevent with implantable cardioverter-defibrillator (ICD).

Chronic ischemic heart disease

- Poor myocardial function due to chronic ischemic damage (with or without infarction); progresses to congestive heart failure (CHF)
- Progressive onset of HF over many years due to chronic ischemic myocardial damage.

Cardiomyopathies

- Group of myocardial diseases that result in cardiac dysfunction.

Dilated cardiomyopathy

- Dilation of all four chambers of the heart; most common form of cardiomyopathy.

- Often idiopathic or familial (due to mutation of TTN gene encoding the sarcomeric protein titin).

- Other causes include:
  - Myocarditis (usually due to coxsackie B): characterized by a lymphocytic infiltrate in the myocardium; Dilated cardiomyopathy is a late complication.
  - Thiamine deficiency (wet beriberi).
  - Chaga's disease.
  - Alcohol abuse.
  - Drugs (doxorubicin, cocaine).
  - Pregnancy (peripartum cardiomyopathy): seen during late pregnancy or soon (weeks to months) after childbirth.

- Results in systolic dysfunction (ventricles cannot pump), leading to biventricular CHF; complications include mitral and tricuspid valve regurgitation and arrhythmia.

- Findings:
  - HF, S3, systolic regurgitant murmur, dilated heart on echocardiogram, balloon appearance of heart on CXR.

- Treatment:
  - Na restriction, ACE inhibitors, β-blockers, diuretics, mineralocorticoid receptor blockers (spironolactone), digoxin, ICD, heart transplant.

Hypertrophic cardiomyopathy

- It is very important to distinguish between hypertrophic cardiomyopathy (HCM) and HOCM. HCM is a reaction to stressors on the heart such as increased blood pressure. The heart hypertrophies to carry the load, but then develops difficulty “relaxing” in diastole. If the heart can’t relax to receive blood, the patient becomes short of breath.

- Left ventricular hypertrophy leads to diastolic dysfunction (ventricle cannot fill).

- HOCM is a genetic disorder with an abnormal shape to the septum of the heart. The asymmetrically hypertrophied septum will literally form an anatomic obstruction between the septum and the valve leaflet to block blood leaving the heart.

- Most cases of HOCM are familial. The transmission is autosomal dominant with variable expression.

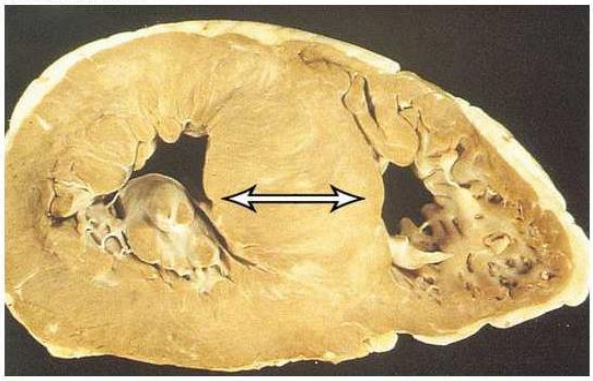
- The patient's autopsy would most likely reveal massive cardiac hypertrophy, especially of the interventricular septum.

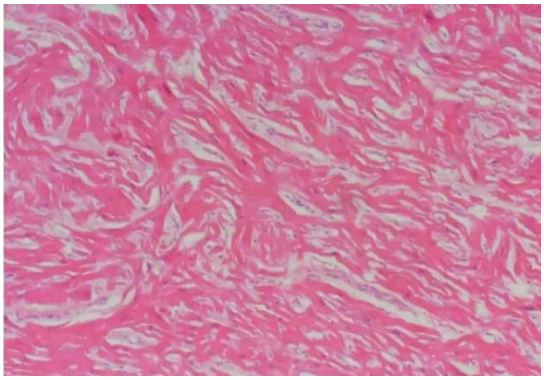
- Almost all cases of HCM are thought to be due to mutations in cardiac sarcomere proteins.

- Specifically, these are predominantly single point missense mutations in the genes for beta-myosin heavy chain and myosin binding protein C.

- Dynamic left ventricular outflow tract obstruction is due to abnormal systolic anterior motion of the anterior leaflet of the mitral valve toward a hypertrophied interventricular septum.

- Extreme myofiber disarray with interstitial fibrosis on cardiac histology strongly suggests hypertrophic cardiomyopathy (HCM).



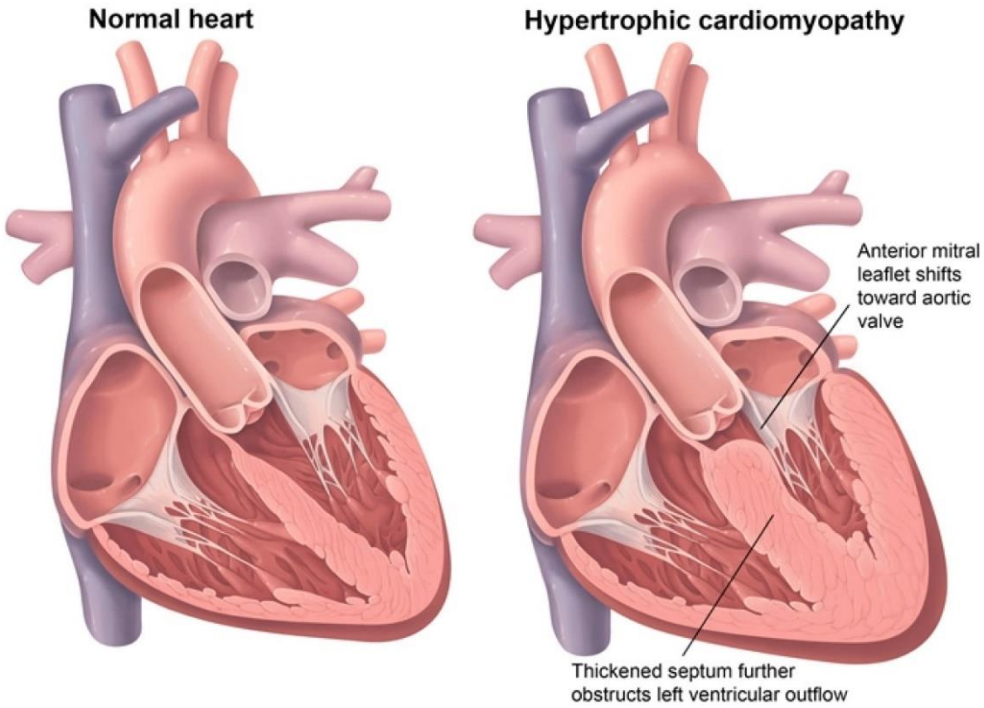


- <u>Clinical features include:</u>

- Syncope with exercise: Subaortic hypertrophy of the ventricular septum results in functional aortic stenosis.

- Hypertrophic obstructive cardiomyopathy (HOCM) is the most common cause of ventricular fibrillation (VF) or ventricular tachycardia that deteriorates to VF in individuals younger than 30 and the most common cause of sudden cardiac death in a young athlete.

- Sudden death in a previously asymptomatic, young, exercising individual should raise strong suspicions of hypertrophic obstructive cardiomyopathy (HOCM).



- Treatment:

- Cessation of high-intensity athletics, use of β-blocker or non-dihydropyridine Ca channel blockers (verapamil). They decrease heart rate and LV contractility to increase LV blood volume, reduce LV outflow tract obstruction, and improve symptoms.

- Therefore, medications that decrease venous return or systemic vascular resistance (dihydropyridine calcium channel blockers, nitroglycerin) should generally be avoided.

- ICD if syncope occurs.

Restrictive/infiltrative cardiomyopathy

- Decreased compliance of the ventricular endomyocardium that restricts filling during diastole.

- Diastolic dysfunction ensues.

- Causes:

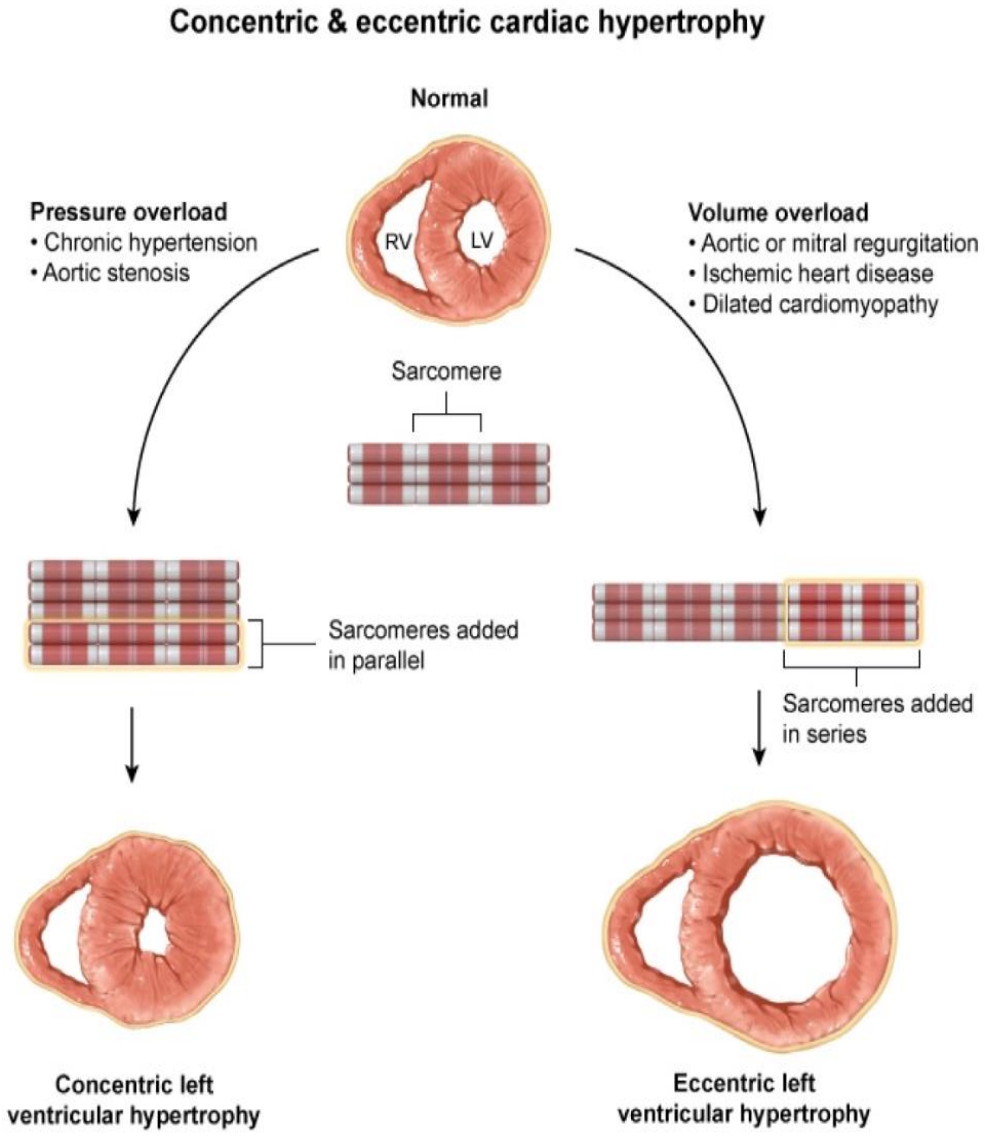
- Postradiation fibrosis, Löffler endocarditis (endomyocardial fibrosis with a prominent eosinophilic infiltrate), Endocardial fibroelastosis (thick fibroelastic tissue in endocardium of young children), Amyloidosis, Sarcoidosis, Hemochromatosis (although dilated cardiomyopathy is more common). Puppy LEASH.

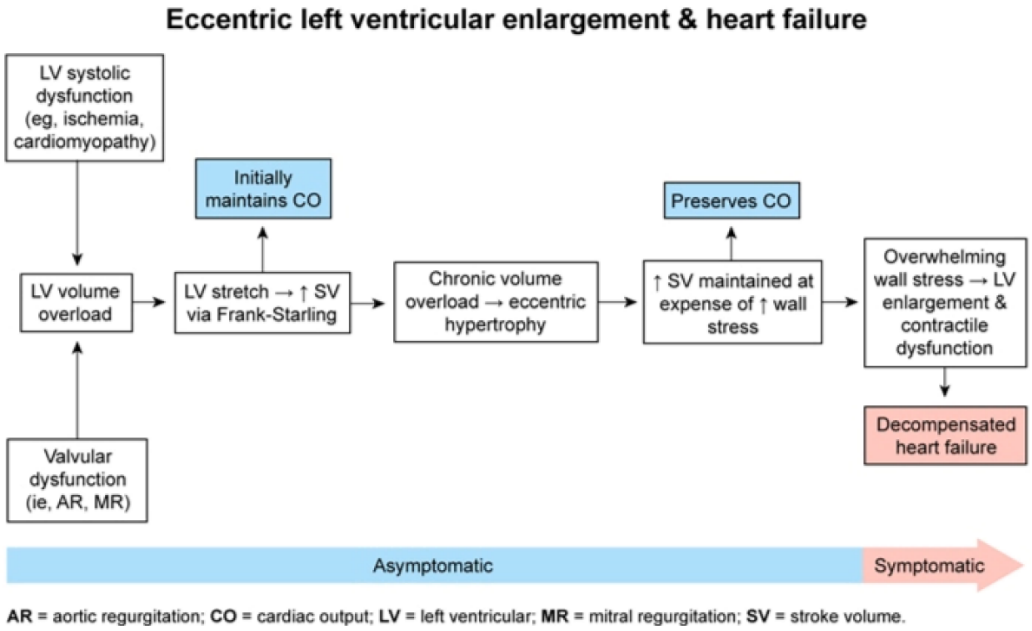
- Can have low-voltage ECG despite thick myocardium (especially in amyloidosis).

❖ N.B:

1. LV hypertrophy is generally defined as an increase in the left ventricular mass due to increased wall thickness (concentric) or cavity size (eccentric).

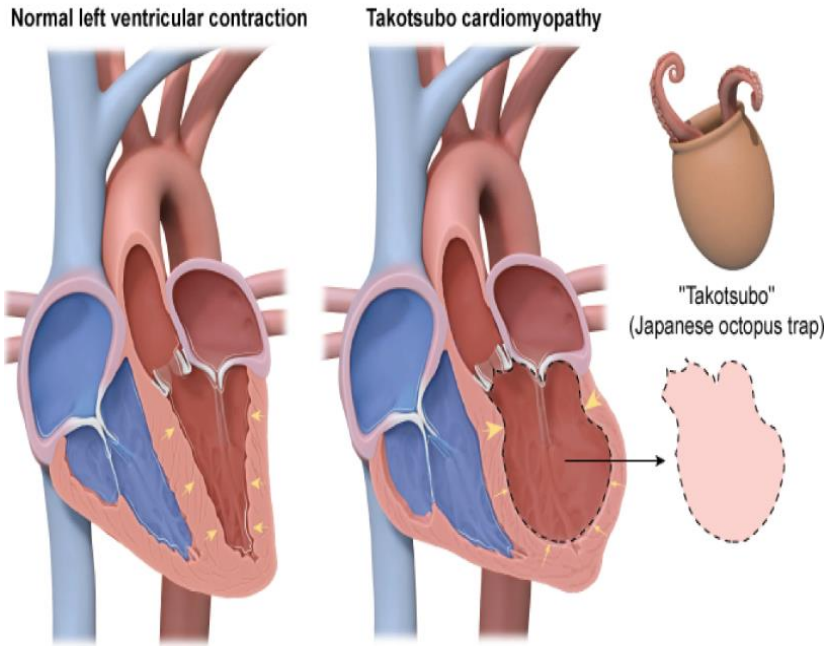
- Concentric hypertrophy is characterized by uniform thickening of the ventricular wall with the outer dimensions of the ventricle remaining almost unchanged, resulting in a narrowed ventricular cavity size.
- It is due to chronic elevation of ventricular pressures during systole, which is usually caused by long-standing hypertension or aortic stenosis (increased LV afterload).
- Eccentric hypertrophy results from the addition of myocardial contractile fibers in series in response to chronic volume overload. The adaptation allows the left ventricle to increase stroke volume and maintain cardiac output; however, LV wall stress increases, resulting in eventual decompensation and the development of heart failure.
- Common causes of eccentric hypertrophy include dilated cardiomyopathy, ischemic heart disease, and chronic aortic or mitral valve regurgitation.





2. Stress-induced (takotsubo) cardiomyopathy is characterized by hypokinesis of the mid and apical segments and hyperkinesis of the basal segments of the left ventricle, resulting in systolic dysfunction and reduced ejection fraction.

- The condition is likely caused by a surge of catecholamines in the setting of physical or emotional stress (death of a loved one).
- It usually affects postmenopausal women and resolves on its own within several weeks.
- The resulting segmental LV dysfunction creates a characteristic balloon shape on echocardiogram that mimics that of an octopus trap (takotsubo means "octopus trap" in Japanese).
- Patients typically have chest pain that can mimic a myocardial infarction and may also have symptoms of heart failure (dyspnea, lower extremity swelling).
- ECG often shows evidence of ischemia (ST elevation, T-wave inversion) in the anterior precordial leads; however, coronary angiography typically reveals an absence of obstructive coronary artery disease.
- The condition usually resolves within several weeks with supportive treatment only.



Heart failure

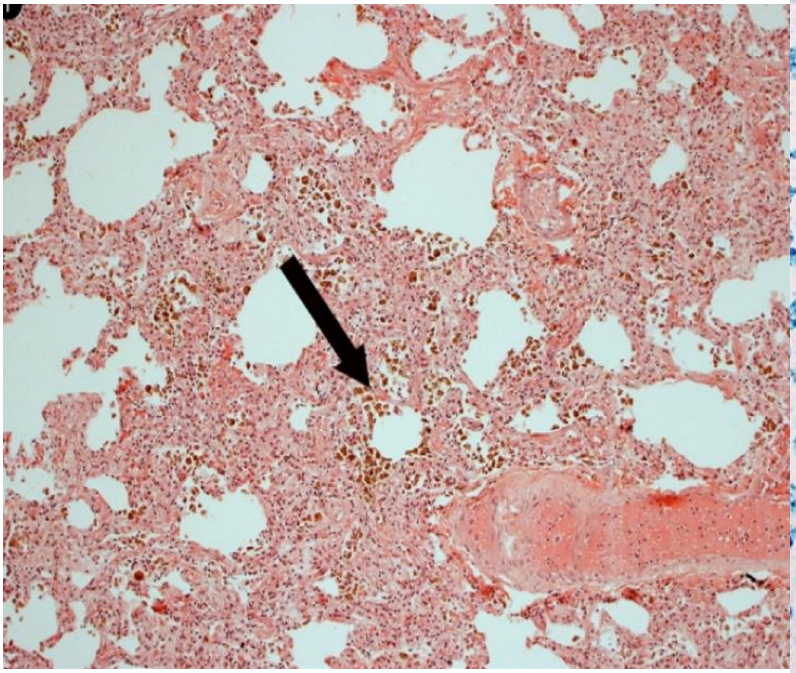
- Clinical syndrome of cardiac pump dysfunction → congestion and low perfusion.
- Systolic dysfunction: reduced EF, ↑ EDV; ↓ contractility often 2° to ischemia/MI or dilated cardiomyopathy.
- Diastolic dysfunction: preserved EF, normal EDV; ↓ compliance (↑ EDP) often 2° to myocardial hypertrophy.
- Treatment:

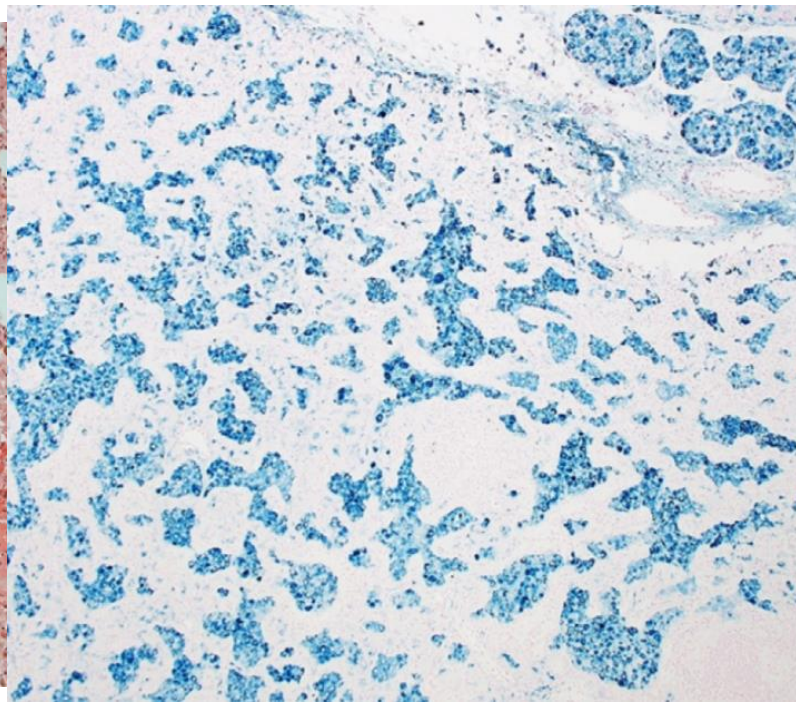
- ACE inhibitors or angiotensin II receptor blockers, β-blockers (except in acute decompensated HF), and spironolactone ↓ mortality.
- Thiazide or loop diuretics are used mainly for symptomatic relief.
- Hydralazine with nitrate therapy improves both symptoms and mortality in select patients.

A. Left-sided heart failure:

- Causes include ischemia, myocardial infarction, hypertension, dilated cardiomyopathy, , and restrictive cardiomyopathy.
- Clinical features are due to decreased forward perfusion and pulmonary congestion.
- Pulmonary congestion leads to pulmonary edema.
- Results in dyspnea, paroxysmal nocturnal dyspnea (due to increased venous return when lying flat), orthopnea, and crackles.
- Supine dyspnea that is relieved by sitting up, known as orthopnea, is a relatively specific sign of advanced left-sided heart failure.
- Small, congested capillaries may burst, leading to intraalveolar hemorrhage and the iron from hemoglobin is converted to hemosiderin; marked by hemosiderin-laden macrophages (heart-failure cells).
- Prussian blue stain detects intracellular iron. In the Prussian blue reaction, colorless potassium ferrocyanide is converted by iron to blue-black ferric ferrocyanide which is consistent with hemosiderin laden macrophages (siderophages).
- The presence of hemosiderin-laden macrophages in pulmonary alveoli indicates chronic elevation of pulmonary capillary hydrostatic pressures, most commonly as a result of left-sided heart failure.

- Decreased flow to kidneys leads to activation of renin-angiotensin system.
- Fluid retention exacerbates CHF.

