Chapter 7

Cardiology step 1 notes

Fetal Erythropoiesis

Definition:

Erythropoiesis is the process of the production of red blood cells. The main drive for erythropoiesis is tissue hypoxia. During fetal embryogenesis, new organs and tissues are being developed and their oxygen demand increases. This results in a state of relative hypoxia which activates different signaling pathways such as SCF, GCs, BMP4 and Hedgehog to activate erythropoiesis.

Differences between Fetal and Adult Hemoglobin:

There are few important differences between fetal and adult hemoglobin, which can be found in the following table.

	Fetal hemoglobin	**adult hemoglobin**
Composition	$\alpha_2\gamma_2$	$\alpha_2\beta_2$
life span in days	80	120
affinity for oxygen	Higher	Lower
binding of 2,3-bpg	Lower	Higher

The purpose of these differences is to facilitate the extraction of oxygen from maternal hemoglobin to fetal hemoglobin across the placenta.

Organs of Fetal Erythropoiesis:

Fetal erythropoiesis occurs in different organs depending on the gestational age.

- The yolk sac is responsible for erythropoiesis in the first 3 to 8 weeks
- Instead of two α and two γ chains, hemoglobin produced by the yolk sac has two α and two ε chains
- Liver takes over from 6 weeks to birth
- The spleen becomes able to produce red blood cells from the tenth week of gestation to the 28th week
- The bone marrow starts erythropoiesis from the 18 weeks of gestation and during adulthood
- While the bone marrow is capable of erythropoiesis during fetal life after 18 weeks of gestation, severe hypoxic stress during fetal life can shift erythropoiesis to the spleen.

Pressure-Volume Loops in Cardiology

Definition

The pressure-volume loop is a diagram or a plot of pressure versus volume. The work done by a pump system, such as the heart, can be effectively assessed in terms of efficiency from a pressure-volume loop.

Normal Pressure-Volume Loop

The normal pressure-volume loop is traced from the right lower corner, to the top right corner, followed by going to the left top corner, then the left bottom corner, and finishes back at the right lower corner of the loop. The corners of the loop represent the opening and closure of the mitral and aortic valves.

The pressure-volume pressure also gives important information about some important cardiac parameters such as the systolic volume (SV), the end diastolic volume, end systolic volume, end diastolic pressure, and end systolic volume and pressure.

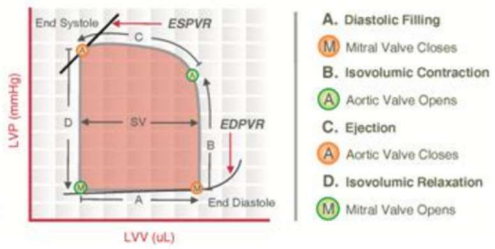


Figure 1: During diastolic filling, the volume of blood in the left ventricle keeps increasing. Eventually, the mitral valve is closed and this represents the end of diastole. Pressure starts building up in the left ventricle during systole until a point where it surpasses that of the systemic circulation and the aortic valve opens. Pressure stops building up, and volume is decreased until the end of systole when the aortic valve closes. At this point, the pressure inside the left ventricle is still high, but because systole has ended it will drop immediately to the baseline, the mitral valve opens, and diastolic filling starts. The stroke volume is equal to the end diastolic volume – the end systolic volume. Source: https://upload.wikimedia.org/wikipedia/commons/1/1c/Cardiac_Pressure_Volume_Loop.jpg

Pressure-Volume Loops in Pathologic Cardiac Conditions:

Pathologies that have an impact on the cardiac cycle such as those associated with increased afterload, preload, or a decrease in end systolic or diastolic volumes will result in a characteristic pressure-volume loop.

The following examples of pathologies show how the pressure-volume loop is different based on the hemodynamic consequences of the pathology.

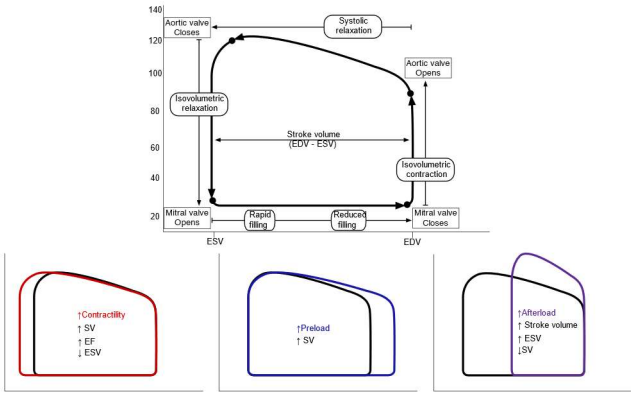


Figure 2: Normal (black) and pathologic cardiac pressure-volume loops. Source: https://commons.wikimedia.org/wiki/File:Cardiac_cycle_(pressure_volume_loop).svg