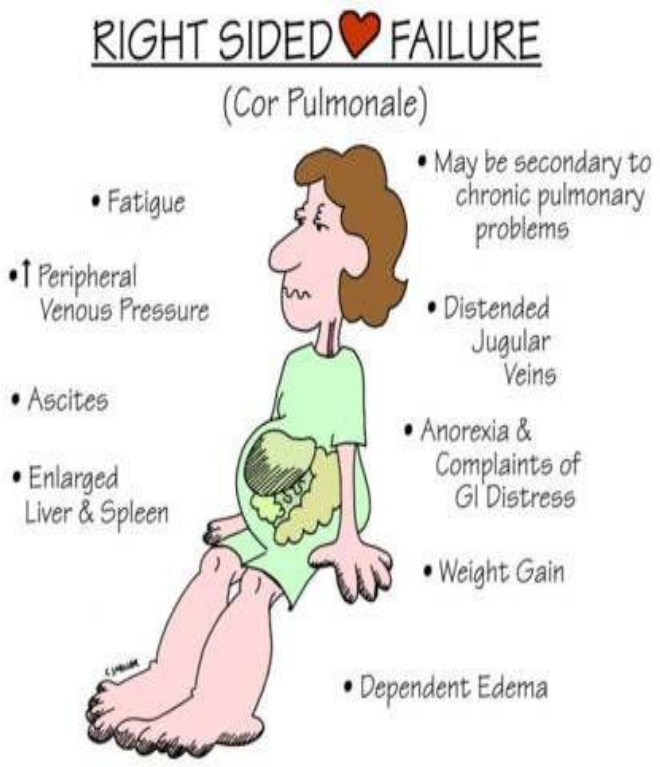




B. Right- sided heart failure:

- Most commonly due to left-sided heart failure; other important causes include left to-right shunt and Cor pulmonale (isolated right HF due to pulmonary cause).
- Most commonly combined left- and right-ventricular failure is observed owing to the fact that the most common cause of right heart failure is left heart failure.
- Clinical features are due to congestion:

- Jugular venous distension.
- Painful hepatosplenomegaly with characteristic 'nutmeg' liver; may lead to cardiac cirrhosis.
- Dependent pitting edema (due to increased hydrostatic pressure)



❖ N.B:

1. Decreased perfusion of peripheral tissues induces a number of neuroendocrine compensatory mechanisms, such as:

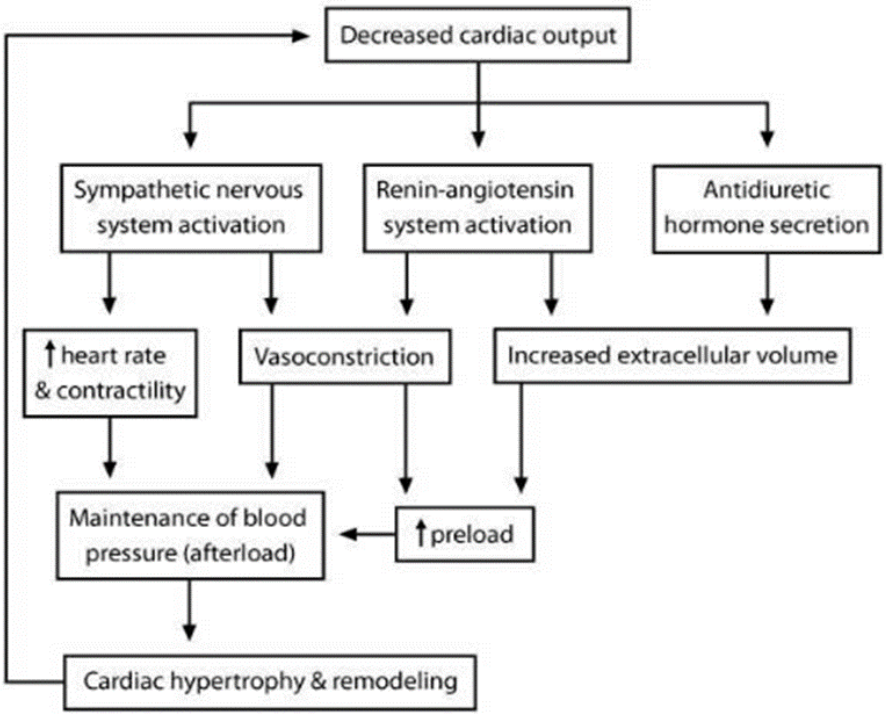
A. Renin-angiotensin-aldosterone mechanism:

- Decreased renal perfusion leads to diminished stretch of glomerular afferent arterioles and increased synthesis of renin.
- Increased angiotensin I is converted to angiotensin II, which is a potent vasoconstrictor.
- By causing vasoconstriction, angiotensin II increases arterial resistance and afterload.
- The failing heart is unable to pump blood to the tissues against the increased afterload induced by angiotensin II, so tissue perfusion decreases and more renin is secreted by the kidney creating a vicious circle.
- Angiotensin II also stimulates the secretion of aldosterone which functions to increase the circulating blood volume (preload) and further exacerbate CHF.

B. Increased sympathetic output:

- It is stimulated by baroreceptors that sense decreased perfusion.
- Epinephrine and norepinephrine increase heart rate and contractility, but these neurotransmitters also increase peripheral arterial resistance thereby increasing afterload.
- Renin-angiotensin-aldosterone activation and increased sympathetic output raise arterial resistance (afterload) and exacerbate heart failure by making it more difficult for the failing heart to pump blood to the tissues.

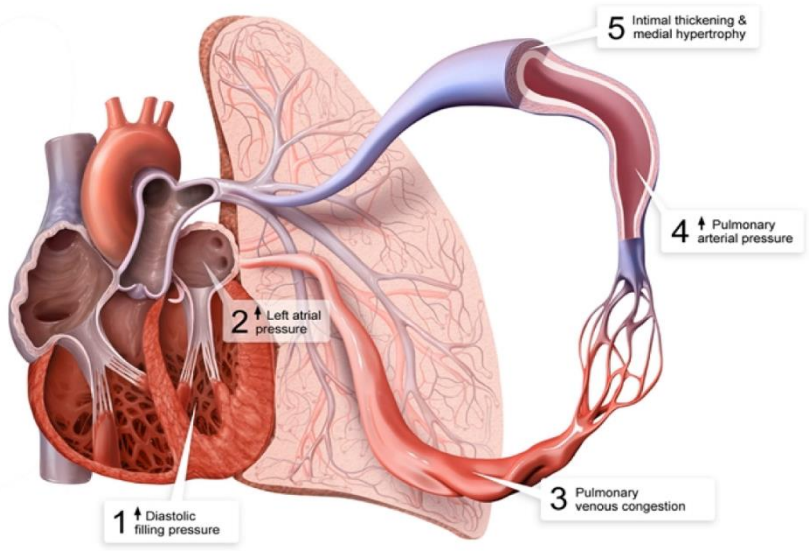
Pathogenesis of congestive heart failure



2. The pathogenesis of Pulmonary Hypertension due to left heart disease begins with a passive increase in pulmonary capillary and arterial pressure secondary to pulmonary venous congestion.

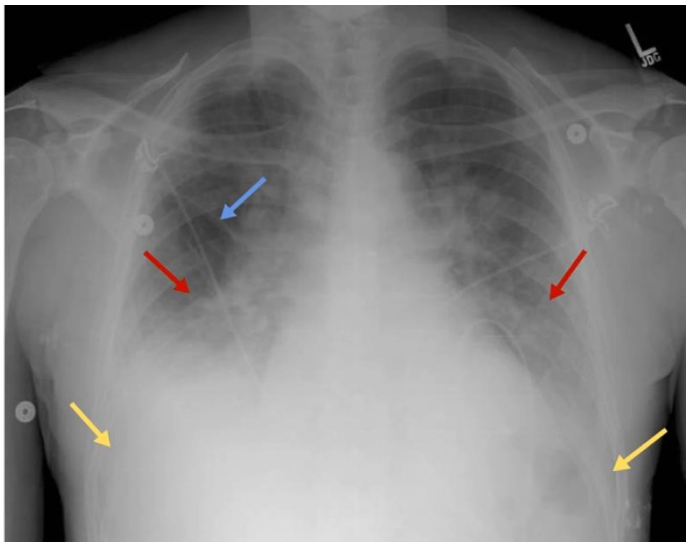
- The high pressures result in endothelial damage and capillary leakage of serum proteins into the interstitium.
- This leads to decreased production of nitric oxide (vasodilator) and increased production of endothelin (vasoconstrictor) by the dysfunctional epithelium, resulting in increased vascular tone.
- Over time, remodeling of the pulmonary vasculature occurs with increased smooth muscle cell proliferation (medial hypertrophy) and collagen (intimal thickening and fibrosis).
- Remodeling is less extensive than in (idiopathic) pulmonary arterial hypertension; therefore. PH due to left heart disease is usually at least partially reversible following correction of the underlying abnormality (LV dysfunction, mitral valve disease).

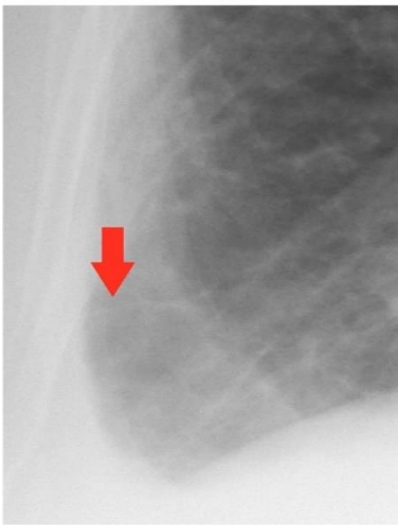
Pulmonary hypertension due to left-sided heart failure



3. Chest x-ray findings below show prominent pulmonary vessels, patchy bilateral airspace opacities (red arrows), blunting of the costophrenic angles (pleural effusions [yellow arrows]), and a fissure sign (created by fluid trapped between the right upper and middle lobe [blue arrow]).

- These findings are consistent with acute decompensated heart failure (ADHF) due to left ventricular systolic or diastolic dysfunction.
- The chest x-ray may also show Kerley B lines (short, horizontal lines perpendicular to the pleural surface that represent edema of the interlobular septa).

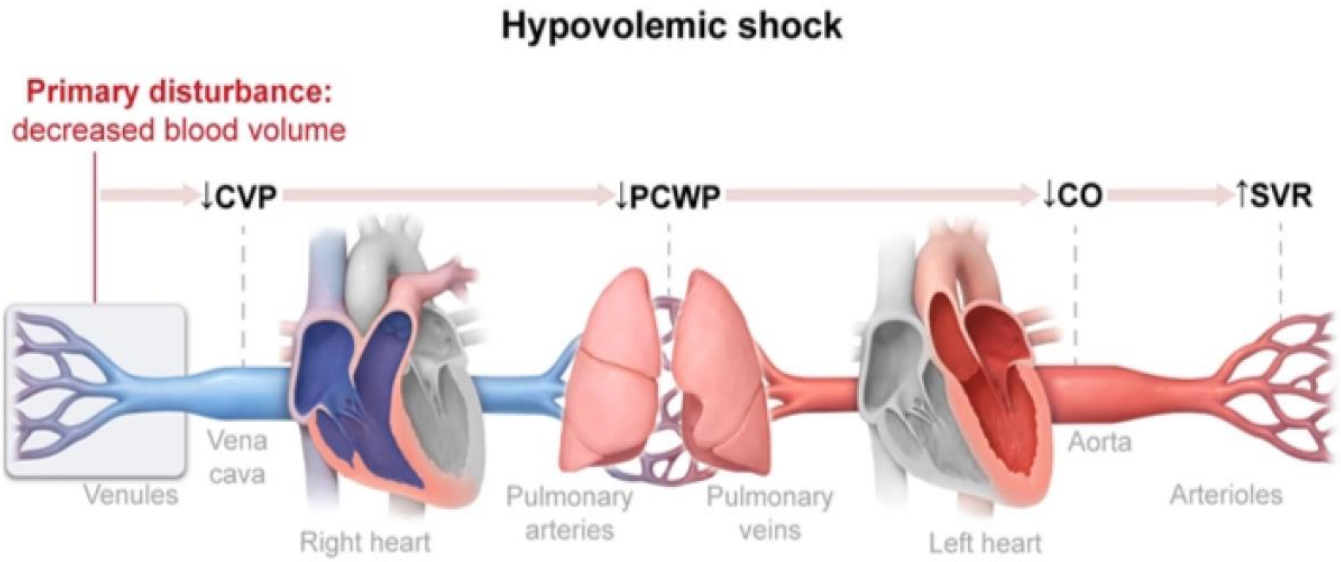




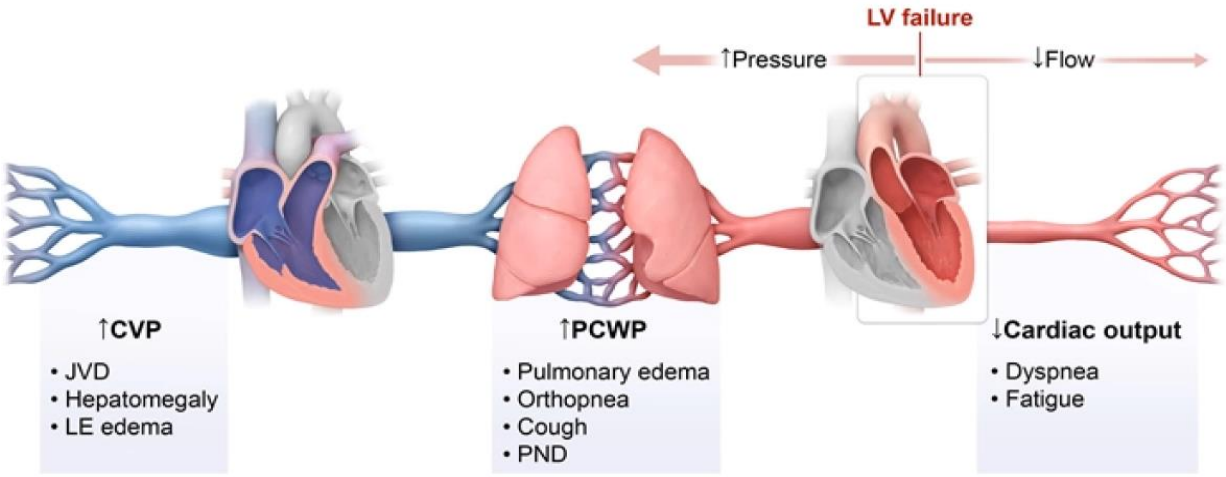
Shock

- Inadequate organ perfusion and delivery of nutrients necessary for normal tissue and cellular function.
- Initially may be reversible but life-threatening if not treated promptly.

	Caused by	Skin	PCWP (Preload)	CO	SVR (Afterload)	Treatment
Hypovolemic	Hemorrhage, dehydration, Burns	Cold, clammy	↓↓	↓	↑	IV fluids
Cardiogenic	Acute MI, HF, valvular dysfunction, arrhythmia	Cold, Clammy	↑	↓↓	↑	Inotropes, diuresis
Obstructive	Cardiac tamponade, pulmonary embolism, Tension pneumothorax		↓			Relieve obstruction
Distributive	Sepsis, anaphylaxis	Warm	↓	↑	↓↓	IV fluids, pressors, epinephrine (anaphylaxis)
	CNS injury	Dry	↓	↓	↓↓	

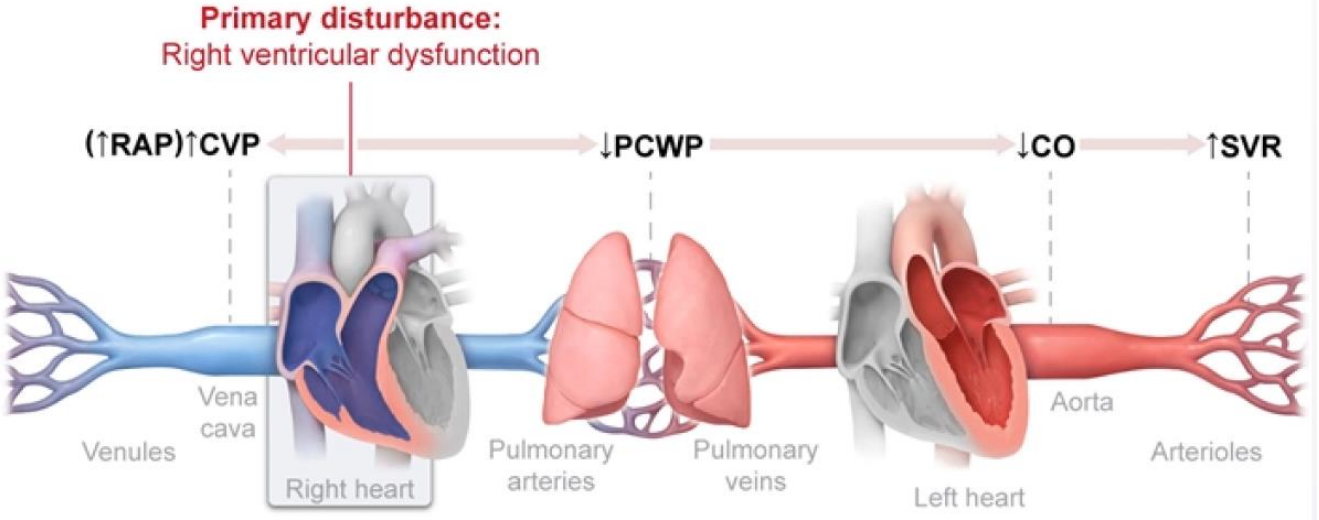


Left-sided heart failure

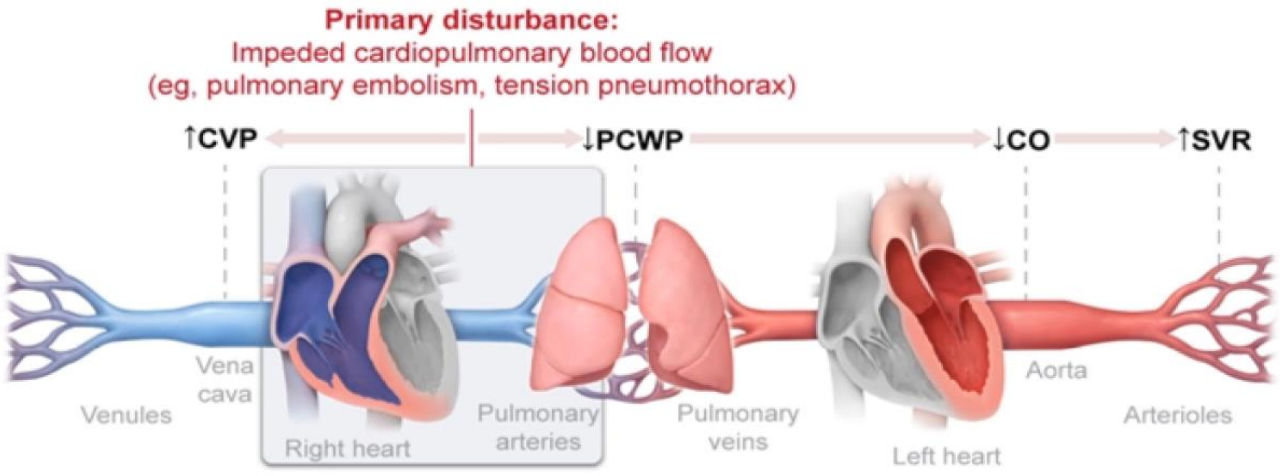


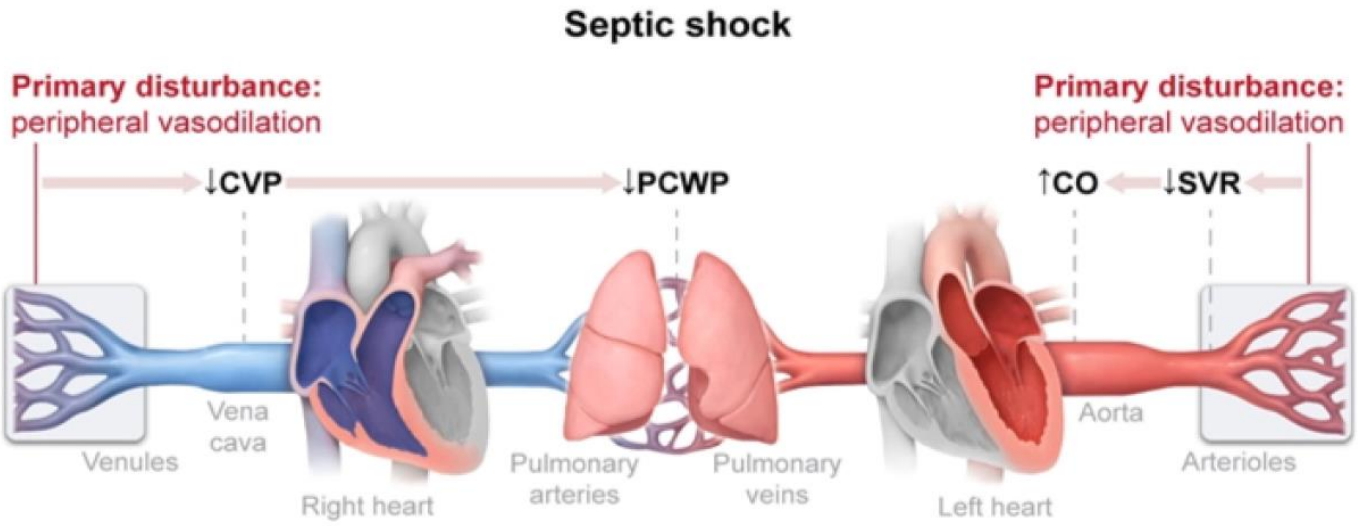
CVP = central venous pressure; **JVD** = jugular venous distension; **LE** = lower extremity; **LV** = left ventricular; **PCWP** = pulmonary capillary wedge pressure; **PND** = paroxysmal nocturnal dyspnea.

Right-sided heart failure



Obstructive shock




Septic shock
Primary disturbance:
peripheral vasodilation
↓CVP
↓PCWP
Primary disturbance:
peripheral vasodilation
↑CO
↓SVR
Venules
Vena cava
Right heart
Pulmonary arteries
Pulmonary veins
Left heart
Aorta
Arterioles

Rheumatic fever

A. Acute rheumatic fever:

- Systemic complication of pharyngitis due to group A β-hemolytic streptococci; affects children 2 - 3 weeks after an episode of streptococcal pharyngitis ("strep throat").

- Caused by molecular mimicry (cross-reactivity of antibodies against bacterial and host antigens); bacterial M protein resembles proteins in human tissue.

- Immune mediated (type II hypersensitivity); not a direct effect of bacteria.

- Most organs are often only mildly and transiently affected in ARF, with the exception of the heart.

- The Jones criteria establish the diagnosis of rheumatic fever. A patient is positive for rheumatic fever when either 2 of the major criteria or 1 major criterion plus 2 minor criteria are present, along with evidence of streptococcal infection (elevated or rising antistreptolysin O titer or DNase).