In the diagram above, we see three pathologies:

Blue Loop:

- The end-diastolic-volume is normal.
- Pressure keeps building up during isovolumetric contraction and it surpasses the pressure maximum of the normal curve
- At some point, systolic ejection occurs but the remaining time of systole is much shorter
- The aortic valve closes earlier than expected, and it goes down to baseline. The end-systolic volume is much larger as compared to normal
- Accordingly, when afterload is increased, the aortic pressure is increased, the end systolic pressure is increased, and the stroke volume is decreased
- This might be seen in aortic stenosis

Green Loop:

- Here, it is better to start with the normal point of the curve, where the end systolic volume is
- Volume keeps adding up and it surpasses that of the normal curve, so the end-diastolic volume in this pathology is larger than normal
- The pressure changes are not significant or abnormal
- Accordingly, the main abnormality here is increased preload and an increase in stroke volume
- This might be seen in aortic regurgitation, where more blood is escaping into the left ventricle after the closure of the aortic valve

Orange Loop:

- Here, contractility is increased for some reason
- More blood volume will be pumped out of the heart
- And when the aortic valve closes and we end at the end-systolic volume, it will be smaller than normal
- Accordingly, the stroke volume is increased

Cardiac Cycle

Definition

The cardiac cycle is a group of events that occur sequentially within the heart when the heart beats. It describes how the blood circulates through pulmonary and systemic circulations in relation to heart beating.

To understand the cardiac cycle, we need to use four different diagrams:

- An illustration of the four heart chambers
- Pressure curves that show how the pressure changes overtime
- Electrocardiogram
- A phonogram to correlate all the above with the different heart sounds

Atrial Systole

- This event starts at the end of diastole. The atria contract to pump any remaining blood to the ventricles
- Because of this, you see a slight increase in the pressure inside the atrium, see the yellow curve, segment a
- An electrical impulse is generated from the SA node which travels to the AV node. The atria contract slightly later than they are depolarized because they allow more blood to pour to the ventricles first. Therefore, this part of the cycle corresponds to the P and PR intervals on the ECG
- In normal conditions, this event should not be associated with any heart sounds. In patients with hypertrophic congestive heart failure, massive pulmonary embolism or cor-pulmonale, a fourth heart sound will be heard during this time period of the cardiac cycle.

Isovolumetric Contraction

- This is the beginning of systole. The following changes happen in the heart and are illustrated in:
    - The atrioventricular valves close

    - This is the interval between the closure of the atrioventricular valves and the opening of the semilunar valves
- The pressure curve shows a rapid build-up in pressure in the ventricle, red curve, which surpasses the diastolic arterial blood pressure, of 80 mmHg
    - The opening of the semilunar valves is dependent on the ventricular pressure surpassing the afterload pressure, i.e. the arterial pressure
- On the ECG, this event corresponds to the QRS complex, which is due to ventricular depolarization
- The normal heart sound, S1 “lub”, is heard during this event. It occurs due to the closure of the atrioventricular valves

Rapid Ejection

- This event can be seen as mid-systole
- During this phase, the semilunar valves open and a large amount of blood volume is pumped out of the ventricles in a short time period
- On the pressure curve, if you trace the red curve you see that the pressure is still rising in the ventricles but now it matches that of the systemic circulation. The peak of this pressure curve is what we measure in systolic arterial blood pressure
- This event does not correspond to any ECG features or heart sounds

Reduced Ejection

- This event marks the end of systole
- Because the ventricles are undergoing repolarization and are at full contraction, the pressure is not building up anymore. Instead, it starts dropping. As long as the pressure is above that of the systemic circulation, the semilunar valves will remain open. Once the pressure drops below 80 mmHg for the systemic circulation, the aortic valve will close, and this marks the end of systole.
- You will see on the pressure curve that the pressure of the ventricles starts to drop during this phase and most of the blood is ejected. The nadir of the volume curve corresponds to the end-systolic-volume.
- This event corresponds to the T-wave on the ECG
- You would not expect to hear any heart sounds during this period

Isovolumetric Relaxation

- This can be seen as the opposite of isovolumetric contraction. Meaning, the ventricular pressure will drop further, the atrioventricular and semilunar valves are closed, and the myocardium is undergoing relaxation. The atria are being filled with blood.
- The pressure curves will show a drop in ventricular pressure to almost zero, and no change in ventricular volume, hence the name isovolumetric.
- This does not correspond to any ECG events
- The second heart sound, S2 “dup”, will occur during this phase. It occurs due to the closure of the semilunar valves. S2 is normally split because the aortic valve closes before the pulmonary valve

Rapid Ventricular Filling

- The AV valves open and blood flows rapidly from the atria to the ventricles
- Accordingly, the ventricular volume is increasing rapidly whereas the ventricular pressure and atrial pressure are unchanged
- This does not correspond to any ECG events
- In pathologic conditions where the ventricular filling is so rapid and vigorous, as occurs in dilated congestive heart failure, an abnormal S3 might be heard

Diastasis:

- Also known as reduced ventricular filling
- Any remaining blood in the atria flows to the ventricles until they are full, however this occurs more slowly
- The ventricular volume will increase further, but slowly. No changes in ventricular or atrial pressure
- No ECG events or heart sounds during this phase

Cardiac and Vascular Function Curves

Definition:

It has been known that cardiac function and systemic vascular function are related to each other. The experimental study of this interrelationship between these two systems resulted in the development of what is known as the cardiac and vascular function curves.

Cardiac Function Curves

The cardiac function curve explains how cardiac output changes depending on the right atrial pressure. Figure 1 shows cardiac function curves in different conditions.

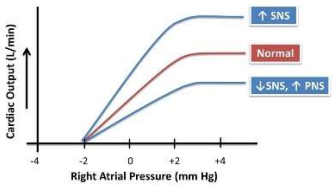


Figure 3: In normal conditions, the red curve, you see that at 0 mmHg pressure in the right atrium, cardiac output is approximately 5 L/min. If you increase the sympathetic nervous system tone, the contractility of the heart increases and cardiac output is increased. When you decrease the sympathetic nervous system tone, the contractility of the heart decreases and the cardiac output drops. Source: http://www.pathwaymedicine.org/cardiac-function-curve

Conditions that alter the inotropy of the heart:

- Increased catecholamines, digoxin, and exercise increase inotropy
- Heart failure with reduced ejection fraction, opioids, and sympathetic inhibition decreases inotropy

Vascular Function Curves:

These curves try to explain how systemic venous return to the right atrium varies with right atrial pressure. See Figure 2.

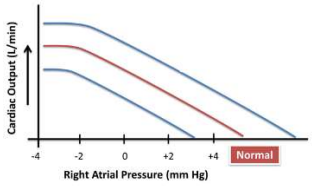


Figure 4: When the circulating volume or venous tone is altered, you see that venous return to the right atrium is also changed. Source: http://www.pathwaymedicine.org/vascular-function-curve

Conditions that alter venous return:

- The right atrial pressure will be altered at a given cardiac output depending on how much blood is being return to the right atrium
- Increased fluid infusion or increased sympathetic nervous system tone will result in increased venous volume and venous tone respectively
- Acute hemorrhage will decrease the circulating volume

Conditions that alter the total peripheral resistance:

- Vasopressors increase the total peripheral resistance
- Exercise decreases the total peripheral resistance

Effect of Maneuvers on Heart Murmurs and Sounds

Inspiration

- While inspiration increases right-sided heart murmurs, left-sided heart murmurs are increased with expiration

Mechanism of effect of inspiration

- Inspiration decreases the intrathoracic pressure
- Venous return increases
- Right atrial pressure decreases
- Preload is increased
- Pulmonary blood volume increases
- Blood flow from the pulmonary circulation to the left atrium decreases
- Accordingly, right-sided heart murmurs will increase intensity, whereas, left-sided heart murmurs will decrease in intensity

Affected heart sounds:

- Right-sided heart sounds are more intense

Hand Grip

Mechanism of effect of handgrip

- Hand grip increases the total peripheral resistance
- Afterload is increased
- It becomes more difficult for blood to be ejected from the left ventricle to the aorta
- Accordingly, forward murmurs will decrease in intensity, whereas backward flow murmurs will increase in intensity

Affected murmurs:

- Forward flow murmurs such as aortic stenosis and HOCM will decrease in intensity

- Regurgitant murmurs such as mitral regurge, aortic regurge, and ventricular septal defect murmurs will increase in intensity
- The click of mitral valve prolapse will occur later

Second Phase of Valsalva Maneuver and Standing Up

Mechanism of effect

- Decreased preload leads to less blood return to the heart
- In HOCM, left ventricular volume is decreased as is stretching of the left ventricular walls
- The left ventricular outflow obstruction is increased
- The intensity of the HOCM murmur is increased
- Because there is less blood to be pumped, the forward flow murmur of aortic stenosis is decreased

Affected murmurs

- Most murmurs will decrease in intensity
- Increased intensity of HOCM murmur
- Earlier onset of the mitral valve prolapse click, and the click will be louder

Rapid Squatting

Mechanism of effect

- Venous return will increase as is preload
- Afterload is also increased
- In HOCM, the left ventricular volume is increased as is stretching of the left ventricular wall
- The left ventricular outflow obstruction is decreased
- More blood is available to be pumped

Affected murmurs

- Most forward murmurs such as aortic stenosis and backward murmurs like mitral regurgitation will increase in intensity
- The murmur of HOCM will decrease in intensity
- The click of mitral valve prolapse will be delayed and softer