- Major criteria:

A. Migratory polyarthritis:

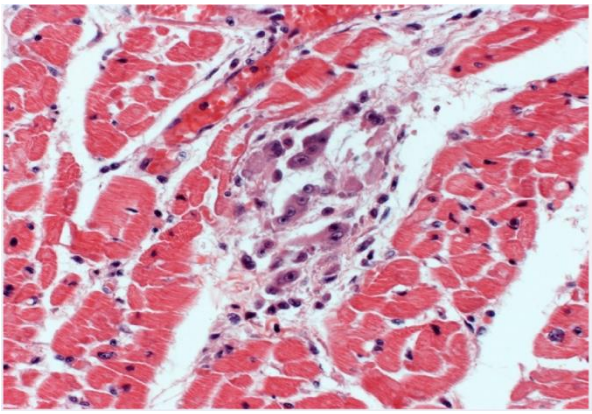
- Swelling and pain in a large joint (wrist, knees, ankles) that resolves within days and "migrates" to involve another large joint.

B. Pancarditis:

- Acute morbidity in RF is most likely due to pancarditis (inflammation of the pericardium, myocardium, and epicardium).

- Endocarditis:
  - Mitral valve is involved more commonly than the aortic valve (high-pressure valves affected most).
  - Characterized by small vegetations along lines of closure that lead to regurgitation.

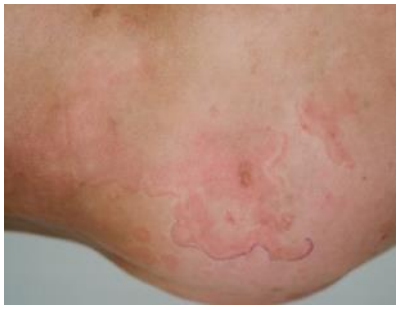
- Myocarditis with Aschotf bodies that are characterized by foci of chronic inflammation, reactive histiocytes with slender, wavy nuclei (Anitschkow cells), giant cells, and fibrinoid material; myocarditis is the most common cause of death during the acute phase.

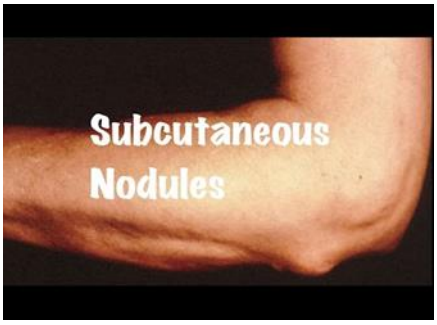


- Pericarditis: leads to friction rub and chest pain.

C. Subcutaneous nodules.

D. Erythema marginatum: annular, nonpruritic rash with erythematous borders, commonly involving trunk and limbs





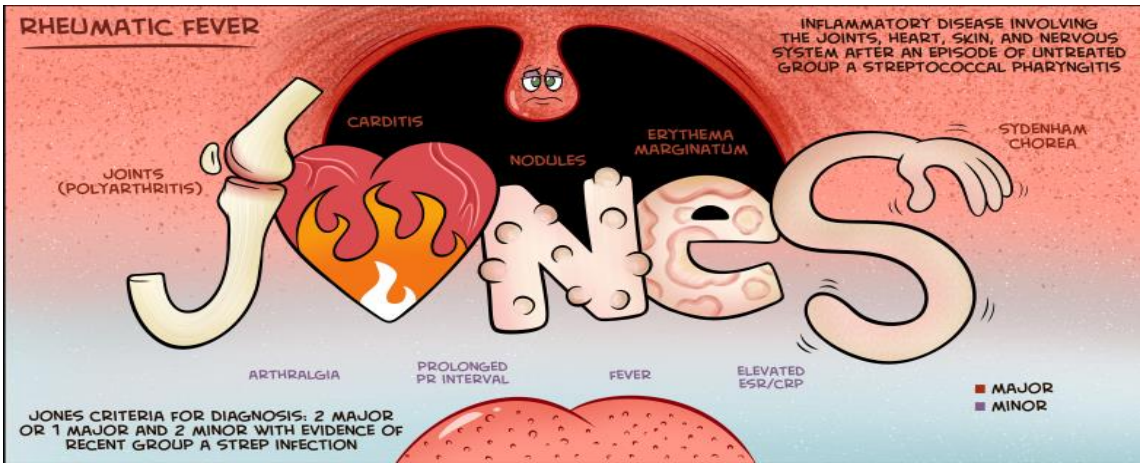
E. Sydenham chorea presents with involuntary, rapid, irregular jerking movements involving the face, arms, and legs. It is caused by a delayed onset autoimmune reaction involving anti-streptococcal antibodies that cross-react with the basal ganglia.

- Minor criteria are nonspecific and include fever, artharagia, elevated ESR/CPR and prolonged PR interval.

- Acute attack usually resolves, but may progress to chronic rheumatic heart disease; repeat exposure to group A β-hemolytic streptococci results in relapse of the acute phase and increases risk for chronic disease.

Acute rheumatic fever		
Epidemiology	• Peak incidence: age 5-15 • Twice as common in girls	
Clinical features	**Major**	• **J**oints (migratory arthritis) • ♥ (Carditis) • **N**odules (subcutaneous) • **E**rythema marginatum • **S**ydenham chorea
	Minor	• Fever • Arthralgias • Elevated ESR/CRP • Prolonged PR interval
Late sequelae	Mitral regurgitation/stenosis	
Prevention	Penicillin for **group A streptococcal** (*Streptococcus pyogenes*) pharyngitis	

CRP = C-reactive protein; **ESR** = erythrocyte sedimentation rate.

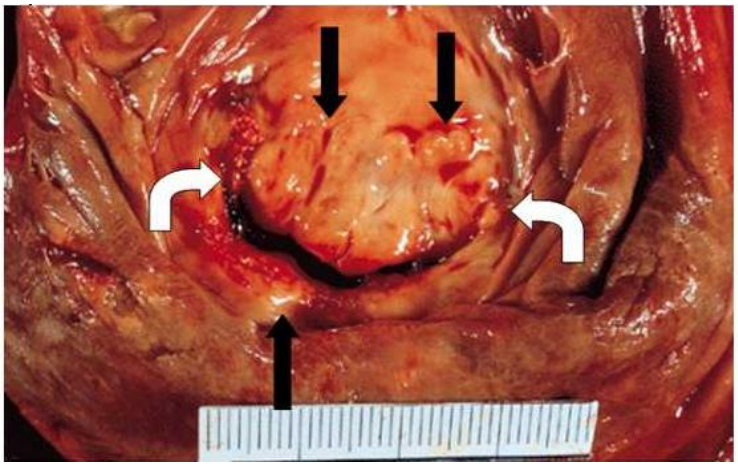


B. Chronic rheumatic heart disease:

- Almost always involves the mitral valve; leads to thickening of chordae tendineae and cusps.
- Fibrous thickening and fusion of the valve leaflets in chronic rheumatic heart disease following acute rheumatic fever is the most common cause of Mitral Stenosis.
- Mitral stenosis can cause atrial enlargement, which may lead to atrial fibrillation and/or atrial mural thromboses.
- Thrombi dislodged from the wall of the left atrium may later cause an embolic stroke.
- Occasionally involves the aortic valve; leads to fusion of the commissures.
- There is often a latency period of 10-20 years between the initial episode of rheumatic fever and symptomatic MS with most patients manifesting during the fourth or fifth decade of life.
- Complications include infectious endocarditis. Chronic valvular inflammation and scarring associated with rheumatic heart disease predispose to an increased risk of infective endocarditis.
- Treatment/prophylaxis: penicillin.

❖ N.B:

- The autopsy specimen below shows diffuse fibrous thickening and some distortion of the mitral valve leaflets (black arrows).
- There may also be some commissural fusion at the leaflet edges (white, curved arrows), and the mitral valve orifice may be somewhat stenotic.
- The relatively large surface area of the walls of the left atrium is consistent with atrial dilatation.
- All of these findings are characteristic of rheumatic mitral valvular disease.



Bacterial endocarditis

- Endocarditis is an infection of the valve of the heart leading to a fever and a murmur.

- About 75% of patients with IE have previously damaged heart valves, with mitral valvular disease being the most common.

- Mitral valve prolapse (with or without mitral regurgitation) is the most common predisposing condition for native valve infective endocarditis (IE) in developed nations.

- It is very rare to have endocarditis develop on normal heart valves with the exception of injection drug users. The risk of endocarditis is directly proportional to the degree of damage of the valves. Regurgitant and stenotic lesions confer increased risk. Prosthetic valves are associated with the highest risk. Infection can develop on normal valves if there is severe bacteremia with highly pathogenic organisms such as occurs with injection drug use and Staphylococcus aureus.

- Dental procedures confer an increased, but very small risk of endocarditis. Even surgery of the mouth or respiratory tract confers no risk unless there is a severe valvular disorder such as from an artificial valve or cyanotic heart disease. Less invasive procedures such as endoscopy confer no increased risk even with a biopsy.

- Viridans group streptococci (Streptococcus sanguinis) typically colonize the oral mucosa and are the most common cause of IE following dental procedures.

- Pathogenesis:

- The initial process involved in the pathogenesis of infective endocarditis (IE) is a disruption of normal endocardial surface.

- This is followed by focal adherence of fibrin and platelets, forming a sterile fibrin-platelet nidus.

- During bacteremia from any cause (dental procedures), microorganisms colonize the sterile nidus on the endothelial surface with subsequent microbial growth leading to further activation of the coagulation system.

- Types:

A. Acute endocarditis:

- S aureus (high virulence).
- Large vegetations on previously normal valves, most commonly the tricuspid.
- Rapid onset.
- Staphylococcus aureus is the most common cause in IV drug abusers.
- In intravenous drug users, it can cause right-sided endocarditis with septic embolization into the lungs.

B. Subacute endocarditis:

- Viridans streptococci (low virulence).
- Smaller vegetations on congenitally abnormal or diseased valves (chronic rheumatic heart disease and mitral valve prolapse).
- Sequela of dental procedures.
- Gradual onset.

- Staphylococcus epidermidis is associated with endocarditis of prosthetic valves.

- Streptococcus bovis (gallolyticus) is associated with endocarditis in patients with underlying colorectal carcinoma.

- HACEK organisms (Haemophilus, Aggregatibacter [formerly Actinobacillus], Cardiobacterium, Eikenella, Kingella) are associated with endocarditis with negative blood cultures.

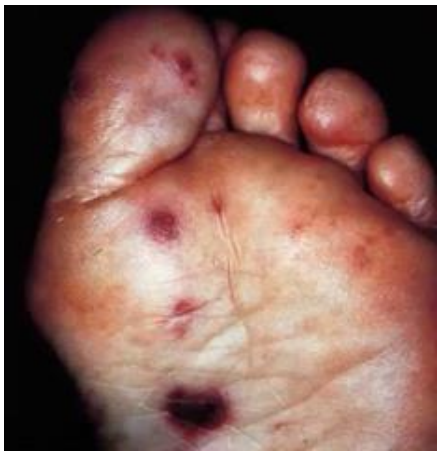
- Coxiella burnetii, Bartonella spp. may also cause culture -ve endocarditis.

- Clinical features of bacterial endocarditis include:

- Fever: due to bacteremia.

- New onset murmur: due to vegetations on heart valve.

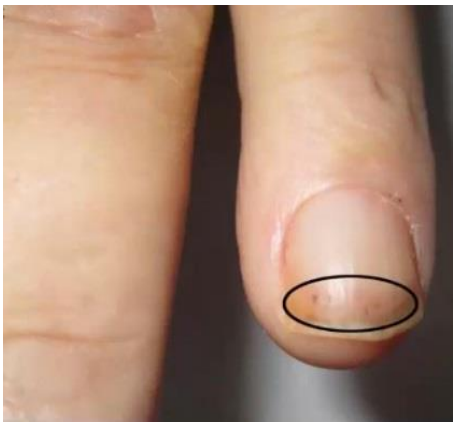
- Janeway lesions:
  - Nontender macular, and erythematous lesions typically located on the palms and soles.
  - They are the result of septic embolization of skin vesseles from valvular vegetations and are composed of bacteria, neutrophils (microabscesses), necrotic material, and subcutaneous hemorrhage.

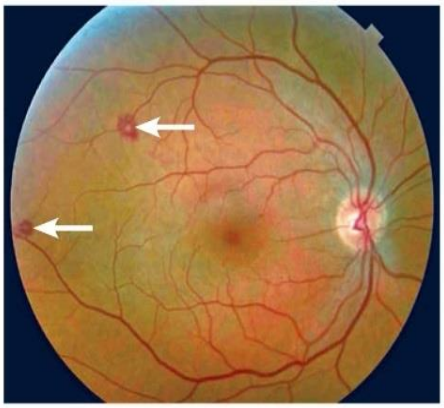


- Osler nodes (Ouchy raised lesions on finger or toe pads due to immune complex deposition).

- Roth spots (round white spots on retina surrounded by hemorrhage).

- Subungual splinter hemorrhages are splinter- or flame-shaped hemorrhagic streaks in the nail bed that appear as a consequence of microemboli of septic vegetations.





- Anemia of chronic disease: due to chronic inflammation.

- Septic emboli to the lung with right heart endocarditis or to the brain and systemic circulation (with left heart endocarditis).

- In some patients, BE may be complicated by acute diffuse proliferative glomerulonephritis secondary to circulating immune complexes and their mesangial and/or subepithelial deposition in the glomeruli.

Vascular & immunologic manifestations of infective endocarditis	
Vascular phenomena	• Systemic emboli (cerebral, pulmonary, or splenic infarcts) • Mycotic aneurysm • Janeway lesions – Macular, erythematous, **nontender** lesions on the palms & soles
Immunologic phenomena	• Osler nodes – **Painful**, violaceous nodules seen on the fingertips & toes • Roth spots – Edematous & hemorrhagic lesions of the retina

- Laboratory findings:

- It is diagnosed with vegetations seen on echocardiogram and positive blood cultures.
- Anemia of chronic disease.

♥ Bacteria FROM JANE ♥:

- Fever.
- Roth spots.
- Osler nodes.
- Murmur.
- Janeway lesions.
- Anemia.
- Nail-bed hemorrhage.
- Emboli.

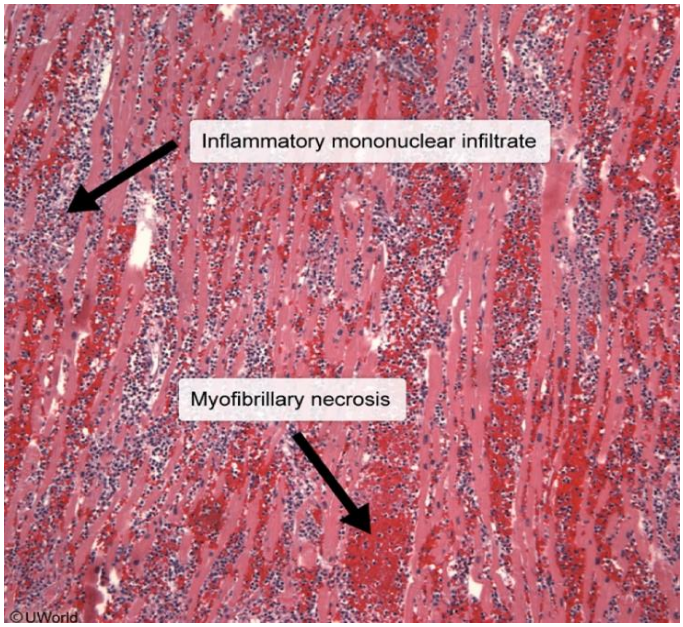
❖ N.B:

- The differential diagnosis for mitral valve thickening with vegetations includes infectious endocarditis, rheumatic valvulitis, Libman-Sacks endocarditis associated with systemic lupus erythematosus (SLE), and non-bacterial thrombotic endocarditis.
- Of these, SLE cause an acute coronary syndrome at a young age even with angiographically normal coronary arteries.
- Libman-Sacks endocarditis is due to sterile vegetations that arise in association with SLE. Vegetations are present on the surface and undersurface of the mitral valve and result in mitral regurgitation.
- Nonbacterial thrombotic endocarditis is due to sterile vegetations that arise in association with a hypercoagulable state or malignancy (underlying adenocarcinoma). Vegetations arise on the mitral valve along lines of closure and result in mitral regurgitation.
- NBTE associated with disseminated cancer is termed "marantic" or "marasrmic" endocarditis, derived from the term for cancer-related wasting of body tissues ("marasmus").

Myocarditis

- Inflammation of myocardium → global enlargement of heart and dilation of all chambers.
- Major cause of SCD in adults < 40 years old.
- Presentation highly variable, can include dyspnea, chest pain, fever, arrhythmias (persistent tachycardia out of proportion to fever is characteristic).
- Multiple causes:

- Viral (adenovirus, coxsackie B, parvovirus B19, HIV, HHV-6); lymphocytic infiltrate with focal necrosis highly indicative of viral myocarditis.



- Parasitic (Trypanosoma cruzi, Toxoplasma gondii).
- Bacterial (Borrelia burgdorferi, Mycoplasma pneumoniae, Corynebacterium diphtheriae).
- Toxins (carbon monoxide, black widow venom).
- Rheumatic fever.
- Drugs (doxorubicin, cocaine).
- Autoimmune (Kawasaki disease, sarcoidosis, SLE, polymyositis/dermatomyositis).

- Complications include sudden death, arrhythmias, heart block, dilated cardiomyopathy, HF, mural thrombus with systemic emboli.

Acute pericarditis

- Definition: Inflammation of the pericardium.

- Causes:

- Any infection, inflammatory disorder (Uremic pericarditis), connective tissue disorder (SLE, rheumatoid arthritis), cardiovascular (postinfarction fibrinous pericarditis or Dressler syndrome), trauma to the chest, or cancer of an organ anatomically near the heart can cause pericarditis.

- The most common infection is viral (Coxsackie B virus); however, Staphylococcus, Streptococcus, fungi, and other agents can cause pericarditis in the same way that virtually any infection can cause pneumonia.

- Systemic lupus erythematosus is the most common connective tissue disorder, but Wegener granulomatosis, Goodpasture syndrome, rheumatoid arthritis, polyarteritis nodosa, and other disorders can cause pericarditis.

- Presentation:

- Pericarditis is associated with sharp chest pain that changes in intensity with respiration (pleuritic) as well as the position of the body (positional).

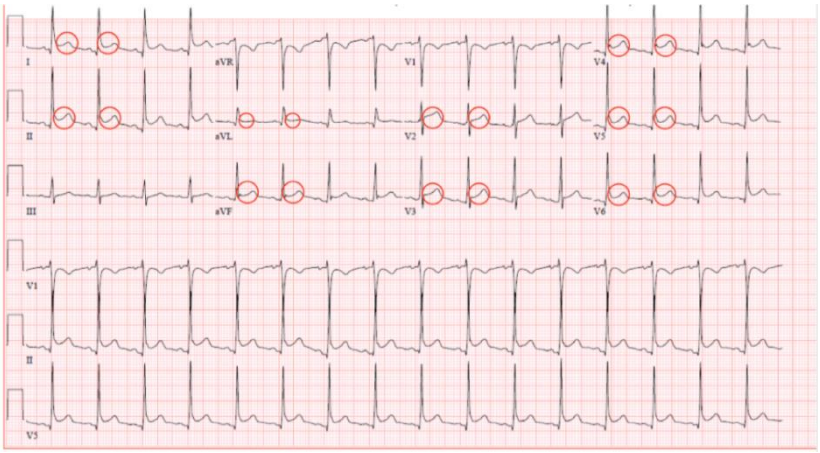
- The pain is worsened by lying flat and improved by sitting up. This is probably from a change in the level of tension or "stretch" of the pericardium.

- The pericardial Friction rub (described as high pitched, leathery, and scratchy) is the most striking physical finding.

- EKG shows ST segment elevation in all leads, but the most specific finding is PR segment depression.

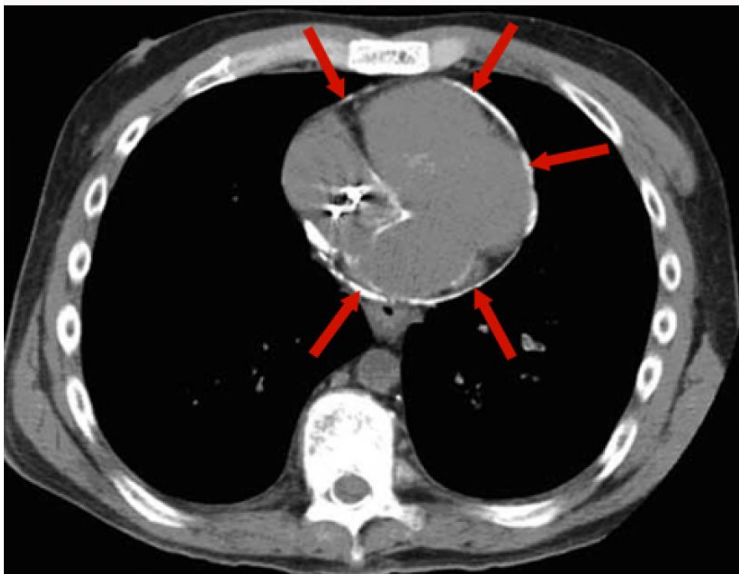
- Often complicated by pericardial effusion.

- Treatment: NSAIDs, colchicine, glucocorticoids, dialysis (uremia).



❖ N.B:

- Constrictive pericarditis is a chronic condition in which the normal pericardial space is replaced by a thick, fibrous shell that restricts ventricular volumes and eventually causes heart failure.
- Possible causes include radiation therapy to the chest, cardiac surgery, and tuberculosis (which is possibly the cause in immigrants from an endemic region).
- Impaired right ventricular filling leads to increased jugular venous pressure and often results in a positive Kussmaul sign.
- Although JVP normally drops during inspiration, patients with constrictive pericarditis frequently have a paradoxical rise in JVP, a finding known as Kussmaul sign. This occurs because the volume-restricted right ventricle is unable to accommodate the inspiratory increase in venous return.
- There may also be a pericardial knock, which occurs earlier in diastole than the S3 heart sound.
- Calcification and thickening of the pericardium are common features of constrictive pericarditis on CT.



Constrictive pericarditis	
Etiology	• Idiopathic or viral pericarditis • Cardiac surgery or radiation therapy • Tuberculosis (in endemic areas)
Pathogenesis	• Rigid pericardium prevents ventricular expansion and restricts diastolic filling • Predominantly right-sided manifestations
Physical examination	• ↑ Jugular venous pressure • Pericardial knock • Pulsus paradoxus • Kussmaul sign

Cardiac tamponade

- Cardiac tamponade is due to fluid accumulation in the pericardial cavity that increases the intrapericardial pressure above the diastolic ventricular pressure.

- This restricts venous return to the heart and lowers right and left ventricular filling. The net result is decreased preload, stroke volume, and cardiac output.

- Lung examination typically shows clear lungs to auscultation due to decreased ventricular filling (preload) rather than volume overload.