Fetal Circulation

Flow of Blood in the Fetal Circulation

- The umbilical vein receives oxygenated blood from the placenta:
    - PO_2 is 30 mmHg
    - Oxygen saturation is 80%
- Blood flows through the umbilical vein to reach the liver:
    - Most of the blood is shunted via the ductus venosus to the systemic circulation bypassing the hepatic circulation
- Blood enters the inferior vena cava to reach the right atrium:
    - Most of the blood is directed to the left atrium via the foramen ovale
- Blood goes down to the left ventricle to be pumped to the aorta to supply the systemic arterial circulation
- Deoxygenated blood from the body enters the superior vena cava to reach the right atrium:
    - The blood goes to the right atrium to be pumped into the pulmonary artery
    - The ductus arteriosus connects the main pulmonary artery with the descending aorta
    - Because fetal pulmonary artery resistance is high, most of the blood will bypass the lungs and enter this shunt to go to the descending aorta
- The two umbilical arteries receive the deoxygenated blood from the aorta and go to the placenta for oxygenation

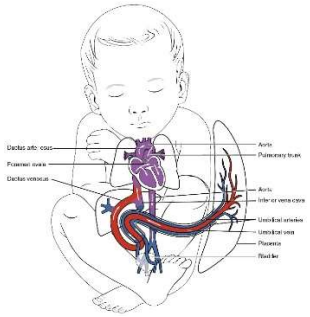


Figure 5: Fetal circulation. Source: https://commons.wikimedia.org/wiki/File:2139_Fetal_Circulation.jpg

Fetal Shunts and Their Importance

The following table summarizes the main fetal shunts and their importance to the fetus.

Shunt	Importance to the fetus
ductus venosus	Shunting of oxygenated blood from the umbilical vein to the inferior vena cava
Foramen ovale	Shunting of oxygenated blood from the right atrium to the left atrium to be pumped to the systemic circulation

ductus arteriosus	Shunting of the deoxygenated blood from the main pulmonary artery to the descending aorta to be delivered to the placenta via the umbilical arteries for reoxygenation

In the next table, we show the fate of the different fetal structures related to the circulatory system in postnatal life.

fetal structure	**postnatal structure**
Ductus venosus	Ligamentum venosum
Ductus arteriosus	Ligamentum arteriosum
Foramen ovale	Fossa ovalis
Urachus	Median umbilical ligament
Umbilical arteries	Medial umbilical ligaments
Umbilical vein	Ligamentum teres hepatis also known as round ligament

Transition from Fetal to Postnatal Circulation

- At birth, the infant takes a breath
- Pulmonary arterial resistance is decreased → blood can now go to the lungs from the pulmonary arteries
- Left atrial pressure becomes higher than the right atrium → shunting from the right atrium to the left atrium is no longer possible
- Foramen ovale closes
- Oxygenation saturation becomes much higher than that of the fetal circulation → less prostaglandins → closure of the ductus arteriosus

Patency of the Ductus Arteriosus

- In some pathologies, you might want to close the ductus arteriosus or keep it open
- For example, if the infant has an isolated patent ductus arteriosus, you might think about providing an intervention to close it. Indomethacin promotes closure of the PDA
- On the other hand, you might want to preserve the patency of the ductus arteriosus in some congenital heart defects. You would administer prostaglandins E1 or E2

Coronary Artery Circulation

Overview:

The circulation of blood in the blood vessels that supply the heart is referred to as the coronary circulation. The coronary arteries supply oxygenated blood to the heart muscle, whereas the cardiac veins drain blood from the heart muscle.

- 5% of cardiac output
- Resting myocardium extracts 70% of oxygen from blood within the coronary arteries
- Working myocardium extracts 90% of oxygen
- Coronary perfusion occurs during diastole
- During systole, coronary arteries are compressed. If the coronary arterial supply is insufficient, this can lead to ischemia

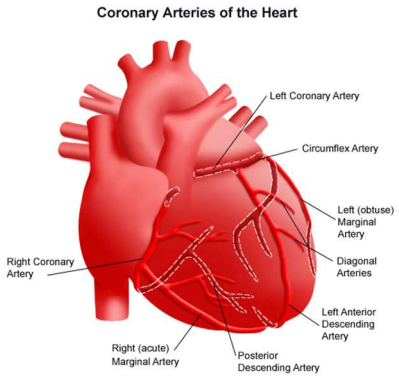


Figure 6: Anatomy of the coronary arteries and blood supply distribution of the heart. Source: https://diseasespictures.com/coronary-artery-disease/

Right Coronary Artery

- Originates from the aorta
- Supplies the SA node
- If occluded → bradycardia or heart block