- Death from cardiac tamponade occurs from obstructive shock, when cardiac output becomes insufficient to provide the necessary oxygen to the patient's tissues.

- Findings:

- Observation of Beck's triad on physical examination - hypotension, distended neck veins (elevated central venous pressure that produces jugular venous distension), and distant or muffled heart sounds on auscultation as well as tachycardia, are together indicative of tamponade.

- As the pressure increases in the pericardial cavity, venous return to the heart is reduced. This leads to profound systemic hypotension and pulseless electrical activity. Failure to relieve the obstruction results in death.

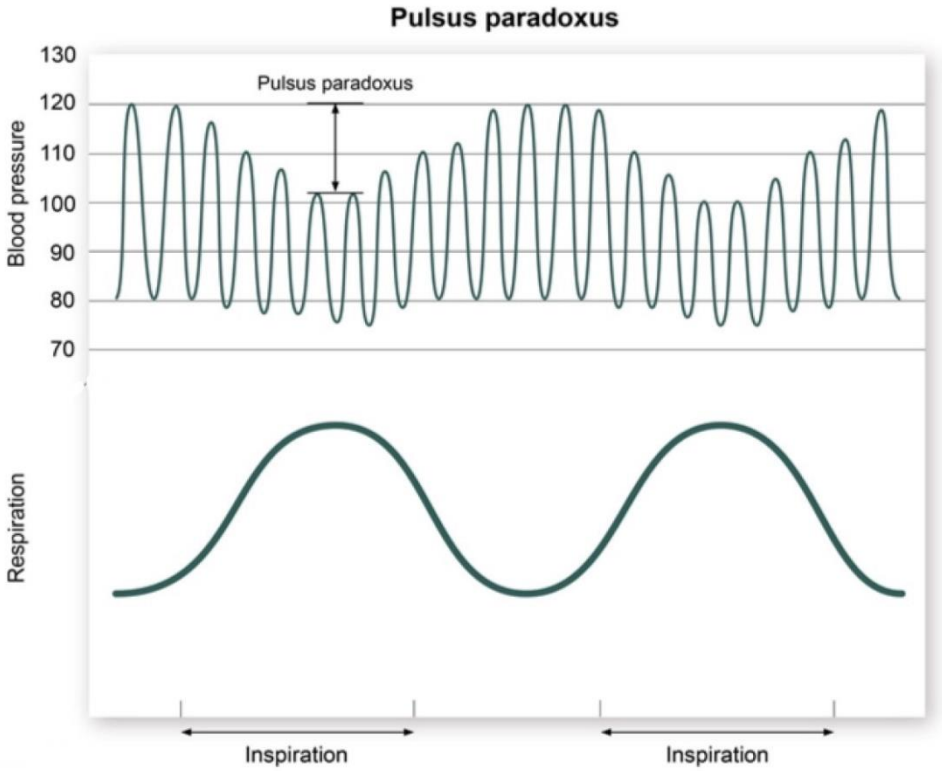
- Pulsus paradoxus is also an important clue to cardiac tamponade. It is defined as a decrease in the systolic pressure of 10 mmHg or more during inspiration as compared with the pressure during exhalation.

- Inspiration causes an increase in systemic venous return, resulting in increased right heart volumes.

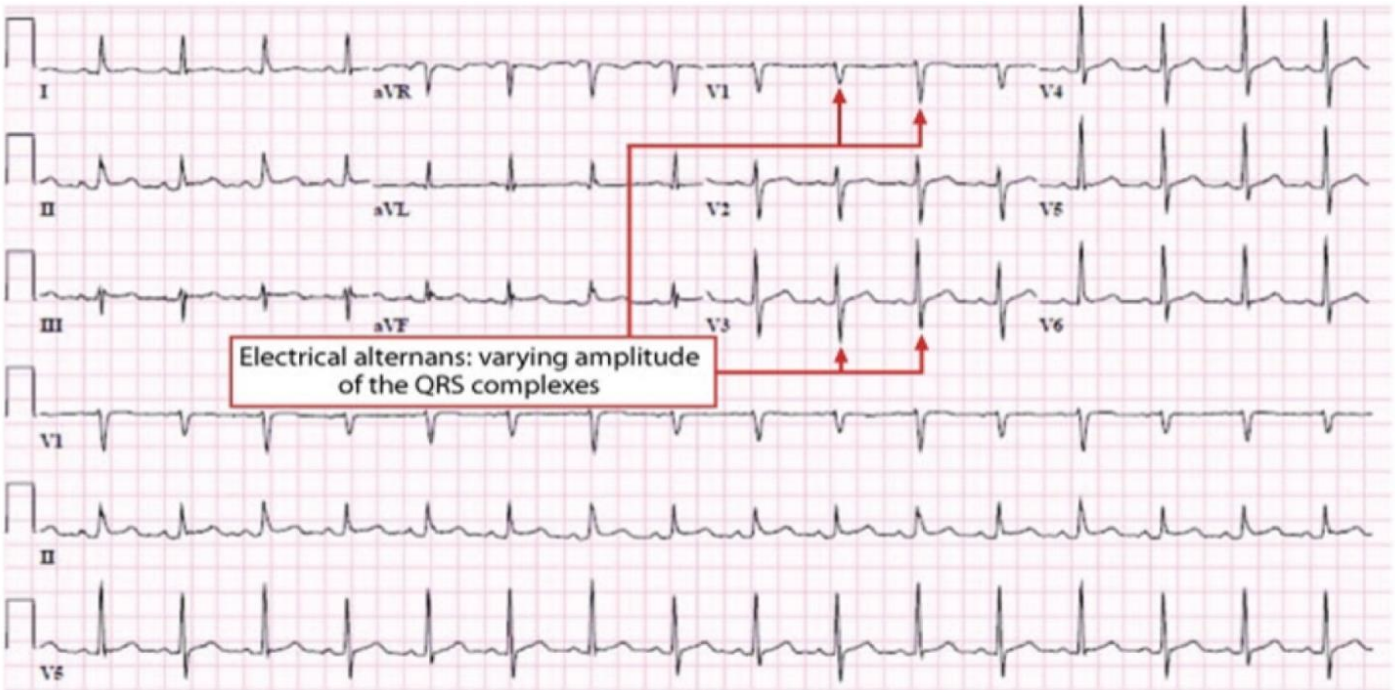
- Under normal conditions, this results in expansion of the right ventricle into the pericardial space with little impact on the left side of the heart resulting in decreased left ventricular stroke volume and a drop in systolic blood pressure (normally < 10 mm Hg).

- However, in conditions that impair expansion into the pericardial space (acute cardiac tamponade, constrictive pericarditis, severe obstructive lung disease, and restrictive cardiomyopathy), the increased right ventricular volume occurring with inspiration leads to bowing of the interventricular septum toward the left ventricle.

- This leads to a decrease in left ventricular (LV) end-diastolic volume and stroke volume, with a resultant decrease in systolic pressure during inspiration > 10 mm Hg.



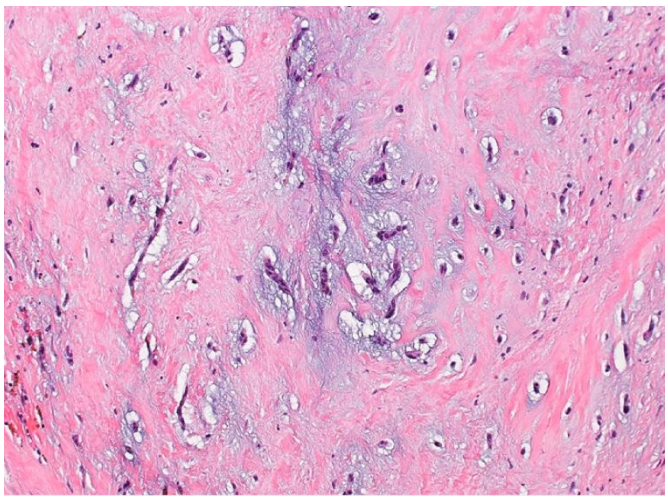
- ECG shows low-voltage QRS and electrical alternans (beat to beat variation in the QRS complex amplitude on ECG due to "swinging" movement of heart in large effusion).

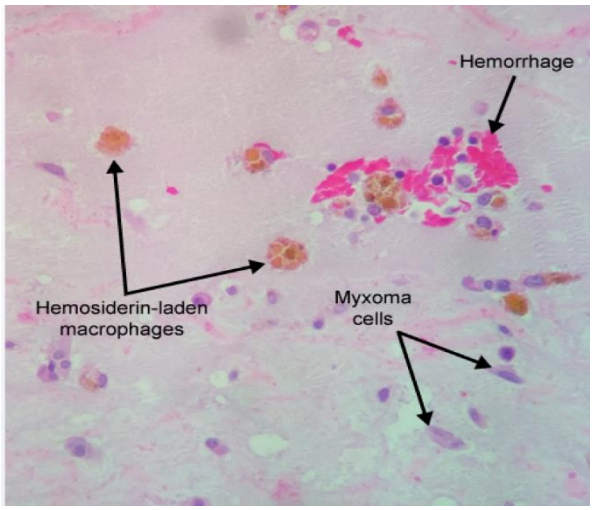


Cardiac tumors

Myxomas

- Myxomas are the most common primary cardiac neoplasm in adults and approximately 80% arise in the left atrium.
- Benign mesenchymal tumor with a gelatinous appearance and abundant ground substance on histology.
- The cardiovascular symptoms are secondary to valve obstruction by the myxoma (forms a pedunculated mass in the left atrium that causes obstruction of the mitral valve), which accounts for why symptoms are position dependent.
- Constitutional symptoms (IL-6 production by tumor → constitutional symptoms as fever, weight loss), a mid-diastolic rumbling murmur heard best at the apex, positional cardiovascular symptoms (dyspnea and syncope), embolic symptoms, and a large pedunculated mass in the left atrium are the typical findings of atrial myxoma.
- Histologically, these tumors are composed of scattered cells within a mucopolysaccharide stroma (myxoma), abnormal blood vessels due to angiogenesis, and hemorrhaging accompanied by hemosiderin laden macrophages.





Rhabdomyoma

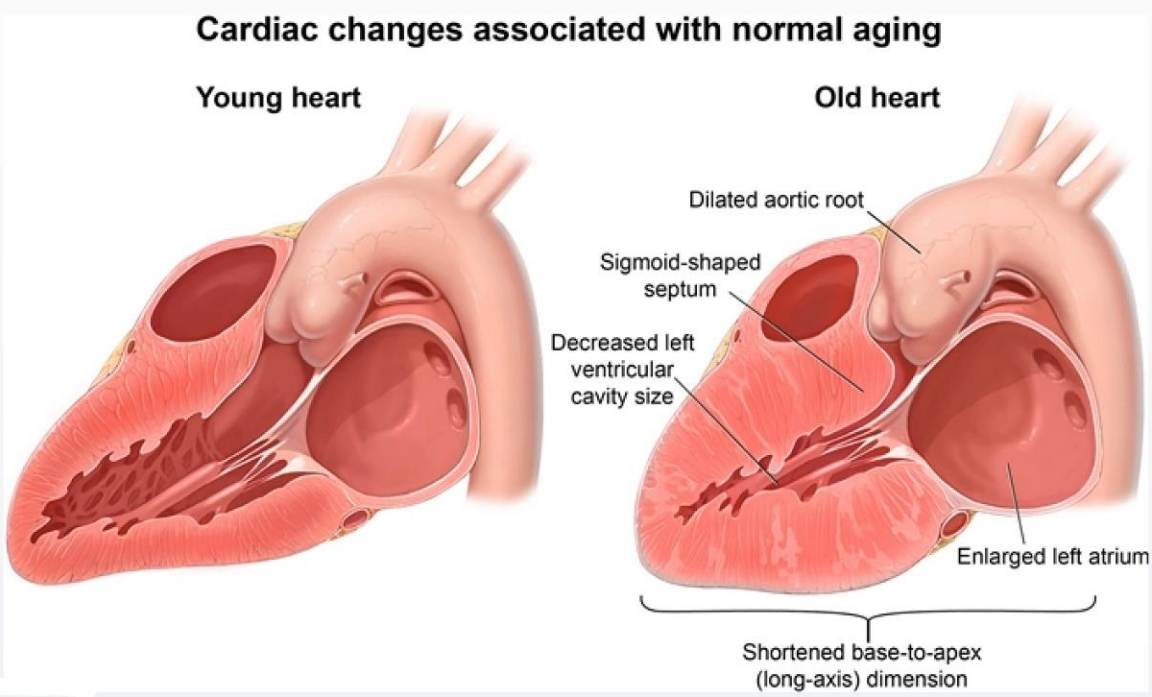
- Benign hamartoma of cardiac muscle.
- Most common primary cardiac tumor in children; associated with tuberous sclerosis
- Usually arises in the ventricle.

Metastasis

- Metastatic tumors are more common in the heart than primary tumors.
- Common metastases to the heart include breast and lung carcinoma, melanoma, and lymphoma.
- Most commonly involve the pericardium, resulting in a pericardial effusion.

❖ N.B:

- Normal morphological changes in the aging heart include a decrease in left ventricular chamber apex-to-base dimension, development of a sigmoid-shaped ventricular septum, myocardial atrophy with increased collagen deposition, and accumulation of cytoplasmic lipofuscin pigment within cardiomyocytes.
- An insoluble pigment composed of lipid polymers and protein-complexed phospholipids, lipofuscin is considered a sign of "wear and tear" or aging.
- This yellow-brown, finely granular perinuclear pigment is the product of free radical injury and lipid peroxidation.
- It is commonly seen in the heart and liver of aging or cachectic, malnourished patients.



Vasculitides

- Inflammation of the blood vessel wall.

- Arterial wall is comprised of three layers: endothelial intima, smooth muscle media, and connective tissue adventitia.

- Clinical features include:

- Nonspecific symptoms of inflammation (fever, fatigue, weight loss, and myalgias).
- Symptoms of organ ischemia: due to luminal narrowing or thrombosis of the inflamed vessels.

- Divided into large-, medium-, and small-vessel vasculitides:

- Large vessel vasculitis: involves the aorta and its major branches.

- Medium vessel vasculitis: involves muscular arteries that supply organs.

- Small vessel vasculitis: involves arterioles, capillaries, and venules.

Large-vessel vasculitis

A. Temporal (Giant Cell) Arteritis:

- Granulomatous inflammation of the media that classically involves branches of the carotid artery.

- Most common form of vasculitis in older adults (> 50 years); usually affects females.

- Presents as unilateral headache (temporal artery involvement), visual disturbances (ophthalmic artery involvement), and jaw claudication (jaw pain when chewing).

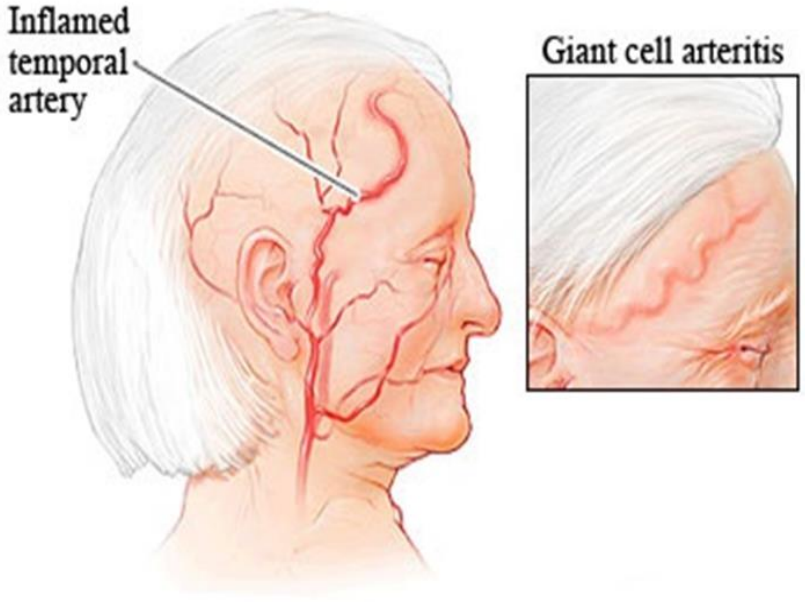
- Proximal stiffness (neck, arms, hips) due to polymyalgia rheumatica, a coexisting condition (seen in >25% of patients with TA).

- All patients will have elevated ESR (100% sensitive). Therefore, the first test to do when TA is suspected is ESR.

- Diagnosis is confirmed by biopsy of the temporal arteries. Biopsy reveals inflamed vessel wall with giant cells and intimal fibrosis.

- Lesions are segmental; diagnosis requires biopsy of a long segment of vessel, and a negative biopsy does not exclude disease.

- Treatment is corticosteroids; high risk of blindness without treatment. Treat with high-dose corticosteroids prior to temporal artery biopsy to prevent blindness.



B. Takayasu Arteritis:

- Granulomatous vasculitis that classically involves the aortic arch at branch points.

- Presents in adults < 40 years old (classically, young Asian females) as visual and neurologic symptoms with a weak or absent pulse in the upper extremity (pulseless disease).

Young Asian woman + Diminished pulses = Takayasu arteritis

- The special features of this vasculitis are TIA and stroke from vascular occlusion.

- The most accurate test for Takayasu is not a biopsy. It is diagnosed with aortic arteriography or magnetic resonance angiography (MRA).

- Treatment is corticosteroids.

❖ N.B:

- Takayasu arteritis and temporal arteritis involve arterial vessels of different sizes and locations (aorta and proximal aortic arterial branch involvement versus more distal carotid artery branch involvement, respectively), and have different clinical presentations.
- Even so, they may share a common pathologic morphology, consisting of granulomatous inflammation of the media.
- Jaw claudication is the most specific symptom of GCA. Headache, facial pain, and vision loss are common symptoms as well. Temporal artery biopsy demonstrates granulomatous inflammation of the media. GCA tends to develop in patients older than 50.
- Takayasu arteritis typically affects the aortic arch. Takayasu arteritis occurs predominantly in females less than 40 years old.
- Thus, the distinction between giant cell lesions of the aorta is oftentimes based on the patient's age.

Medium-vessel vasculitis

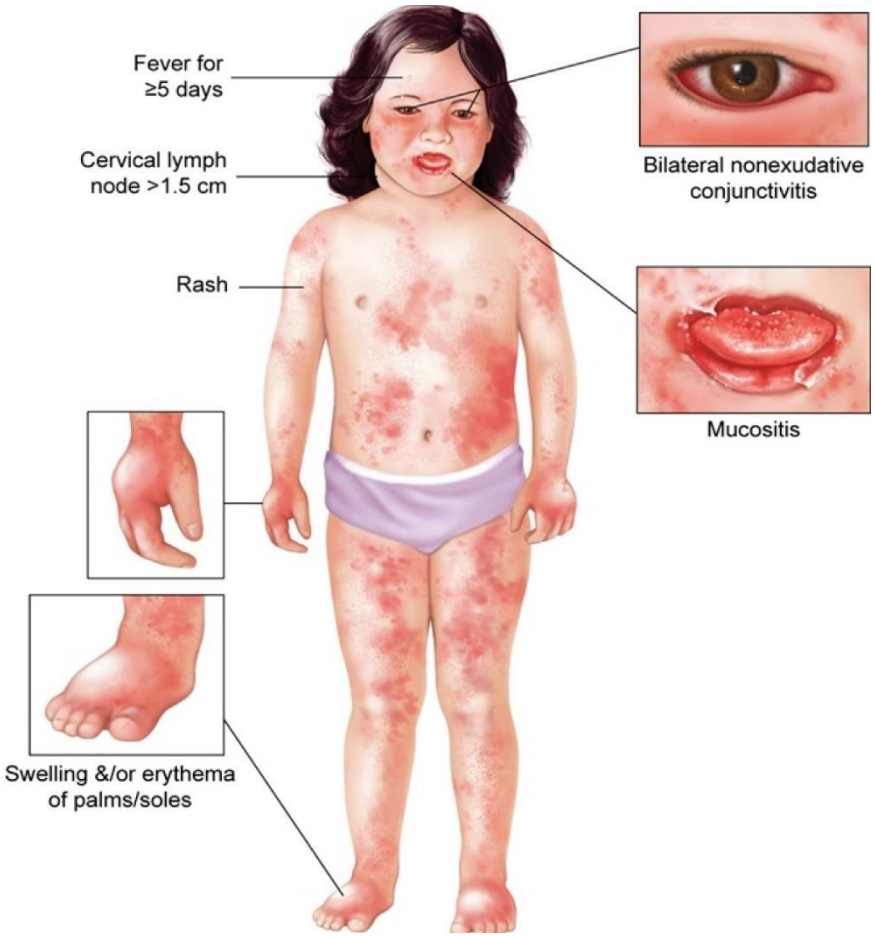
A. Polyarteritis Nodosa:

- PAN is a segmental, transmural, necrotizing inflammation of medium to small sized arteries in any organ.
- Usually middle-aged men.
- PAN is associated with hepatitis B infection in 10 to 30% of cases.
- The disease can affect nearly any site in the body, except the lungs. It has a predisposition for organs such as the skin, kidney, nerves, and GI tract.
- Classically presents in young adults as hypertension (renal artery involvement), abdominal pain with melena (mesenteric artery involvement), neurologic disturbances (peripheral neuropathy).
- Up to one-third of patients experience cutaneous manifestations, including livedo reticularis (a purplish network-patterned discoloration) and palpable purpura.
- There is also a propensity for bead-like aneurysm formation, especially in the mesenteric circulation.
- Early lesion consists of different stages of transmural inflammation with fibrinoid necrosis; eventually heals with fibrosis, producing a 'string-of-pearls' appearance on imaging.
- Treatment is corticosteroids and cyclophosphamide; fatal if not treated.

B. Kawasaki Disease:

- Kawasaki disease is necrotizing febrile vasculitis of medium-sized vessels that primarily affects the coronary blood vessels.
- The incidence of KD is greatest among children of East Asian ethnicity < 5 years.
- Diagnosis is based on clinical presentation. The patient should have fever for >5 consecutive days as well as 4 of the following 5 findings:
  - Conjunctivitis: bilateral, nonexudative, spares limbus.
  - Rash.
  - Cervical Adenopathy: >1.5 cm, usually unilateral, least consistent finding (present in <25%-50% of patients).
  - Oral mucosal changes: erythema, fissured lips, "Strawberry tongue".

- Hands and foot changes: erythema, edema, desquamation of the hands and feet, usually the last manifestation.



- CRASH and burn on a Kawasaki.

- Although the systemic inflammation in Kawasaki disease (KD) typically self-resolves in about 12 days without intervention, untreated patients are at risk for life-threatening cardiovascular sequelae, especially coronary artery aneurysms.

- The dilated arteries are prone to thrombotic occlusion and consequent myocardial ischemia and death.

- Treatment is aspirin and IVIG; disease is self-limited.

C. Buerger Disease (thromboangiitis obliterans):

- Necrotizing vasculitis involving digits.

- Highly associated with heavy smoking; treatment is smoking cessation.

- This condition may result from direct endothelial cell toxicity from tobacco products or from hypersensitivity to them.

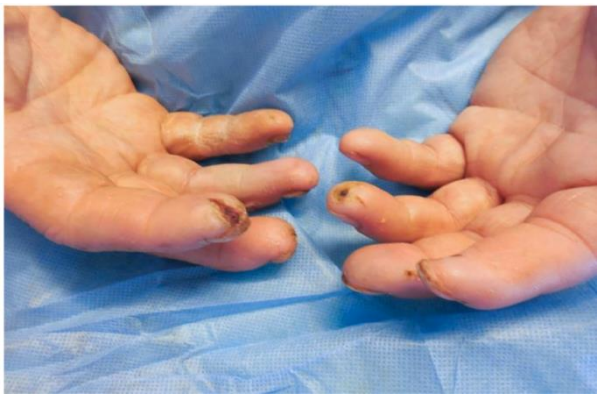
- Presents with intermittent claudication may lead to gangrene, autoamputation of digits, superficial nodular phlebitis.

- Raynaud phenomenon is often present.

- Histologically, there is acute and chronic inflammation of the arterial walls, often with thrombosis of the lumen, which can undergo organization and recanalization.

- This segmental thrombosing vasculitis often extends into contiguous veins and nerves (a feature rarely seen in other types of vasculitis).

- The inflammatory process may eventually encase all three structures (arteries, veins, and nerves) in fibrous tissue.



Small-vessel vasculitis

A. Granulomatosis with polyangiitis (Wegener):

- Necrotizing granulomatous vasculitis involving nasopharynx, lungs, and kidneys.

- Necrotizing vasculitis of the upper and lower respiratory tract (causing nasopharyngeal ulcerations, sinusitis, hemoptysis with bilateral nodular lung infiltrates) and rapidly progressive glomerulonephritis-producing a variable degree of renal failure is characteristic of granulomatosis with polyangiitis (Wegener's).

- Cytoplasmic-staining antineutrophil cytoplasmic antibodies (c-ANCAs) are virtually pathognomonic for granulomatosis with polyangiitis, with a better than 90% specificity and sensitivity.

- Biopsy reveals large necrotizing granulomas in the lung and upper airway.

- Treatment is cyclophosphamide and steroids; relapses are common.

B. Microscopic Polyangiitis:

- Necrotizing vasculitis commonly involving lung, kidneys, and skin with pauci-immune glomerulonephritis and palpable purpura.

- Presentation is similar to Wegener granulomatosis, but nasopharyngeal involvement and granulomas are absent.

- Serum p-ANCA levels correlate with disease activity.

- No granulomas in lung biobsy.

- Treatment is corticosteroids and cyclophosphamide; relapses are common.

C. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome):

- Necrotizing granulomatous inflammation associated with adult-onset asthma, eosinophilia, and p-ANCA.

- Additional clinical criteria for this diagnosis include a history of allergy, mono-or polyneuropathy (wrist or foot drop), migratory/transient pulmonary infiltrates, and paranasal sinus abnormalities.

- Asthma and peripheral eosinophilia are often present.

- Serum p-ANCA levels correlate with disease activity.

❖ N.B:

- The presence of antibodies against neutrophil myeloperoxidase, also known as perinuclear staining antineutrophil cytoplasmic antibodies (p-ANCA), suggest microscopic polyangiitis or Churg-Strauss vasculitis in this patient.
- The additional findings of asthma and eosinophilia makes Churg-Strauss syndrome the most likely diagnosis.
- Antineutrophil Cytoplasmic antibodies are also called "ANCA":
- C-ANCA = anti-proteinase-3 antibodies.
- P-ANCA = anti-myeloperoxidase antibodies.

Wegener: C-ANCA. Churg-Strauss and microscopic polyangiitis: P-ANCA.

D. Henoch-Schönlein Purpura (Immunoglobulin A vasculitis:

- Vasculitis due to IgA immune complex deposition; most common vasculitis in children.

- Usually occurs following an upper respiratory tract infection.

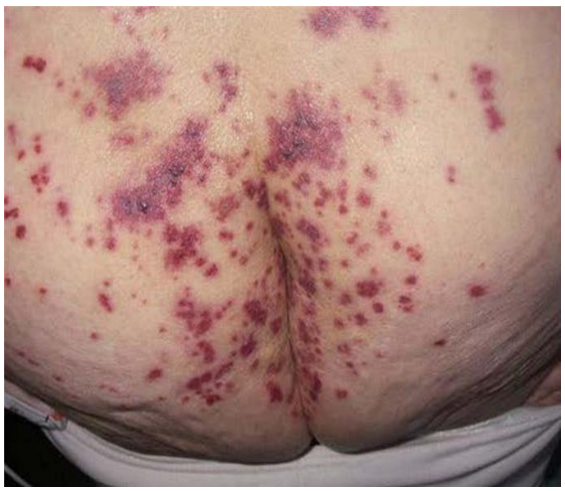
- A systemic hypersensitivity disease of uncertain etiology, HSP produces leukocytoclastic angiitis in small vessels of the dermis and the gastrointestinal (GI) tract.

- Clinically, a purpuric rash (100%), colicky abdominal pain (85%), and polyarthralgia (70%) may result.

- The rash is palpable and usually occurs on the lower extremities and buttocks.

- Although usually self-limiting, patients afflicted with HSP should be observed carefully because glomerulonephritis (IgA nephropathy) and even end-stage renal disease are possible complications.

- Disease is self-limited, but may recur; treated with steroids, if severe.



Mixed cryoglobulinemia

- Cryoglobulinemia is associated with chronic hepatitis C and sometimes hepatitis B.

- In addition to renal involvement, Cryoglobulinemia is an immune complex disorder (IgM against anti-hepatitis C virus IgG) most commonly due to chronic hepatitis C.

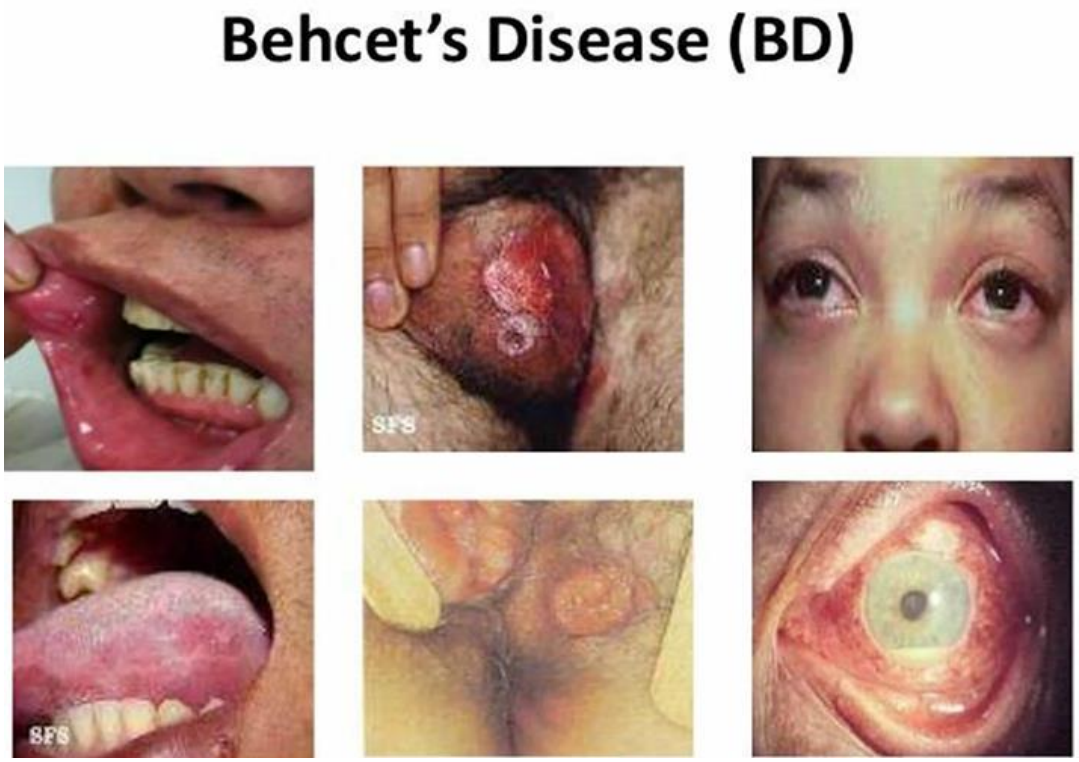
- Patients may develop vasculitis involving the skin, kidney, nerves, or joints:
  - Joint pain.
  - Skin lesions.
  - Hepatosplenomegaly.

- May also have peripheral neuropathy and renal disease (glomerulonephritis).

- Cryoglobulins are immunoglobulins that precipitate in the Cold.

Behçet syndrome

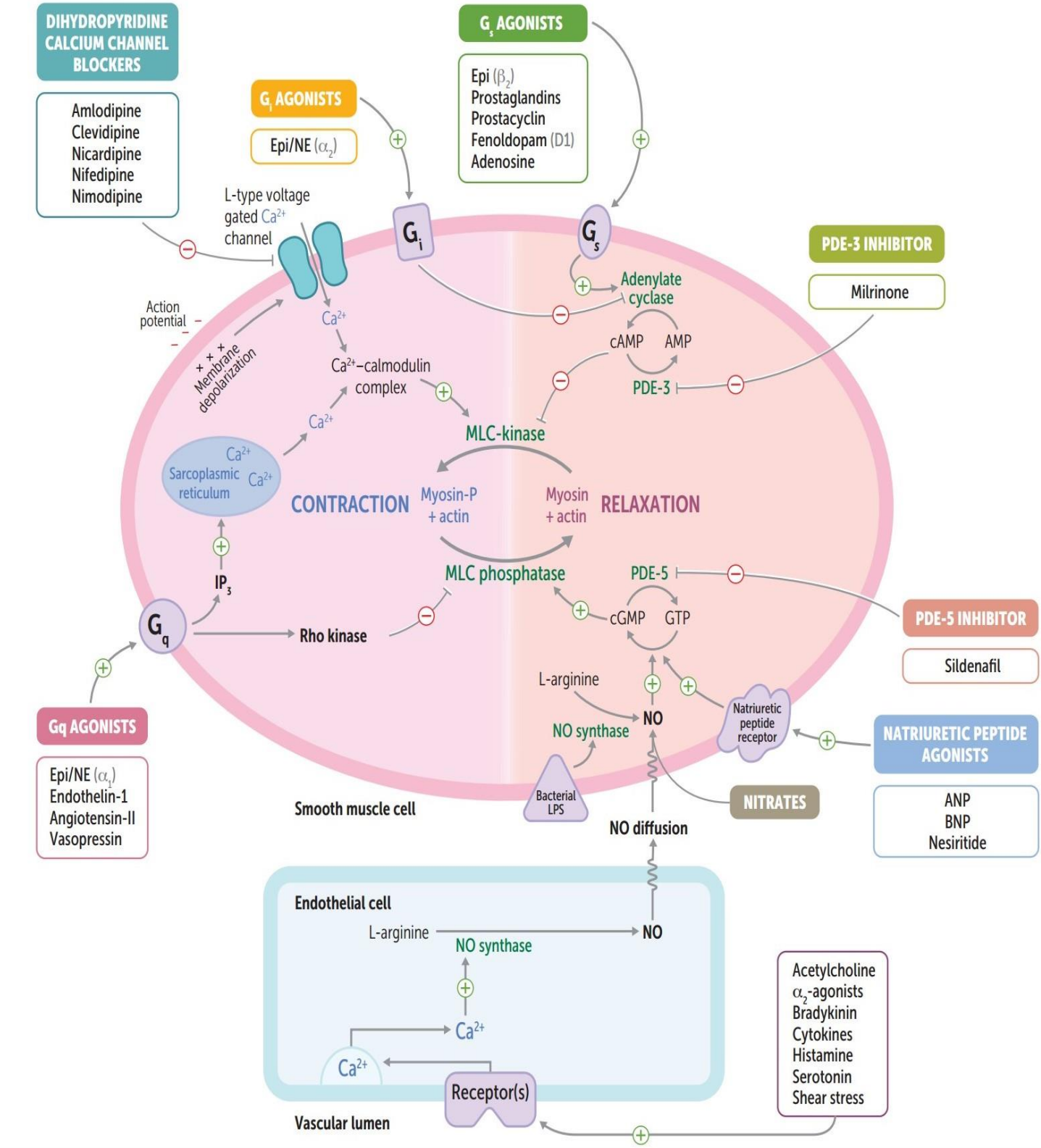
- High incidence in people of Turkish and eastern Mediterranean descent.
- Recurrent aphthous ulcers, genital ulcerations, uveitis, erythema nodosum.
- Can be precipitated by HSV or parvovirus.
- Flares last 1-4 weeks.
- Immune complex vasculitis.
- Associated with HLA-B51 (play rule in immune cell regulation).



CHAPTER 5

Pharmacology

Cardiac therapy



Antihypertensives

- Drug strategy:
- ↓ TPR (Blood vessels).
- ↓ CO (Heart).
- ↓ body fluid volume (Kidney).
- ↓ BP may result in homeostatic regulation:
  - Reflex tachycardia (↑ sympathetic activity).
  - Edema (↑ renin activity).

Calcium channel blockers (CCBs)

- Drugs:
- Amlodipine, clevidipine, nicardipine, nifedipine, nimodipine (dihydropyridines, act on vascular smooth muscle); diltiazem, verapamil (non-dihydropyridines, act on heart).

- Mechanism of action:
- Block voltage-dependent L-type calcium channels of cardiac and smooth muscle → ↓ muscle contractility.
- Vascular smooth muscle: amlodipine = nifedipine > diltiazem > verapamil.
- Heart: verapamil > diltiazem > amlodipine = nifedipine.

- Clinical Uses:
- Dihydropyridines:
  - Hypertension, angina (including Prinzmetal), Raynaud phenomenon.
  - Nimodipine: subarachnoid hemorrhage (prevents cerebral vasospasm).
  - Nifedipine causes peripheral vasodilatation which may result in reflex tachycardia. Therefore, this antihypertensive drug is useful for hypertensive patients with bradycardia.
- Non-dihydropyridines: hypertension, angina, atrial fibrillation/flutter.

- Side effects:
- Gingival hyperplasia.
- Non-dihydropyridine: cardiac depression, AV block, hyperprolactinemia (verapamil increases prolactin level), constipation.
- Dihydropyridine: peripheral edema, flushing, dizziness.

Drugs altering sympathetic activity

A. β blockers:

- Mechanism of action: (See ANS section).

- Side effects:

- Cardiovascular depression.
- Fatigue.
- Sexual dysfunction.
- ↑ LDLs and TGs.

- Cautions in use:

- Asthma.
- Vasospastic disorders (prinzemtal angina).
- Diabetics (alteration of glycemia and masking of tachycardia due to hypoglycemic events).

❖ N.B:

- Beta blockers are useful for treating hypertensive patients with comorbid conditions such as migraine, essential tremor, angina pectoris/prior myocardial infarction, and atrial fibrillation.
  Beta blockers lower blood pressure via 2 mechanisms:
- Reducing myocardial contractility and heart rate.
- Decreasing renin release by the kidney.
- Renin release is mediated in part through sympathetic stimulation of beta-1 receptors located on juxtaglomerular cells. Therefore, beta-adrenergic blocking drugs (metoprolol) act to inhibit renin release, which in turn reduces the conversion of angiotensinogen to angiotensin I and reduces the levels of angiotensin II (a potent vasoconstrictor) and aldosterone (decreasing renal sodium and water retention)

B. α_1 blockers:

- Drugs:

- Prazosin, doxazosin, terazosin. Tamsulosin is an α_1 blocker that acts only on prostate (no effect on blood vessels).

- Mechanism of action:

- ↓ arteriolar and venous resistance (nonselective on vasculature).

- Clinical Uses:

- Hypertension:
  - Alpha1-blockers such as Doxazosin, Prazosin and Terazosin are useful for the treatment of both benign prostatic hyperplasia and hypertension.
  - They act by blocking the alpha-1 adrenergic receptor leading to a relaxation of smooth muscle in arterial and venous walls leading to a decrease in peripheral vascular resistance. They do not have an effect on the chronotropy or inotropy of the heart.

- BPH:
  - via their blockade of the alpha-1 adrenergic receptor, these drugs induce relaxation of smooth muscle in the bladder neck and prostate leading to a decrease in urinary obstruction caused by benign prostatic hyperplasia (BPH). Thus, they are useful both as a treatment for hypertension and as a medical treatment for BPH.

- Side effects:

- First-dose syncope: The most notable issue with these medications is their tendency to cause hypotension when treatment is first started; this is known as a first-dose effect and can be ameliorated by starting with a very small first dose.

- Orthostatic hypotension: Decreased peripheral vascular resistance can lead to orthostatic hypotension and vertigo which are common side effects of this class of drugs.

- Urinary incontinence.

- Advantage: good effect on lipid profile (↑ HDL, ↓ LDL).

❖ N.B:
- Orthostatic hypotension is a frequent cause of lightheadedness and syncope and is defined as a decrease in systolic (>20 mm Hg) or diastolic (>10 mm Hg) blood pressure on standing from the supine position.
- Medications (α1-adrenergic antagonists, diuretics), volume depletion, and autonomic dysfunction are common causes of orthostatic hypotension.

C. Central α_2 agonists:
- Drugs: clonidine and methyldopa (prodrug).

- α_2 stimulation:
- ↓ in sympathetic outflow.
- ↓ TPR but also ↓ HR.

- Uses:
- Mild-to-moderate hypertension (both).

- Opiate withdrawal (clonidine).

- Hypertensive management in pregnancy (methyldopa).

▪ Side effects:
- Abrupt discontinuation of clonidine → upregulation of α_1 receptors on blood vessels → rebound hypertension.

- Positive Coombs test because 20% of patients get autoimmune hemolytic anemia (methyldopa).

- CNS depression (both).

Direct acting vasodilators

A. Drugs Acting Through Nitric Oxide:

1. Hydralazine:

▪ Mechanism of action:
- ↑ cGMP → smooth muscle relaxation.

- Vasodilates arterioles > veins; afterload reduction.

▪ Clinical Use:
- Severe hypertension (particularly acute), HF (with organic nitrate).

- Frequently coadministered with a β-blocker to prevent reflex tachycardia.

- Preeclampsia (safe in pregnancy).

▪ Side effects:
- SLE-like syndrome in slow acetylators.

- Edema.

- Reflex tachycardia (contraindicated in angina/CAD).

2. Nitroprusside:

▪ Mechanism of action:
- ↓ TPR via dilation of both arterioles and venules.

▪ Clinical Use: hypertensive emergencies (used IV).

▪ Side effect:
- Cyanide toxicity can occur in patients treated with nitroprusside.

- Cyanide is a potent mitochondrial toxin that binds to Fe^3 in cytochrome c oxidase, inhibiting the electron transport chain and halting aerobic respiration in the cell.

- Cyanide toxicity presents with altered mental status, seizures, cardiovascular collapse, lactic acidosis, and bright red venous blood.

- Antidotal treatment of cyanide toxicity can be achieved by 3 different strategies:
  - Direct binding of cyanide ions (hydroxocobalamin).
  - Induction of methemoglobinemia (sodium nitrite).
  - Use of detoxifying sulfur donors (sodium thiosulfate).

- Nitroprusside-induced cyanide toxicity is most likely to occur in patients receiving higher doses/prolonged infusions or those with renal insufficiency.

- Cyanide is normally metabolized in the tissues by rhodanese, an enzyme that transfers a sulfur molecule to cyanide to form thiocyanate, which is less toxic and excreted in the urine. Cyanide overdose depletes the available sulfur donors, allowing cyanide to accumulate in toxic amounts.

- Sodium thiosulfate works as an antidote by providing additional sulfur groups for rhodanese, enhancing cyanide detoxification. It is used in conjunction with hydroxocobalamin and sodium nitrite in the management of cyanide toxicity.

B. Drugs Acting to Open Potassium Channels (Minoxidil and diazoxide):

▪ Mechanism of action:

- Open K channel, causing hyperpolarization of smooth muscle → Results in arteriolar vasodilation (arteriole specific).

▪ Clinical Uses:

- Insulinoma (diazoxide).

- Severe hypertension (minoxidil).

- Baldness (topical minoxidil).

▪ Side effects:

- Hypertrichosis (minoxidil).

- Hyperglycemia (↓ insulin release [diazoxide]).

- Edema.

- Reflex tachycardia.

Hypertensive emergency

- A hypertensive emergency occurs when hypertension is severe enough to cause end-organ damage.
- Most commonly, nitroprusside, labetalol, or the D1 agonist fenoldopam is given intravenously as therapy.
- The management of hypertensive emergency requires immediate but gradual blood pressure reduction over minutes to hours to minimize target organ damage.
- The most important point in management is not to lower the pressure too far (not <95-100 mm Hg diastolic) so as not to compromise myocardial or cerebral perfusion. The initial goal is to reduce BP by no more than 25% within the first 1–2 hours.
- Because nitroprusside needs monitoring with an arterial line, this is not usually the first choice.
- Fenoldopam is a newer parenteral agent that is classified as a selective dopamine-1 receptor agonist.
- In contrast to dopamine, it is a selective dopamine-1 receptor agonist with no effect on alpha or beta receptors.
- Fenoldopam is indicated for short term management of severe hypertension and can be safely used in all hypertensive emergencies.
- Dopamine-1 receptor stimulation activates adenylyl cyclase and raises intracellular cyclic AMP, resulting in vasodilation of most arterial beds, especially renal, mesenteric, and coronary beds.
- It causes arteriolar dilation and natriuresis leading to decreased systemic vascular resistance and blood pressure reduction.
- Since fenoldopam is the only intravenous agent that improves renal perfusion, it may be exceptionally beneficial in hypertensive patients with concomitant renal insufficiency.

❖ Use of Antihypertensive Drugs in Comorbid Conditions:

- In medical practice, patients are often prescribed so many medications that they have trouble keeping track of them.

- In order to give them an opportunity for best compliance with your medical treatment, it is desirable to choose medications which can address multiple issues at once by taking advantage of the multiple effects of certain drugs on the body.

	Drugs	Notes
Primary (essential) hypertension	Thiazide diuretics, ACE inhibitors, angiotensin II receptor blockers (ARBs), dihydropyridine Ca channel blockers.	
Hypertension with heart failure	Diuretics, ACE inhibitors/ARBs, β-blockers (compensated HF), aldosterone antagonists.	β-blockers must be used cautiously in decompensated HF and are contraindicated in cardiogenic shock. In HF, ARBs may be combined with the neprilysin inhibitor sacubitril.
Hypertension with diabetes mellitus	ACE inhibitors/ARBs, Ca channel blockers, thiazide diuretics, β-blockers.	ACE inhibitors/ARBs are protective against diabetic nephropathy. β-blockers can mask hypoglycemia symptoms.
Hypertension in asthma	ARBs, Ca channel blockers, thiazide diuretics, cardioselective β-blockers.	Avoid nonselective β-blockers to prevent β2-receptor-induced bronchoconstriction. Avoid ACE inhibitors to prevent confusion between drug or asthma-related cough.
Hypertension in pregnancy	Hydralazine, labetalol, methyldopa, nifedipine.	"He likes my neonate"
Hypertensive emergency	Clevidipine, nicardipine, fenoldopam, labetalol, nitroprusside.	