Right Marginal Artery

- Originates from the right coronary artery
- Supplies the right ventricle
- If occluded → inferior wall myocardial infarction/ischemia

Posterior Descending Artery

- Originates from the right coronary artery in 82% of people
- Originates from the left circumflex artery in 8% of people
- Originate from both right coronary artery and left circumflex artery in the rest of people
- Supplies AV node, the posterior one third of the interventricular septum, posterior two thirds of ventricles, and posteromedial papillary muscle
- If occluded → heart block, posterior wall myocardial infarction/ischemia, posteromedial papillary muscle rupture

Left Coronary Artery

- Originates from the aorta
- Gives rise to the left circumflex artery, left anterior descending artery, and left marginal artery

- If occluded → massive anterolateral myocardial infarction

Left Circumflex Artery

- Originates from the left coronary artery
- Supplies the lateral and posterior walls of left ventricle
- Supplies the anterolateral papillary muscle
- If occluded → lateral myocardial infarction, anterolateral papillary muscle rupture

Left Anterior Descending Artery

- Originates from the left coronary artery
- Supplies the anterior two thirds from interventricular septum, anterolateral papillary muscle, and anterior surface of left ventricle
- If occluded → anterior myocardial infarction, anterolateral papillary muscle rupture
- Most common site of coronary artery occlusion

Left Marginal Artery

- Originates from the circumflex artery
- Travels across the left margin of the heart to the apex

Heart Sounds

Overview:

Heart sounds are heard with a stethoscope during cardiac examination. The normal heart sounds occur due to the closure of the atrioventricular or semilunar valves. The abnormal heart sounds occur during diastole and are related to the dynamic filling of a pathologic ventricle.

Where to Listen:

In Figure 1, you can see the main places that you are supposed to put your stethoscope on while auscultating the heart.

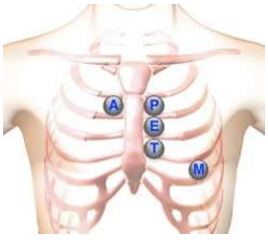


Figure 7: A. Right upper sternal border. P Left upper sternal border. T. Left lower sternal border. M. Apex

- The aortic area or right upper sternal border lies between the first and second intercostal spaces
- Opposite to it, the left upper sternal border is the pulmonic area
- If you go down to the left lower sternal border in the fourth intercostal space, you find the tricuspid area
- Finally, you should finish your auscultation by listening to the apex of the heart which is in the mid-clavicular line in the fifth intercostal space

Normal Heart Sounds:

Normal heart sounds are S1 "lub" and S2 "dub". They occur due to the closure of the atrioventricular and semilunar valves. S2 is normally split.

S1:

- This sound occurs due to the closure of the atrioventricular "mitral and tricuspid" valves
- It can be heard more clearly at the mitral or tricuspid area

S2:

- This sound occurs due to the closure of the semilunar valves "aortic and pulmonic"
- Because the aortic valve closes before the pulmonic valve, there is splitting
- It can be heard in the upper right or left sternal borders clearly

Abnormal Heart Sounds:

When the left ventricle is stiff, or the left ventricle is dilated/there is increased return of blood to the left ventricle, additional abnormal heart sounds might be heard.

S3:

- During rapid ventricular filling, after S2, a third sound can be heard in patients with:
  - Dilated congestive heart failure
  - Massive pulmonary embolism
- It occurs due to rapid and vigorous flow of blood from the left atrium to the left ventricle

S4:

- During atrial systole, right before S1, a fourth heart sound can be heard in patients with:
  - A stiff left ventricle
  - Congestive hypertrophic heart failure

It occurs due to the striking of the stiff ventricle by the blood ejected from the left atrium during atrial systole.

Valvular Heart Disease: Mitral Stenosis

Definition

- Mitral stenosis occurs when the mitral valve opening is narrowed. Blood flow from the left

atrium to the left ventricle is obstructed. Because the mitral valve is open during diastole, you would expect to find abnormalities on auscultation of the heart during this phase.

Epidemiology

- The currently estimated incidence is 1 in 100,000. Because the most common cause of mitral stenosis is rheumatic fever, and the later has been declining, the incidence of mitral stenosis is also declining.
- Mitral stenosis is more common in females
- Onset of symptoms in the 3rd or 4th decade of life
- Prognosis is improved in patients who undergo surgical or percutaneous valve replacement/repair
- The 5-year survival rate, if unoperated and severe, is 44%

Etiology and Pathophysiology

- The most common cause is rheumatic fever
- Other less common causes include malignant carcinoid disease, SLE, and rheumatoid arthritis
- Normal mitral valve orifice area is 4 to 6 cm2
- Symptoms start to occur when the mitral valve orifice area is 2.5 cm2 or less
- Left atrial pressure increased → transudation of fluid into lung interstitium
- Hemoptysis can occur
- Pulmonary hypertension can develop because of:
- Retrograde transmission of left atrial pressure
- Pulmonary arteriolar constriction
- Obliterative changes in the pulmonary vasculature
- Pulmonary interstitial edema

Clinical Findings:

- When the condition progresses, patients develop dyspnea and fatigue
- Atrial fibrillation due to left atrium dilatation
- Hemoptysis
- Symptoms and signs of right heart failure because of severe pulmonary hypertension → very late in the disease process
- In Figure 1, you can see the main places that you are supposed to put your stethoscope on while auscultating the heart.