❖ N.B:

1. Drugs that work by selective arteriolar vasodilation cause significant vasodilation and reductions in arterial pressure, subsequently stimulating baroreceptor mediated activation of the sympathetic system.

- Reflex sympathetic activation leads to increased heart rate, contractility, and increased renin activity resulting in sodium and fluid retention.
- Thus, although direct arteriolar vasodilators like hydralazine and minoxidil are effective in lowering blood pressure, they often cause reflex tachycardia and edema.
- Due to these bothersome side effects, these agents are rarely used first line and are usually reserved for patients with severely uncontrolled hypertension who are resistant to other drugs.
- To counteract these side effects, these agents are often given in combination with sympatholytics (beta blockers) and diuretics.

2. Chronic (preexisting) hypertension in pregnancy is often treated with methyldopa or labetalol, while preeclampsia (new-onset hypertension in pregnancy) is treated with labetalol or hydralazine.

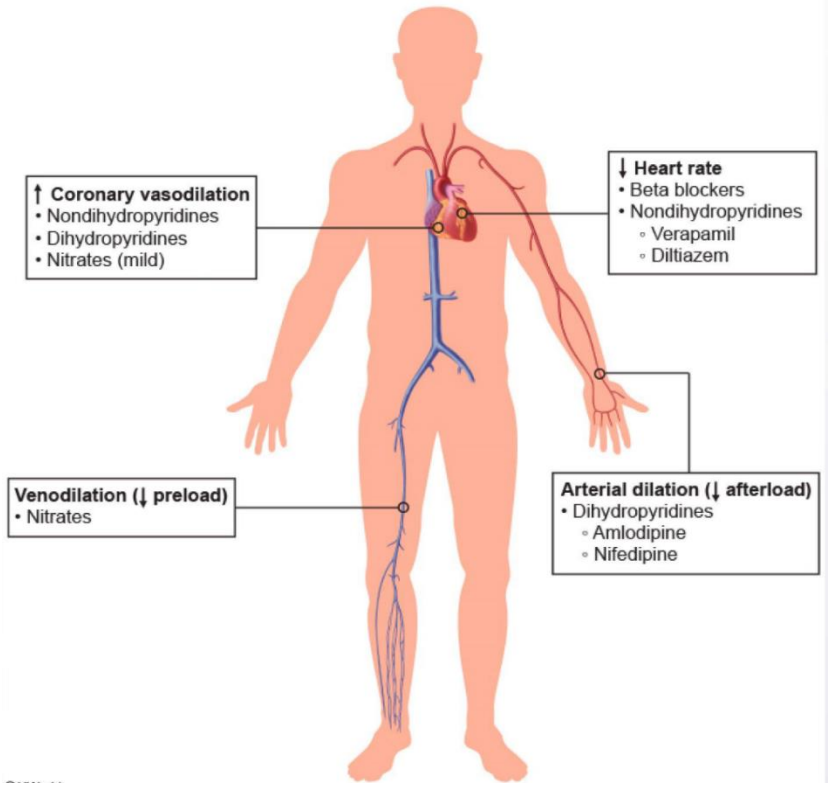
3. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) reduce the risk of chronic kidney disease in patients with hypertension and diabetes.

4. In patients with hypertension and chronic ischemic myocardial failure, ACE inhibitors are considered to be the most effective long-term treatment option, as they inhibit myocardial remodeling and the associated deterioration of ventricular contractile function, in addition to reducing blood pressure.
   - A beta-blocker would also be beneficial for these patients.

5. Isolated systolic hypertension is a common form of hypertension, especially in the elderly, where the systolic pressure is elevated while the diastolic is not.
   - Thiazide diuretics and dihydropyridine calcium antagonists are presently first-line drugs to treat isolated systolic hypertension in nondiabetic patients (where an ACEI or ARB would be utilized first).

Antianginal Drugs

- Drug strategies in stable and vasospastic angina involve:
- ↓ oxygen requirement by ↓ TPR, CO, or both (nitrates, CCBs, and beta blockers).
- ↑ oxygen delivery by ↓ vasospasm (nitrates and CCBs).



Nitrate

- Drugs:
- Nitroglycerin:
  - Sublingual, transdermal, and IV formulations.
  - Sublingual nitroglycerin is absorbed directly from oral mucosa into the venous circulation and has a higher bioavailability.

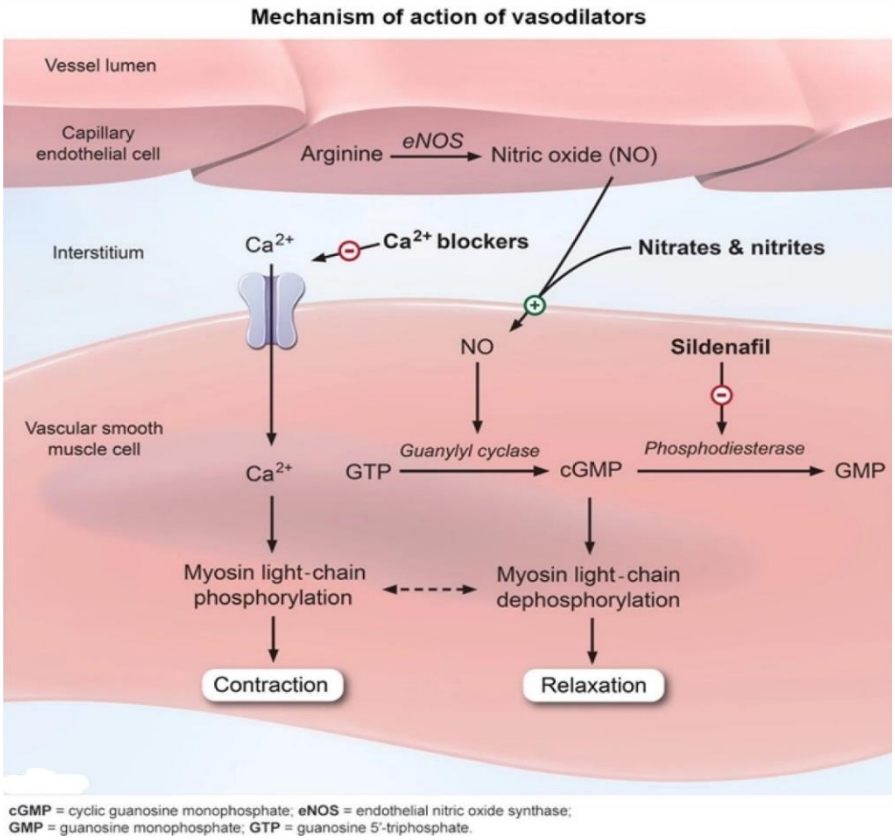
- Isosorbide:
  - Oral, extended release for chronic use.
  - Isosorbide dinitrate has a low bioavailability due to extensive first-pass hepatic metabolism prior to release in systemic circulation leading to the need for much higher doses of oral formulations as compared to sublingual nitroglycerin.

- Mechanism of action:
- Nitrates are metabolized within vascular smooth muscle cells to nitric oxide, which activates guanylate cyclase and promotes the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP).

- Increased levels of cGMP lead to decreased intracellular calcium, resultant decreased activity of myosin light-chain kinase, and, finally, myosin light chain dephosphorylation and vascular smooth muscle relaxation.

- Nitrates are primarily venodilators and increase peripheral venous capacitance, thereby reducing cardiac preload and left ventricular end-diastolic volume and pressure which decreases left ventricular wall stress and myocardial oxygen demand to relieve anginal symptoms.

- Nitrates also have a modest effect on arteriolar dilation and cause a decrease in systemic vascular resistance and cardiac afterload.



cGMP = cyclic guanosine monophosphate; **eNOS** = endothelial nitric oxide synthase; **GMP** = guanosine monophosphate; **GTP** = guanosine 5'-triphosphate.

- Clinical use:

- Angina, acute coronary syndrome, pulmonary edema.

- Side effects:

- Cutaneous Flushing, headache (because of the vasodilatory properties of nitrates in the meninges and skin).

- Orthostatic hypotension.

- Reflex tachycardia and fluid retention.

- Monday disease in industrial exposure: Development of tolerance for the vasodilating action during the work week and loss of tolerance over the weekend → tachycardia, dizziness, headache upon reexposure.

- Cautions and contraindications:

- Contraindicated in right ventricular infarction and hypertrophic cardiomyopathy, and with concurrent PDE-5 inhibitor use.

- Using nitrates together with phosphodiesterase (PDE) inhibitors (sildenafil) used for erectile dysfunction and pulmonary hypertension causes a profound systemic hypotension because they both increase intracellular cGMP which causes vascular smooth muscle relaxation. Their use together is absolutely contraindicated.

❖ N.B:

- Around-the-clock nitrate administration (in any form) rapidly results in development of tolerance to nitrates.
- This is why a nitrate-free interval must be provided every day in patients that are using daily long acting nitrates to avoid tolerance to the drug.
- The mechanism by which this occurs has not been fully demonstrated, but it is theorized that it is due to a decreased vascular sensitivity to nitrates and an increased sensitivity to endogenous vasoconstricting agents.
- Usually the nitrate-free period is timed to occur during the night when the patient is sleeping and cardiac work is the least.

Component	Nitrates	β-Blockers	Nitrates + β-Blockers
End-diastolic volume	↓	No effect or ↑	No effect or ↓
Blood pressure	↓	↓	↓
Contractility	↑ (reflex response)	↓	Little or no effect
Heart rate	↑ (reflex response)	↓	No effect or ↓
Ejection time	↓	↑	Little or no effect
MVO2 (myocardial O2 consumption)	↓	↓	↓↓

- Pindolol and acebutolol: partial β-agonists contraindicated in angina (they have intrinsic sympathomimetic activity).

- Drugs that decrease mortality in patients with stable angina include aspirin, nitroglycerin, and beta blockers.

Ranolazine

- Mechanism of action:

- Inhibits the late phase of sodium current thereby reducing diastolic wall tension and oxygen consumption.

- Does not affect heart rate or contractility.

- Clinical use: Angina refractory to other medical therapies.

- Adverse effects:

- Side effects include constipation and nausea.

- Increased QT makes the drug contraindicated in patients with long QT syndrome or taking drugs which increase QT.

Drugs for Heart failure

- Pharmacotherapy aimed at:

- ↓ preload: diuretics, ACEIs, ARBs, and venodilators.

- ↓ afterload: ACEIs, ARBs, and arteriodilators.

- ↑ contractility: digoxin, beta agonists, PDE III inhibitors.

- ↓ remodeling of cardiac muscle: ACEIs, ARBs, spironolactone, beta blockers.

- Whereas digoxin does not improve survival, ACEIs, ARBs, beta blockers, and spironolactone have been proven beneficial in CHF (all drugs that have been shown to improve survival do so by inhibiting remodeling).

Digoxin

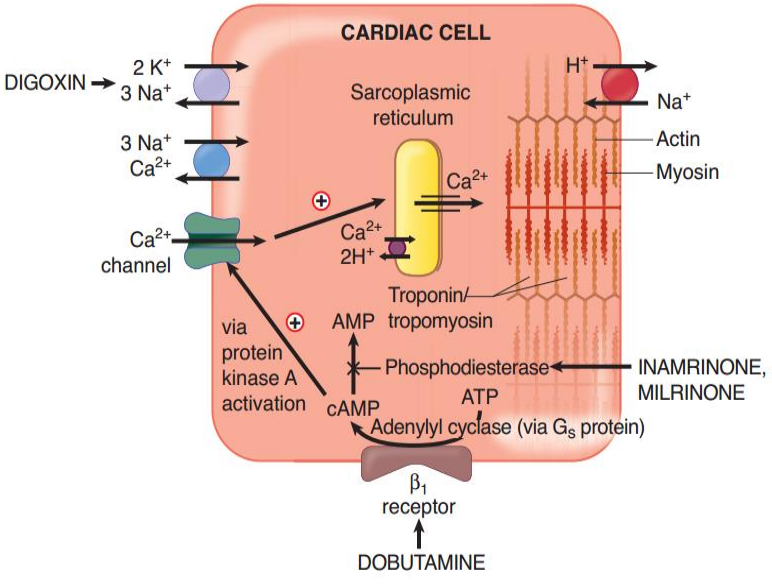
- Mechanism of action:

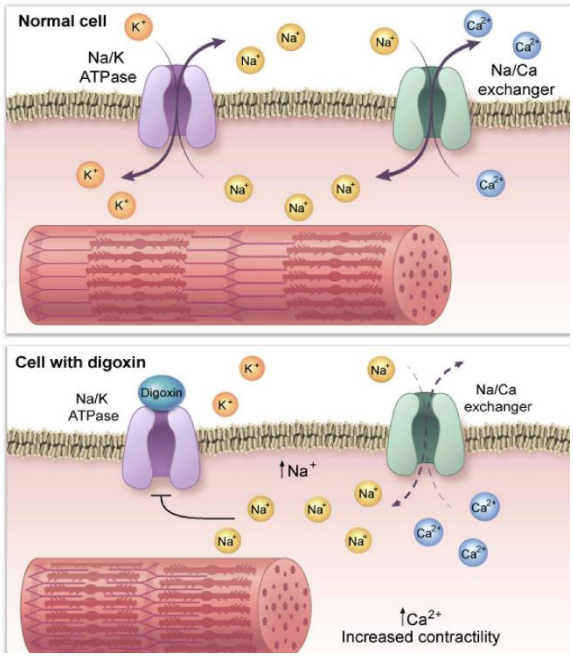
- Direct effect:
  - Inhibition of cardiac Na-K ATPase → Results in decreased sodium efflux and ↑ intracellular Na → ↓ Na/Ca exchange → ↑ intracellular Ca →↑ Ca release from sarcoplasmic reticulum → ↑ actin-myosin interaction → ↑ contractile force.

- Indirect effect:
  - Inhibition of neuronal Na-K ATPase → Results in ↑ vagal activity → Good for supraventricular arrhythmia.

- Pharmacokinetics:

- Long t1/2: need loading dose (LD).





- Renal clearance: caution in renal impairment.

- Clinical Uses:

- CHF:
  - Digoxin is a positive inotropic agent and provides symptomatic relief in patients with acute decompensated heart failure due to left ventricular systolic dysfunction.

- Supraventricular tachycardias, except Wolff-Parkinson-White syndrome:
  - It has an anti-adrenergic effect (via increased parasympathetic tone) with slowing of conduction through the atrioventricular node, which can help improve cardiac function in patients with rapid ventricular rate.

- Side effects:

- Digoxin has a narrow therapeutic index, making toxicity relatively common.

- Factors predisposing to toxicity: Renal failure (↓ excretion), hypokalemia (permissive for digoxin binding at K-binding site on Na/K ATPase), drugs that displace digoxin from tissue-binding sites, and ↓ clearance (verapamil, amiodarone, quinidine).

- Digoxin toxicity presents with nonspecific gastrointestinal (anorexia, nausea, vomiting) and neurologic (fatigue, confusion, weakness) symptoms.

- Changes in color vision (Blurry yellow vision) are a more specific, but rarer, finding.

- The most serious complication of digoxin toxicity is the development of potentially fatal cardiac arrhythmias of virtually any type.

- Hyperkalemia is another sign of digoxin toxicity and is caused by inhibition of Na-K-ATPase pumps. Digoxin and potassium compete with each other for Na-K-ATPase; thus digoxin toxicity results in hyperkalemia.

- Management of toxicity:

- Slowly normalize K, cardiac pacer, anti-digoxin Fab fragments, Mg.

- Drug interactions:

- Diuretics → hypokalemia → Hypokalemia enhance digoxin toxicity.

- Quinidine and verapamil (displace digoxin from tissue binding sites and ↓ clearance).

❖ N.B:

1. Digoxin is a second-line treatment for atrial fibrillation with rapid ventricular response (AF with RVR) because of its ability to slow conduction through the AV node.

- Calcium channel blockers such as diltiazem and cardioselective beta-blockers are frequently used as first line.
- Digoxin causes increased parasympathetic tone through its action on the vagus nerve, which leads to a decreased rate of AV conduction.
- Thus, with slowed AV conduction the atria will continue to fibrillate or flutter, but the ventricles will contract at a more normal rate.
- RVR is a serious condition because there is inadequate diastolic filling time leading to poor cardiac output and backup of blood in the lungs (heart failure).

2. Digoxin is is predominantly cleared by the kidneys.

- As patients age, renal function decreases progressively. This decrease in renal function is often not accompanied by a concomitant rise in serum creatinine, as creatinine is derived from muscle tissue and lean body mass also decreases with age.
- Therefore, elderly patients (even those with a normal serum creatinine) should receive reduced doses of renally cleared medications to prevent toxicity.

Phosphodiesterase inhibitors

- Drugs:

- Inamrinone and milrinone.

- Clinical Use:

- Acute CHF only.

- Mechanism of action:

- Milrinone is a selective phosphodiesterase (PDE)-3 enzyme inhibitor that can be used in patients with refractory heart failure due to left ventricular systolic dysfunction.

- The PDE-3 enzyme is normally responsible for degrading cyclic adenosine monophosphate (cAMP) to AMP; the inhibition of cAMP degradation via milrinone has 2 positive effects on heart failure:

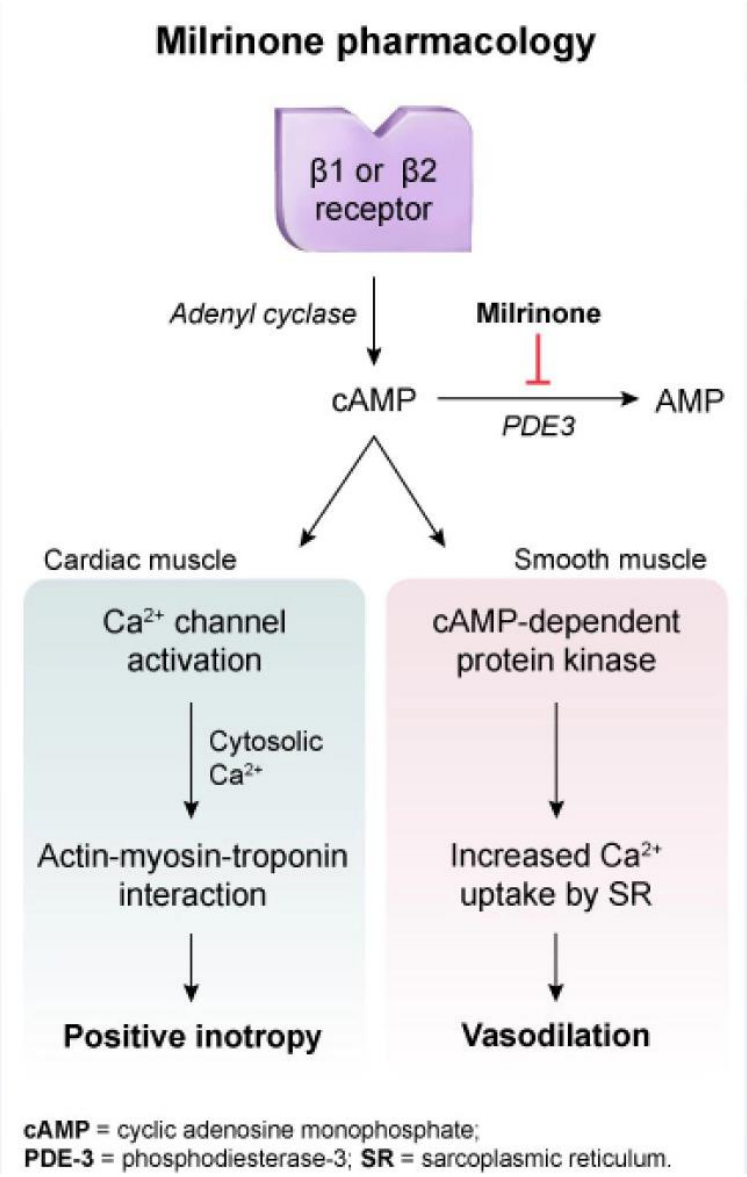
  - In cardiomyocytes: intracellular calcium influx is increased, which increases cardiac contractility (positive inotropy) to improve stroke volume and cardiac output.

  - In vascular smooth muscle: uptake of calcium by the sarcoplasmic reticulum is increased, which reduces calcium-myosin light chain kinase interaction to stimulate relaxation and vasodilation. Venous vasodilation reduces preload and arterial vasodilation reduces afterload to provide a cumulative reduction in cardiac work.

- Although the vasodilatory action of milrinone can lead to hypotension, this effect is often compensated for by an increase in stroke volume that maintains blood pressure.

- Side effects:

- In vascular smooth muscle, increases in cAMP cause vasodilation, a well-known side effect of phosphodiesterase inhibitors which can occasionally limit their use in hypotensive patients.



Sympathomimetics: dobutamine and dopamine

- Clinical Use: acute CHF only.

- Dobutamine is a beta-adrenergic agonist with predominant activity on beta-1 receptors, weaker activity on beta-2 receptors, and minimal activity on alpha-1 receptors.

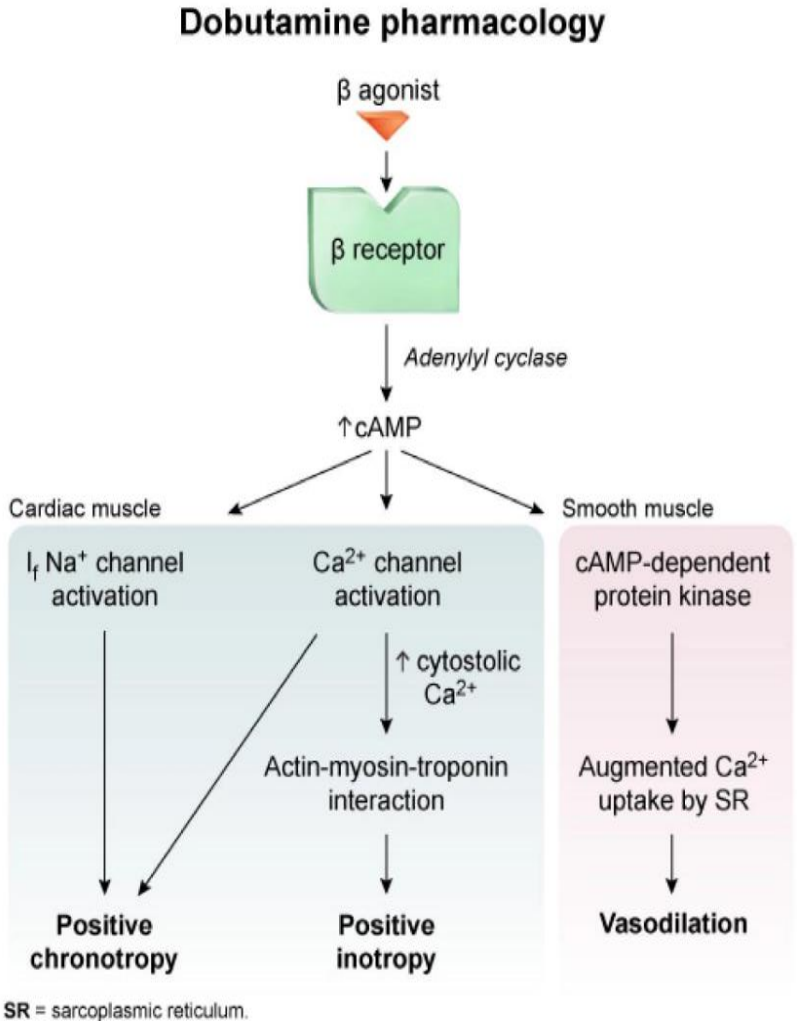
- It is used for management of refractory heart failure associated with severe left ventricular systolic dysfunction and cardiogenic shock.

- Stimulation of beta adrenergic receptors results in causes Gs protein GTP binding, leading to activation of adenylyl cyclase and increased production of cAMP in the target cells and causes the following effects:

- Positive inotropy and chronotropy: Increased cardiac contractility (potent effect) and heart rate (weaker effect), leading to increased cardiac output (improves end-organ perfusion) and decreased left ventricular filling pressures (improves pulmonary congestion/edema).

- Mild vasodilation: Decreased systemic vascular resistance that often causes a slight reduction in blood pressure; this avoids the increase in afterload seen with other vasopressor/inotropic agents (norepinephrine) but limits its usefulness in severely hypotensive patients.

- The strong inotropic effect of dobutamine significantly increases myocardial oxygen consumption, which can trigger or exacerbate myocardial ischemia. As such, dobutamine should not be used routinely in patients with decompensated heart failure. However, in patients with cardiogenic shock, this drawback is often outweighed by improvement in cardiac output and end-organ perfusion.



Sacubitril

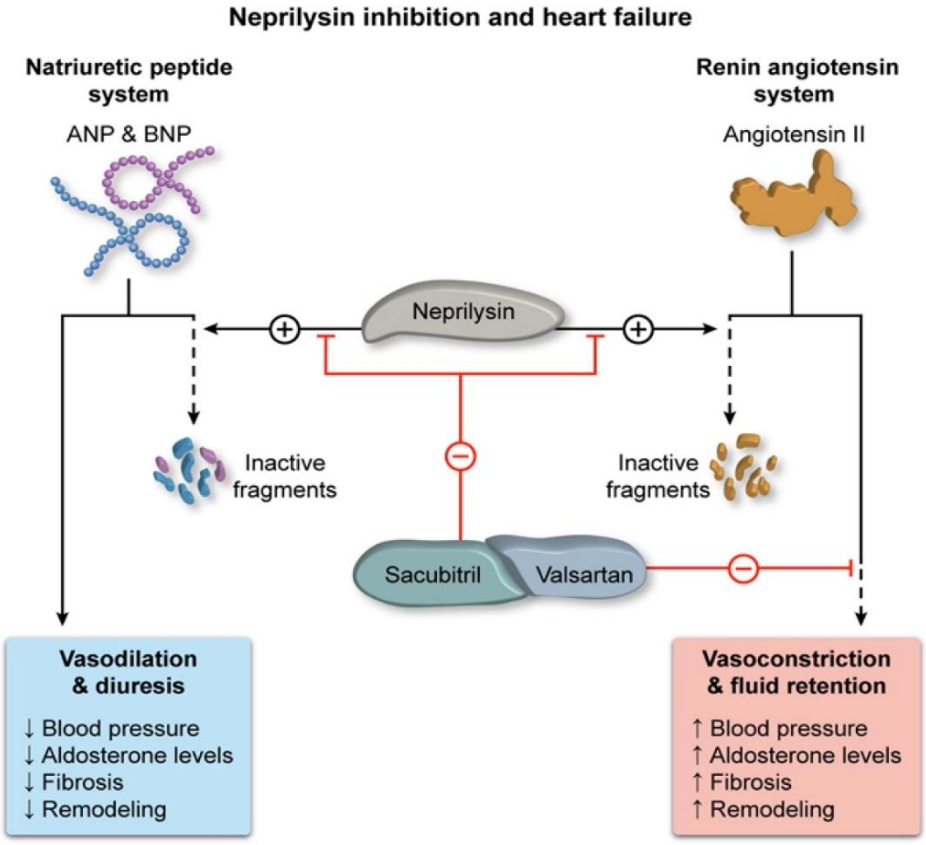
- Mechanism of action:

- Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are released from the myocardium in response to high atrial and ventricular filling pressures (myocardial stretch).

- These peptides induce vasodilation and diuresis by antagonizing the actions of RAAS and also protect against the deleterious myocardial remodeling and fibrosis that occur in heart failure.

- Neprilysin is a metalloprotease that cleaves and inactivates both ANP and BNP. Therefore, medications that inhibit neprilysin (sacubitril) lead to increased levels of ANP and BNP and promote beneficial effects in heart failure.

- However, because neprilysin is also responsible for inactivating angiotensin II, inhibition of neprilysin further stimulates deleterious vasoconstriction and fluid retention via increased angiotensin II levels. Therefore, in treating heart failure, neprilysin inhibitors are combined with an angiotensin II-receptor blocker (sacubitril-valsartan) to mitigate these negative effects.



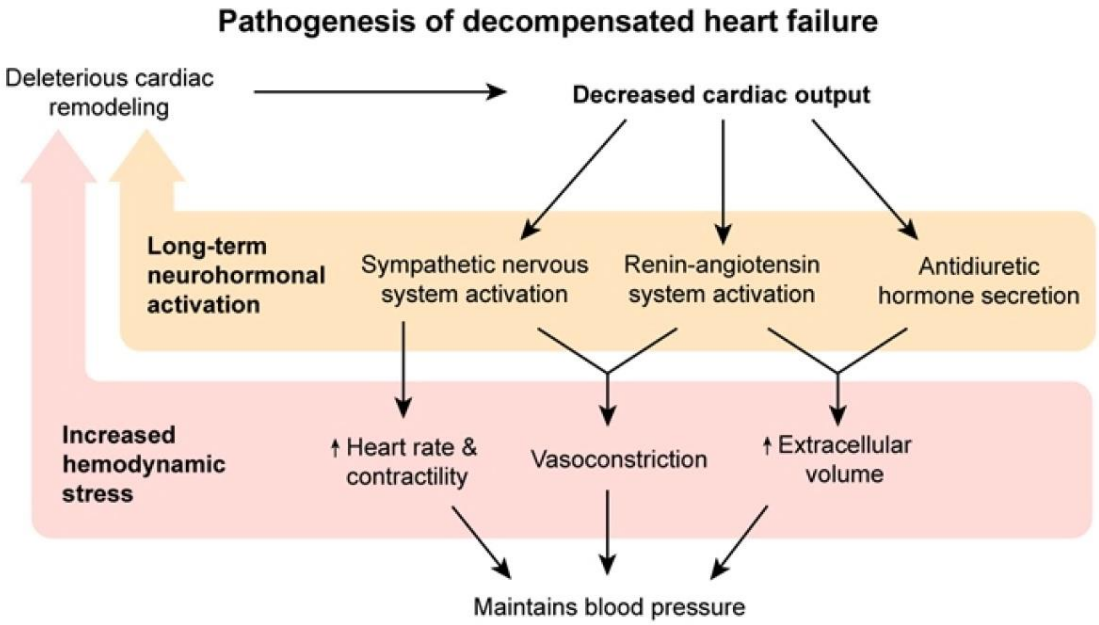
- Clinical use: Used in combination with valsartan (an ARB) to treat HFrEF.

- Adverse effects: Hypotension, hyperkalemia, cough, dizziness; contraindicated with ACE inhibitors due to angioedema.

❖ N.B:

1. Much of this mortality benefit is likely related to a reduction in deleterious cardiac remodeling.

- Increased activity of the sympathetic nervous system and renin-angiotensin-aldosterone system both promote deleterious cardiac remodeling. In particular, elevated angiotensin II and aldosterone levels increase pathologic cardiomyocyte hypertrophy and stimulate collagen deposition by fibroblasts (cardiac fibrosis).
- Accordingly, ACE inhibitors (lisinopril), angiotensin-receptor blockers (losartan), and mineralocorticoid receptor antagonists (spironolactone, epleronone) reduce mortality in patients with FIFrEF via a reduction in angiotensin ll-mediated (and downstream aldosterone-mediated) cardiac remodeling.
- Beta blockers (metoprolol, carvedilol) also reduce mortality in patients with chronic HFrEF, likely by reducing hemodynamic factors (increased wall stress) that promote pathologic cardiac remodeling.



2. After initial stabilization, long-term use of beta blockers (carvedilol, metoprolol) has been shown to improve survival in patients with HF due to left ventricular systolic dysfunction.

- Beta blockade decreases myocardial work and oxygen demand by slowing the ventricular rate and reducing contractility. It also lowers peripheral resistance (afterload) by decreasing circulating levels of vasoconstricting hormones (renin).
- These effects are cardioprotective and help reduce cardiomyocyte death and limit deleterious cardiac remodeling.
- Beta blockers should not be initiated in patients with unstable (decompensated) HF, as they can further impair cardiac output; they should be introduced slowly after the patient has been stabilized.

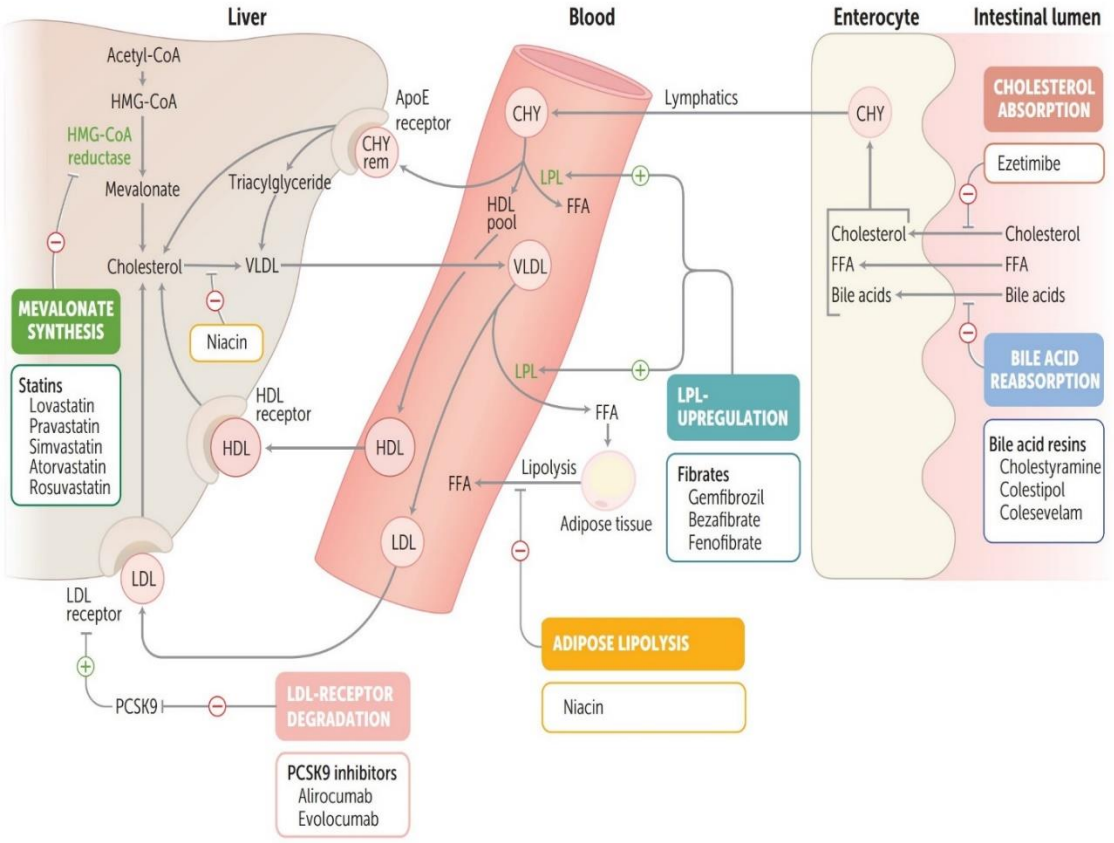
Pharmacotherapy for chronic heart failure with reduced ejection fraction	
Agent	**Mortality benefit**
ACE inhibitor (eg, lisinopril) or **Angiotensin receptor blocker** (eg, losartan) or **Neprilysin inhibitor-angiotensin receptor blocker** (eg, sacubitril-valsartan)	Yes
Beta blocker (eg, metoprolol)	Yes
Mineralocorticoid receptor antagonist (eg, spironolactone)	Yes
Diuretics (eg, furosemide, metolazone)	No*
Digoxin	No**

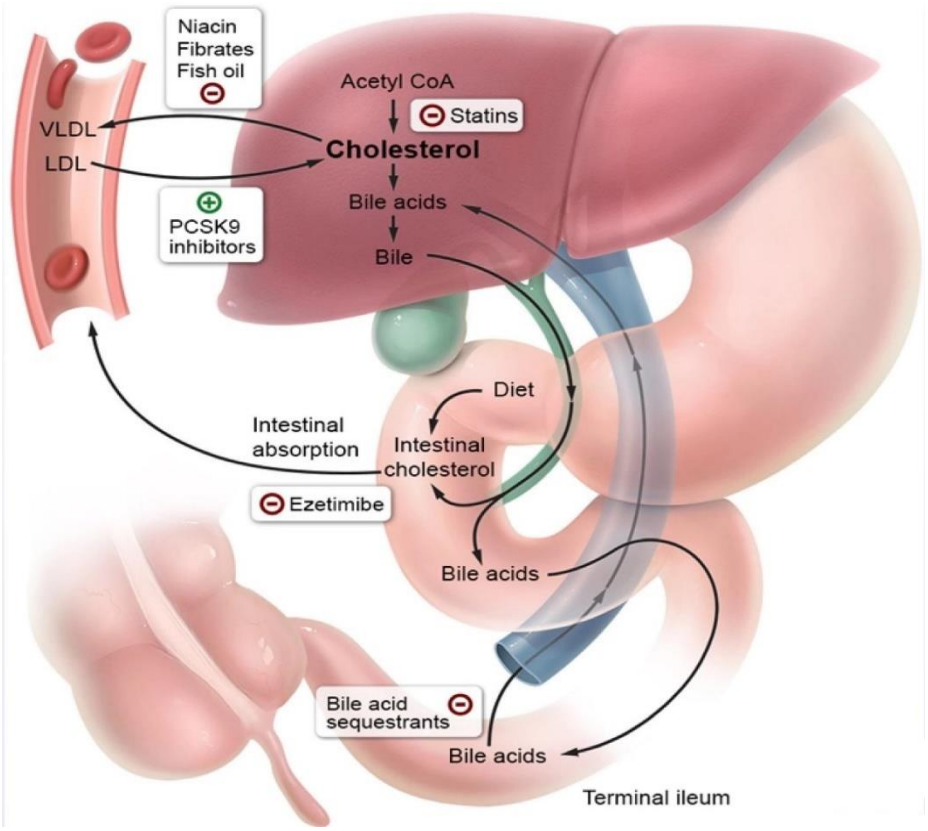
*Improves symptoms & reduces hospitalization.

**Reduces hospitalization.

Antihyperlipidemic

- Treatment goal is to ↓ LDL cholesterol and atheroma plaque formation.





HMG-CoA reductase inhibitors

- Drugs:

- Atorvastatin, rosuvastatin, and other "–statins"

- Mechanism of action:

- Statins are the first-line therapy for most patients with hypercholesterolemia.

- These drugs competitively inhibit HMG CoA reductase, the enzyme responsible for the conversion of HMG CoA to mevalonate (the rate limiting step in hepatic cholesterol synthesis).

- This inhibition decreases hepatic cholesterol synthesis.

- The resulting upregulation of LDL receptors causes increased uptake of LDL from the circulation.

- ↓ VLDL synthesis results in → ↓ triglyceridemia.

- Clinical uses:

- Statins are the most effective lipid-lowering drugs for primary and secondary prevention of cardiovascular events, regardless of baseline lipid levels.

- Statins are commonly prescribed for patients who have suffered a myocardial infarction because they have been shown to significantly decrease both the incidence of a second myocardial infarction and mortality in these patients.

- These benefits are due to statins' cholesterol lowering effects, as well as to statins' direct ability to stabilize atheromatous plaques.

- Side effects:

- Myalgia, myopathy and myositis (check creatine kinase).

- Myositis causes elevations of creatinine kinase and usually occurs when higher doses of statins are used, whereas myalgias are a more common symptom not associated with a rise in serum creatinine kinase.

- Rhabdomyolysis (Acute renal failure is a possible sequela of rhabdomyolysis).

- The risk of statin myopathy is increased when fibrates and/or niacin are used concomitantly.

- Hepatotoxicity (Hepatic transaminases should be checked prior to initiating therapy and repeated if symptoms of hepatic injury occur).

- Drug interaction:

- Gemfibrozil ↑ rhabdomyolysis: Fibrates impair hepatic clearance of statins, increasing the risk of severe myopathy.

- Most statins are metabolized by cytochrome P-450, with the exception of pravastatin. Concomitant administration of drugs that inhibit statin metabolism (CYP450 inhibitors) is associated with increased incidence of statin-induced myopathy and rhabdomyolysis.

CYP 450 Inducers	CYP 450 Inhibitors
Carbamazepine	Cimetidine
Phenobarbital	Ciprofloxacin
Phenytoin	Erythromycin
Rifampin	Azole antifungals
Griseofulvin	Grapefruit juice
	Isoniazid
	Ritonavir (protease inhibitors)

Bile acid sequestrants

- Drugs:

- Cholestyramine, colesevelam and colestipol.

- Mechanism of action:

- Bile acid-binding resins work by binding bile acid in the gastrointestinal tract, thereby interfering with its enterohepatic circulation.

- Bile acid production is increased 10-fold in patients on these medications because of the interruption in the enterohepatic circulation of bile acids.

- LDL is reduced as a result, because hepatic cholesterol is used up for the re-synthesis of bile acids, which in turn increases the uptake of LDL from the circulation.

- Hepatic production of triglycerides and VLDL is increased as well, which results in an increase in serum triglyceride levels.

- Side effects:
- GIT upset: The main side effects of bile acid-binding resins are gastrointestinal upset, and impaired absorption of nutrients (fat soluble vitamins) and drugs.

- Cholesterol gallstone: Bile acid-binding agents increase the cholesterol content of bile, thus increasing the risk for formation of cholesterol gallstones.

- Hypertriglyceridemia.

- Drug interactions:
- Drug interactions with orally administered drugs (warfarin, thiazides, digoxin, etc).

- Bile acid-binding resins are primarily used in combination with statins. Simvastatin decreases hepatic cholesterol production, while cholestyramine increases hepatic cholesterol and bile acid synthesis. Combination therapy results in a synergistic reduction in plasma LDL level. Concurrent administration of these two drug types results in decreased statin absorption. For this reason, it is recommended that these agents be administered at least four hours apart.

- Contraindication:
- Because of this tendency for bile acid-binding agents to increase serum triglyceride levels, they should not be used in hypercholesterolemia patients who have concomitant hypertriglyceridemia.

Gemfibrozil, Fenofibrate (fibrates)

- Mechanism of action:
- Fibrates work by activating peroxisome proliferator-activated receptor alpha (PPAR-α), which leads to decreased hepatic VLDL production and increased lipoprotein lipase activity.

- Lipoprotein lipase (LPL) hydrolyzes triglycerides in chylomicrons and VLDL to release free fatty acids, which can be used for energy or converted back to triglycerides for storage in adipose tissue → ↑ TG clearance.

- Clinical uses:
- Used in hypertriglyceridemia. Fibrates (gemfibrozil) are the first-choice drug class and can rapidly lower triglycerides by 25-50% or more.

- Side effects:
- Myopathy (↑ risk with statins).

- Gallstones (↑ risk with bile acid resins).

Niacin

- Drugs:
- Nicotinic acid (vitamin B_3).

- Mechanism of action:
- Inhibits lipolysis (hormone sensitive lipase) in adipose tissue; reduces hepatic VLDL synthesis, results in →↓ plasma VLD, ↓ plasma LDL, ↑↑ plasma HDL (↓ clearance).

- Side effects:
- Niacin's main side effects are cutaneous (flushing, warmth, itching). This side effect may be mediated by prostaglandins, as evidenced by the fact that 325mg of aspirin taken 30-60 minutes before nicotinic acid administration significantly reduces these cutaneous symptoms.

- Hyperglycemia: Niacin use is also associated with increased insulin resistance, which sometimes manifests as acanthosis nigricans.

- Hyperuricemia: there is an increase in serum uric acid in some patients being treated with niacin. Therefore, patients with gout should be cautious when niacin is started.

- Hepatotoxicity can occur with high doses of nicotinic acid.

Ezetimibe

- Mechanism of action:
- Prevents cholesterol absorption at small intestine brush border → results in ↓ LDL.

- Side effect: gastrointestinal upset, Rare ↑ LFTs.

PCSK9 inhibitors

- Drugs: Alirocumab, evolocumab.

- Mechanism of action:
- Inactivation of LDL-receptor degradation → ↑ removal of LDL from bloodstream

- Side effects:
- Myalgias, delirium, dementia, other neurocognitive effects

Fish oil and marine omega-3 fatty acids

- Mechanism of action:

- ↓ VLDL synthesis and Apoproteins B sysnthesis → ↓ TGs.

- Side effects: Nausea, fish-like taste.

❖ N.B:

- Although low HDL concentration is associated with increased cardiovascular risk, the use of medications to raise HDL levels does not improve cardiovascular outcomes.

Antihyperlipidemic medications

Drug	Mechanism	Major lipid effects	Side effects
Statins	• Inhibit HMG-CoA reductase	• ↓↓ **LDL** • ↓ Triglycerides	• Hepatotoxicity • Muscle toxicity
Ezetimibe	• ↓ Intestinal cholesterol absorption	• ↓ LDL	• ↑ Hepatotoxicity if given with statins
Bile acid sequestrants	• Prevent reabsorption of bile acids in the intestine	• ↓ LDL	• Nausea, bloating, cramping • Impaired absorption of drug & fat-soluble vitamin
Niacin	• ↓ Fatty acid release • ↓ VLDL synthesis • ↓ HDL clearance	• ↓ LDL • ↑↑ HDL	• Flushing & pruritus • Hepatotoxicity • Hyperuricemia/gout
Fibrates	• Activate PPAR-α • ↓ VLDL synthesis	• ↓↓ **Triglycerides** • ↑ HDL	• Muscle toxicity • Gallstones
Fish oil/omega-3 fatty acids	• ↓ VLDL synthesis • ↓ Apolipoprotein B synthesis	• ↓ Triglycerides • ↑ HDL	• Fishy taste

PPAR-α = peroxisome proliferator-activated receptor-alpha.