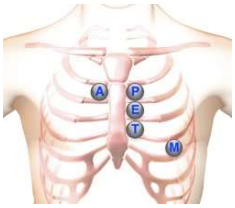


Figure 8: A. Right upper sternal border. P Left upper sternal border. T. Left lower sternal border. M. Apex

- If you hear a diastolic murmur at the mitral area, the most likely diagnosis is mitral stenosis
- S1 is louder
- There is a diastolic snap followed by the diastolic murmur
- The diamond-shaped low-frequency murmur is best heard with the bell of the stethoscope
- A second murmur can be heard during atrial systole

Murmur Grading

- Grade I: the murmur is barely audible
- Grade II: The murmur is soft
- Grade III: the murmur is easily audible
- Grade IV: the murmur is loud

Note: The more severe the mitral valve stenosis, the earlier the opening snap will be heard.

Diagnosis and Treatment

In addition to auscultation, echocardiography provides valuable information about the mitral valve pathology, allow for the measurement of different parameters related to hemodynamics, and can assess in determining the severity of mitral stenosis.

Treatment options include:

- Decreasing preload with diuretics, beta-blockers, and calcium channel blockers
- Valve repair by a catheter
- Valve replacement

Valvular Heart Disease: Mitral Regurgitation

Definition

Mitral regurgitation occurs when there is mitral valve insufficiency, so that the mitral valves do not keep closed during systole. This can be seen in patients with left

ventricular dilatation. The left atrium is also usually enlarged in patients with mitral regurgitation.

Epidemiology

Mitral regurgitation can be classified into acute and chronic. Chronic mitral regurgitation is seen in patients with rheumatic fever, whereas, acute regurgitation might be seen in patients with acute myocardial infarction. The incidence of mitral regurgitation is 5 in 10,000.

- 2nd most common valvular disease
- Myxomatous degeneration is a more common cause than rheumatic fever in the United States
- More common in females

Risk factors:

- Advanced age
- Low body mass index
- Renal disease
- Prior myocardial infarction
- History of mitral valve stenosis

Etiology and Pathophysiology:

- The most common cause is myxomatous degeneration
- Rheumatic fever and ischemic heart disease are other common causes of mitral regurgitation
- Patients with acute mitral regurgitation have the following abnormalities:
    - Increased end diastolic volume
    - Decreased end systolic volume
    - Increased total stroke volume
    - Most of the blood is pumped backward into the left atrium
    - Accordingly, increased left atrial pressure
    - Preload is increased, whereas, afterload is decreased
- Patients with chronic mitral regurgitation have the following abnormalities when decompensated:
    - Dilated left ventricle and left atrium
    - Decreased total stroke volume
    - Higher end systolic and end diastolic volumes
    - Elevated left atrial and left ventricular pressures
    - If untreated, cardiogenic shock

Clinical Findings:

- When the condition progresses, patients develop dyspnea and fatigue
- Atrial fibrillation due to left atrium dilatation
- Hemoptysis
- Symptoms and signs of right heart failure because of severe pulmonary hypertension → very late in the disease process
- Systolic dysfunction is rarely seen

In Figure 1, you can see the main places that you are supposed to put your stethoscope on while auscultating the heart.

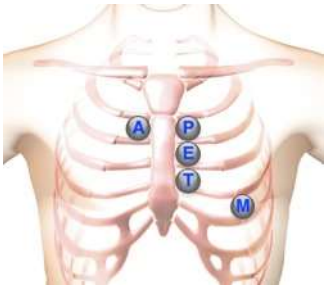


Figure 9: A. Right upper sternal border. P Left upper sternal border. T. Left lower sternal border. M. Apex

- If you hear a holosystolic murmur at the mitral area, the most likely diagnosis is mitral regurgitation
- S1 is normal, whereas S2 is unsplit
- Third heart sound, S3 gallop

Diagnosis and Treatment:

In addition to auscultation, echocardiography provides valuable information about the mitral valve pathology, allow for the measurement of different parameters related to hemodynamics, and can assess in determining the severity of mitral regurgitation.