Antiarrhythmic Drugs

Sodium channel blockers (class I)

- Class I agents are divided into three groups (IA, IB and IC) based upon their effect on the length of the action potential:

- Ia lengthens the action potential (right shift).
- Ib shortens the action potential (left shift).
- Ic does not significantly affect the action potential (no shift).

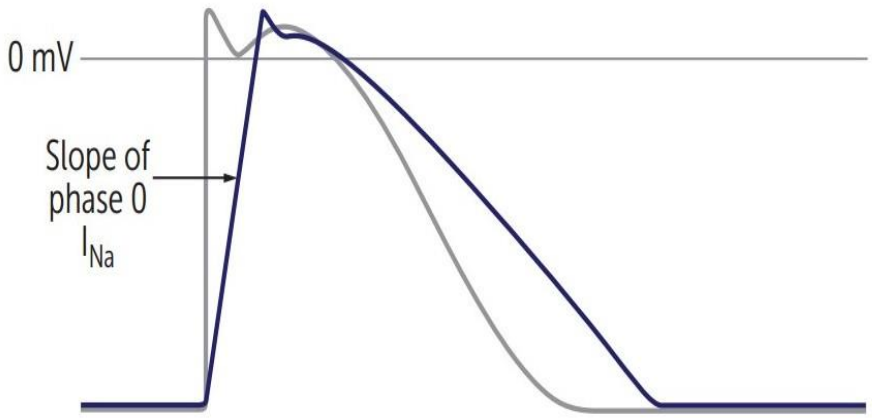
- Slow or block conduction (selectively depress tissue that is frequently depolarized [tachycardia]).

1. Class 1A:

- Mechanism of action:

- Moderate Na channel blockade:
  - Preferentially in the open or activated state "state-dependent" blockade → ↓ slope of phase 0 depolarization.

- Blocks K channel (prolongs repolarization) → ↑ AP duration, ↑ effective refractory period (ERP) in ventricular action potential, ↑ QT interval.



- Drugs:

- Quinidine, Procainamide, Disopyramide.

- "The Queen Proclaims Diso's pyramid".

- Clinical use:

- Both atrial and ventricular arrhythmias, especially re-entrant and ectopic SVT and VT.

A. Quinidine:

- Mechanism of action:

- In addition to the above, causes muscarinic receptor blockade, which can ↑ HR and AV conduction.

- May also cause vasodilation via alpha block with possible reflex tachycardia.

- Clinical use:

- In atrial fibrillation, need initial digitalization to slow AV conduction.

- Adverse effects:

- Cinchonism (GI, tinnitus, ocular dysfunction, CNS excitation), hypotension, prolongation of QRS and ↑ QT interval associated with syncope (torsades).

B. Procainamide:

- Mechanism of action:

- Less muscarinic receptor block and no alpha blockade effect.

- Metabolized via N-acetyltransferase (genotypic variation) to N-acetyl procainamide (NAPA), an active metabolite.

- Adverse effects:

- Systemic lupus erythematosus (SLE) like syndrome (30% incidence) more likely with slow acetylators; hematotoxicity (thrombocytopenia, agranulocytosis); CV effects (torsades).

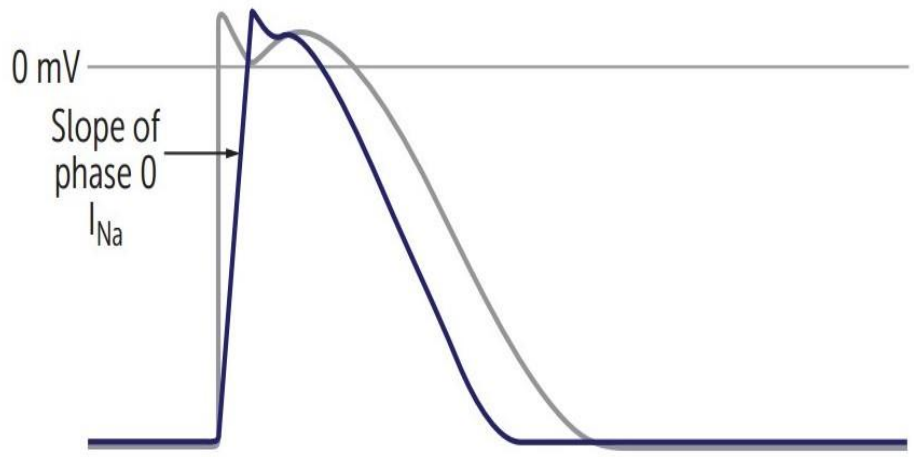
2. Class 1B:

- Mechanism of action:

- Weak Na channel blockade

- Preferentially affect hypoxic and ischemic tissues.

- Shortening of APD.



- Drugs:

- Lidocaine (also a local anesthetic), Mexiletine.

- Phenytoin can also fall into the IB category.

- Clinical use:

- Class 1B antiarrhythmics are useful for treating ischemia-induced ventricular arrhythmias, one of the most common causes of death in the short term following acute myocardial infarction, digitalis-induced arrhythmias.

- IB is Best post-MI.

A. Lidocaine:

- Clinical uses: Post-MI, Open-heart surgery and Digoxin toxicity.

- Side effects: CNS toxicity (seizures); least cardiotoxic of conventional anti-arrhythmics.

- IV use because of first-pass metabolism.

B. Mexiletine:

- Same uses as lidocaine.

- Oral formulations.

❖ N.B:

- Lidocaine is a class 1B antiarrhythmic agent which very specifically binds rapidly depolarizing and depolarized cells.
- Ischemic myocardium is depolarized tissue; this is why lidocaine is specific for ischemic tissue and is the agent of choice for prevention and treatment of post-myocardial infarction arrhythmias.
- Currently amiodarone has replaced the lidocaine in the management of ventricular tachycardia.

3. Class 1C:

- Mechanism of action:

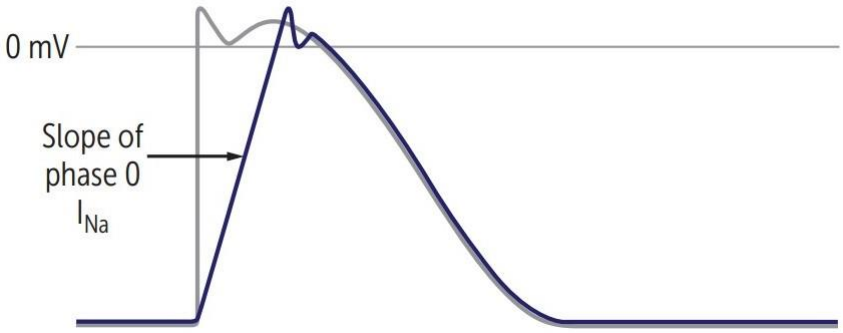
- Strong Na channel blockade.

- Class 1C antiarrhythmics bind avidly to the fast sodium channels responsible for phase 0 depolarization, blocking the inward sodium current and prolonging the QRS duration.

- NO effect on AP duration.

- Class 1C drugs are the slowest of the class 1 agents to dissociate from the sodium channel.

- This results in a phenomenon known as use-dependence, in which their sodium blocking effects intensify as the heart rate increases due to less time between action potentials for the medication to dissociate from the receptor.



- Drugs: Flecainide and propafenone.

❖ Flecainide:

- Clinical use:

- Only as a last resort in refractory VT.

- Limited use because of proarrhythmogenic effects, leading to ↑ in sudden death post-MI and when used prophylactically in VT.

- Adverse effects:

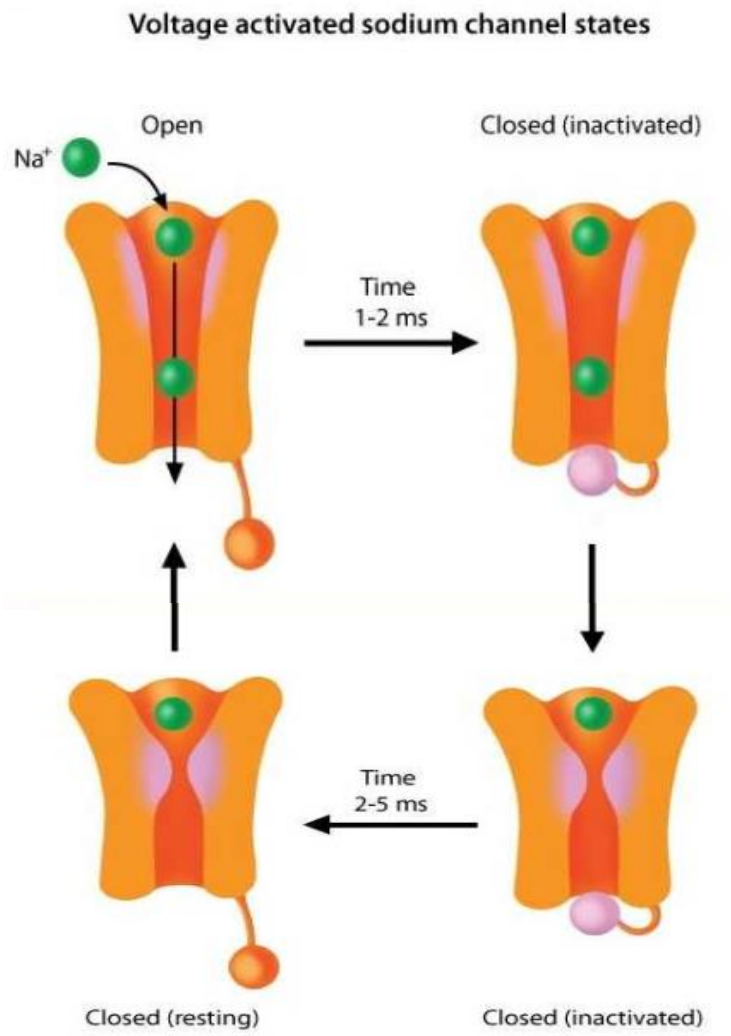
- Proarrhythmic, especially post-MI (contraindicated).

- IC is Contraindicated in structural and ischemic heart disease.

Class I (sodium channel-blocking) antiarrhythmics			
	Specific agents	**Inhibition of phase 0 depolarization**	**Effect on length of action potential**
Class IA	Quinidine, procainamide, disopyramide	Intermediate	Prolonged
Class IB	Lidocaine, mexiletine	Weak	Shortened
Class IC	Flecainide, propafenone	Strong	No change

❖ N.B:

- Class I antiarrhythmic drugs preferentially bind to and block activated and inactivated voltage-gated sodium channels in cardiac pacemaker cells and myocytes.
- Dissociation of the drug from the channel occurs during the resting state, a conformational state distinct from the inactivated state that occurs following repolarization.
- Class I antiarrhythmics exhibit use dependence, a phenomenon in which tissues undergoing frequent depolarization become more susceptible to blockage.
- Use dependence occurs because the sodium channels in rapidly depolarizing tissue spend more time in the activated and inactivated states, thus allowing more binding time for the drug.
- For class I antiarrhythmics, sodium-channel-binding strength is IC > IA > IB.
- Use dependence is more pronounced in class 1 C antiarrhythmics because of their slow dissociation from the sodium channel, which allows their blocking effects to accumulate over multiple cardiac cycles.
- This effect is enhanced with tachycardia, and the resulting increase in sodium channel blockade helps to slow conduction speed and terminate tachyarrhythmias.
- Class IB antiarrhythmics (lidocaine, mexiletine, and tocainide) bind less avidly to sodium channels than the other class I antiarrhythmics.
- Dissociation from the channels occurs so rapidly that there is minimal cumulative effect over multiple cardiac cycles, resulting in little use dependence.



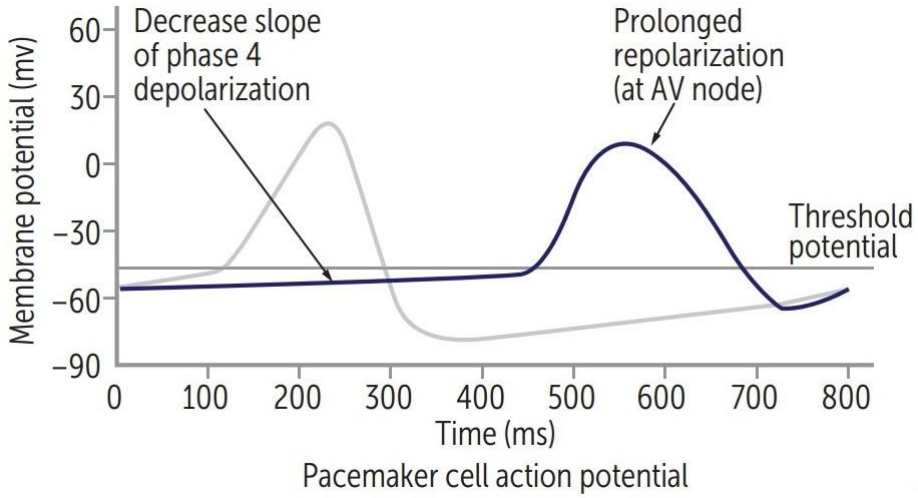
β-blockers (class II)

- Mechanism of action:

- Decrease SA and AV nodal activity by ↓ cAMP, ↓ Ca currents.

- Suppress abnormal pacemakers by ↓ slope of phase 4.

- AV node particularly sensitive: ↑ PR interval.



Pacemaker cell action potential

- Drugs:

- Metoprolol, propranolol, esmolol (very short acting), atenolol, timolol, carvedilol.

- Clinical Uses:

- SVT, ventricular rate control for atrial fibrillation and atrial flutter.

- Esmolol (IV) is used in acute SVTs.

- Adverse effects:

- Impotence, exacerbation of COPD and asthma, cardiovascular effects (bradycardia, AV block, HF), CNS effects (sedation, sleep alterations).

- May mask the signs of hypoglycemia.

- Propranolol can exacerbate vasospasm in Prinzmetal angina.

- β-blockers (except the nonselective α- and β-antagonists carvedilol and labetalol) cause unopposed α1-agonism if given alone for pheochromocytoma or for cocaine toxicity (unsubstantiated).

- Metoprolol can cause dyslipidemia.

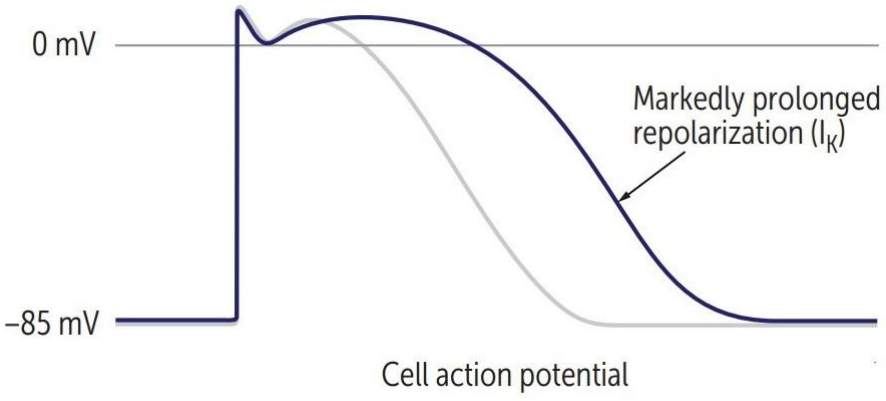
- β-blocker overdose with saline, atropine, glucagon.

Potassium channel blockers (class III)

- Mechanism of action:

- ↓ I_K (delayed rectifier current) slowing phase 3 (repolarization) of AP.

- ↑ AP duration, ↑ ERP, ↑ QT interval.



- Drugs:

- Amiodarone, Ibutilide, Dofetilide, Sotalol (AIDS).

- Clinical use:

- Atrial fibrillation, atrial flutter; ventricular tachycardia (amiodarone, sotalol).

A. Amiodarone:

- Mechanism of action:

- Mimics classes I, II, III, and IV (blocks Na, Ca, K channels and beta adrenoreceptors).

- Increase APD and ERP in all cardiac tissues.

- Clinical Uses: any arrhythmias.

- t1/2 > 80 days.

- Side effects:

- Pulmonary fibrosis.

- Thyroid dysfunction:

  - Amiodarone is 40% iodine by weight. It can cause hypothyroidism due to decreased production of thyroid hormone. Amiodarone can also cause hyperthyroidism due to increased thyroid hormone synthesis or destructive thyroiditis with release of preformed thyroid hormone.

- Hepatic necrosis.

- Remember to check PFTs, LFTs, and TFTs when using amiodarone.
- Blue pigmentation of the skin ("smurf skin").
- Acts as hapten (corneal deposits, blue/ gray skin deposits resulting in photodermatitis).
- Cardiovascular effects (bradycardia, heart block, HF). Unlike other drugs that cause QT prolongation, amiodarone has very little risk of inducing torsades de pointes.

B. Sotalol:

▪ Mechanism of action:

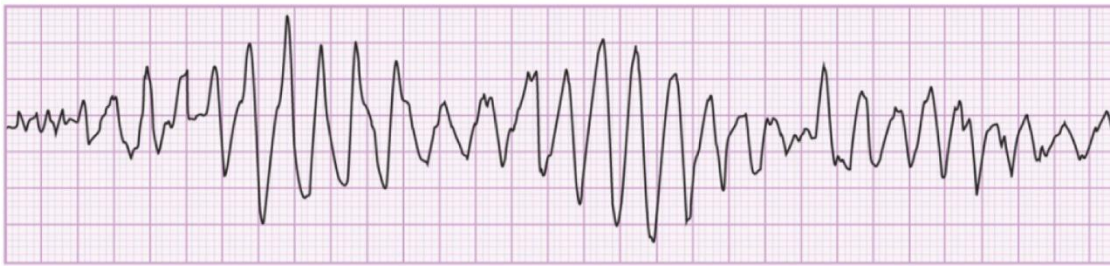
- ↓ I_K, slowing phase III.
- Non-selective beta blocker: β1 blockade, leading to ↓ HR, ↓ AV conduction.
- Sotalol is the only class III antiarrhythmic with beta-adrenergic blocking abilities (causing mild bradycardia) as well as class III effects (causing the QT interval prolongation).
- It prolongs both the PR interval and the QT interval.

▪ Clinical Use: life-threatening ventricular arrhythmia.

▪ Side effects: torsades de pointes, excessive β blockade.

❖ N.B:

▪ The QT interval represents the time required for ventricular depolarization and repolarization; it can be thought of as a rough estimate of the Action Potential Duration (APD).
▪ Drugs that prolong the cardiac action potential (class IA and III antiarrhythmics) will cause prolongation of the QT interval.
▪ Prolonged QT is associated with a form of ventricular tachycardia called torsades de pointes (polymorphic ventricular tachycardia).



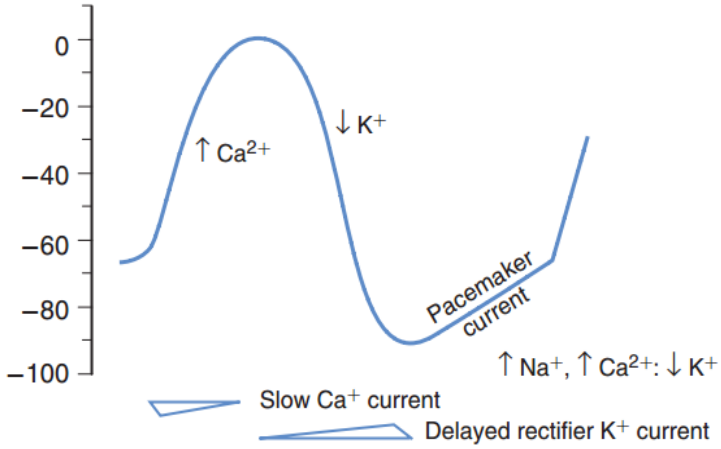
Calcium channel blockers (class IV)

- Mechanism of action:

- Block slow cardiac Ca channels.

- These drugs exert their primary action by blocking the L-type calcium channels, thereby decreasing phase 0, phase 4 and conduction velocity in the sinoatrial and AV nodes.

- This leads to slowing of the sinus rate and conduction through the AV node.



- Drugs: Verapamil and diltiazem.

- Clinical Uses:

- Supraventricular arrhythmias (atrial flutter, AF, paroxysmal supraventricular tachycardia).

- Side effects:

- Constipation (verapamil), bradycardia, atrioventricular conduction block (negative chronotropic effect), and worsening of heart failure in patients with reduced left ventricular function (negative inotropic effect).

- Drug interaction:

- Combined use of non-dihydropyridine calcium channel blockers (verapamil, diltiazem) and β-adrenergic blockers (atenolol) or digoxin can have additive negative chronotropic effects yielding severe bradycardia and hypotension.

- Verapamil displaces digoxin from tissue-binding sites.

❖ N.B:

- Atrial fibrillation is the most common arrhythmia in the United States.
- The primary goals for treatment are: ventricular rate control with beta blockers, CCBs, or digoxin; and anticoagulation (warfarin).

Unclassified antiarrythmic

A. Adenosine:

- Mechanism of action:

- Activates adenosine receptors.

- It acts by slowing conduction through the AV node by hyperpolarizing the nodal pacemaker (↑ K efflux) and conducting cells.

- Uses: DOC for paroxysmal supraventricular tachycardias and AV nodal arrhythmias.

- Administered IV.

- t1/2 < 10 seconds.

- Side effects:

- Flushing, sedation, dyspnea (due to bronchospasm), hypotension and high-grade AV block.

- Adenosine is antagonized by methylxanthines (theophylline and caffeine are adenosine receptor antagonists).

B. Magnesium:

- Clinical Use:

- Torsades de pointes and digoxin toxicity.

❖ Antiarrhythmic in a nutshell:

- SVTs: II, IV, adenosine, digoxin.

- VTs: I, III.

Antiarrhythmic drugs – Vaughan Williams classification		
Class	**Drugs**	**Predominant actions**
IA	**Sodium channel blockers** • Disopyramide • Procainamide • Quinidine	• Slows AP conduction velocity • Prolongs APD
IB	• Lidocaine • Mexiletine • Phenytoin	• No effect on AP conduction velocity • Shortens APD
IC	• Flecainide • Propafenone	• Slows AP conduction velocity • Minimal effect on APD
II	**Beta receptor blockers** • Atenolol • Metoprolol • Esmolol • Carvedilol	• Slows sinus node discharge rate • Slows AV nodal conduction & prolongs refractoriness
III	**Potassium channel blockers** • Amiodarone • Dronedarone • Dofetilide • Sotalol (also class II)	• No effect on AP conduction velocity • Prolongs APD
IV	**Non-dihydropyridine calcium channel blockers** • Verapamil • Diltiazem	• Slows sinus node discharge rate • Slows AV nodal conduction & prolongs refractoriness

AP = action potential; **APD** = action potential duration; **AV** = atrioventricular.