Treatment options include:

Medical treatment with nitrates or antihypertensives to decrease afterload
Intra-aortic balloon counter-pulsation in acute MR with hemodynamic instability
Anticoagulation for patients with atrial dilatation and atrial fibrillation
Valve surgery for replacement or repair

Valvular Heart Disease: Tricuspid Regurgitation

Definition

- When there is damage to the tricuspid valve or leaflets, tricuspid regurgitation can occur. Blood

backflow through the tricuspid valve from the right ventricle to the right atrium.

Epidemiology

- The estimated incidence of tricuspid regurgitation is 9 per 1000
- Equal occurrence in males and females
- Age of onset varies based on the etiology:
- Ebstein anomaly: at birth or early childhood
- Rheumatic valvular disease: 15 years and early adulthood
- Carcinoid, bacterial endocarditis, or heart failure: older adults
- The prognosis of the patient is dependent on the presence of pulmonary hypertension and dilated cardiomyopathy rather than on the mere presence of tricuspid regurgitation

Etiology and Pathophysiology:

- Acquired causes of tricuspid regurgitation include: rheumatic fever, endocarditis, carcinoid, trauma, SLE, and right ventricular dilatation secondary to pulmonary hypertension
- Chronic tricuspid regurgitation → right ventricular volume overload
- If untreated → right-sided congestive heart failure:
    - Hepatic congestion
    - Ascites
    - Peripheral edema

Clinical Findings:

- Patients present with dyspnea on exertion
- Orthopnea
- Ascites
- Peripheral edema

In Figure 1, you can see the main places that you are supposed to put your stethoscope on while auscultating the heart.

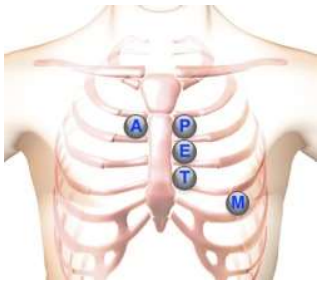


Figure 10: A. Right upper sternal border. P Left upper sternal border. T. Left lower sternal border. M. Apex

- If you hear a holosystolic murmur at the tricuspid area, the most likely diagnosis is tricuspid regurgitation or ventricular septal defect
- Third heart sound, S3 gallop

Diagnosis and Treatment:

- In addition to auscultation, echocardiography provides valuable information about the tricuspid valve pathology, allow for the measurement of different parameters related to hemodynamics, and can assess in determining the severity of tricuspid regurgitation.

Treatment options include:

- When there is a structural deformity of the valve, or significant destruction by bacterial endocarditis → annuloplasty or valve replacement
- If tricuspid regurgitation is secondary to left-sided heart failure → treat left-sided heart failure to alleviate tricuspid regurgitation

Valvular Heart Disease: Tricuspid Stenosis

Definition:

Tricuspid stenosis is caused by rheumatic fever and is usually associated with mitral and aortic stenosis. The damaged tricuspid valve will allow regurgitation during systole in addition to the characteristic murmur heard because of stenosis in diastole.

Epidemiology:

- The condition is rare and affects approximately 1% of the population
- It is more common in females
- Mortality rate is 5%

Etiology and Pathophysiology:

- Rheumatic valvular disease affects the tricuspid valve and results in structural alterations
- This leads to improper excursion of the valve leaflets
- Tricuspid valve stenosis always occurs with concomitant aortic and mitral valve stenosis
- Right atrial pressure increases → right atrial enlargement
- Because of the elevated right atrial pressure, the patient develops hepatomegaly and peripheral edema
- Pulmonary blood flow is decreased

Clinical Findings:

- Fatigue

- Signs suggestive of venous congestion: hepatomegaly and ascites
- Atrial fibrillation
- Dyspnea
- Because the condition commonly occurs along with mitral stenosis:
    - Hemoptysis and orthopnea are less severe when compared to mitral stenosis alone because of decreased pulmonary blood flow

In Figure 1, you can see the main places that you are supposed to put your stethoscope on while auscultating the heart.

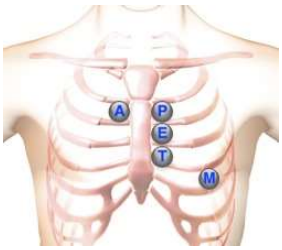


Figure 11: A. Right upper sternal border. P Left upper sternal border. T. Left lower sternal border. M. Apex

- Increased intensity of the first heart sound
- In the tricuspid area, a tricuspid opening snap followed by a rumbling low-frequency diastolic murmur can be heard with the bell of the stethoscope
- The intensity of the murmur increases with inspiration

Diagnosis and Treatment:

In addition to auscultation, echocardiography provides valuable information about the tricuspid valve pathology, allow for the measurement of different parameters related to hemodynamics, and can assess in determining the severity of tricuspid stenosis and concomitant mitral or aortic valve disease.

Treatment options include:

Tricuspid stenosis requires valvular repair or replacement of the valve

Valvular Heart Disease: Mitral Valve Prolapse

Definition:

Because of the sudden tensing of the chordae tendinea, the mitral valve might prolapse in late systole. This is the most common valvular lesion.

Epidemiology

- More common in people with heritable connective tissue disorders such as Marfan and Ehlers-Dantos syndromes
- It is found in up to 4% of the general population
- Female to male ratio is 2:1
- Most patients are asymptomatic, however up to 10% progress to severe mitral regurgitation
- Even if mitral regurgitation occurs, the prognosis is still excellent when compared to mitral regurgitation without history of mitral valve prolapse

Etiology and Pathophysiology

- The exact cause is unknown; however, it is more common in people with inherited connective tissue disorders
- Myxomatous degeneration of the mitral valve leaflets → redundancy of the anterior and posterior leaflets and chordal apparatus → mitral valve prolapse in late systole
- If mitral regurgitation is severe → elevated left atrial pressure and volume → atrial fibrillation → pulmonary congestion → pulmonary hypertension → right-sided heart failure

Clinical Findings

- Mitral valve prolapse can be primary or syndromic
- Primary mitral valve prolapse rarely progresses to become symptomatic
- Symptomatic patients have symptoms and signs due to mitral regurgitation

In Figure 1, you can see the main places that you are supposed to put your stethoscope on while auscultating the heart.

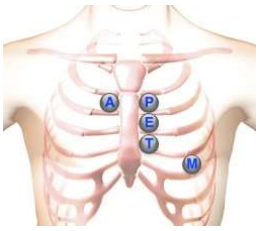


Figure 12: A. Right upper sternal border. P Left upper sternal border. T. Left lower sternal border. M. Apex

- In the mitral area, you can hear a medium-pitched crescendo late systolic murmur after a mid-systolic click

- The murmur's intensity increases when the patient stands up
- The murmur's intensity decreases when the patient does a hand grip maneuver

Diagnosis and Treatment:

In addition to auscultation, echocardiography provides valuable information about the mitral valve pathology, and allow for the measurement of different parameters related to hemodynamics.

Treatment options include:

- Asymptomatic patients with minimal disease require no treatment
- Patients with severe mitral regurgitation require surgical management

Valvular Heart Disease: Aortic Stenosis

Definition:

The obstruction of the blood outflow across the aortic valve is known as aortic stenosis. It is currently believed that a period of latent asymptomatic aortic stenosis of 10 to 20 years precede symptomatic stenosis. Mortality is very high.

Epidemiology:

- Aortic sclerosis is a precursor to calcific degenerative aortic stenosis. It is present in up to 30% of those older than 65 years
- The prevalence of aortic stenosis in the elderly is up to 9%
- Survival rate after the onset of symptoms in patients with severe aortic stenosis who are medically treated is 50% at two years

Etiology and Pathophysiology:

- The etiology is age dependent. Etiologies that are common in patients younger than 70 years of age: from most common to least common
  - Bicuspid AV
  - Rheumatic fever
  - Degenerative calcific stenosis
  - Hypoplastic
  - Unknown
- The etiology on those older than 70 years: from most common to least common
  - Degenerative
  - Bicuspid
  - Rheumatic fever
  - Hypoplastic
- Aortic valve stenosis → outflow tract obstruction → increased LV systolic pressure → left ventricular hypertrophy → normal systolic function but decreased diastolic compliance
- If untreated → LV EDP rises → increased pulmonary capillary pressure → diastolic dysfunction → decreased cardiac output. If the contractility of the myocardium is decreased this can also lead to systolic dysfunction
- Because of increased LV mass, the myocardial oxygen demand increases. Coronary blood flow is usually decreased, which leads to ischemia → angina pectoris

Clinical Findings:

- Syncope
- Angina
- Dyspnea on exertion

In Figure 1, you can see the main places that you are supposed to put your stethoscope on while auscultating the heart.

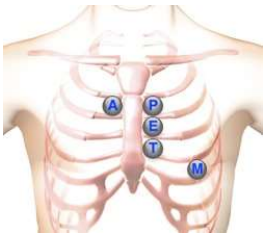


Figure 13: A. Right upper sternal border. P Left upper sternal border. T. Left lower sternal border. M. Apex

- In the aortic area: a crescendo-decrescendo systolic ejection murmur and a soft S2. Ejection click might be audible
- Murmur radiates to the carotid arteries
- S4 gallop

Diagnosis and Treatment:

In addition to auscultation, echocardiography provides valuable information about the aortic valve pathology, and allow for the measurement of different parameters related to hemodynamics.

Treatment options include:

- Aortic valve replacement

Murmurs

Aortic Regurgitation

- Due to aortic root dilatation, bicuspid aortic valve, or damage to the aortic valve leaflets

- Blood flows backward to the left ventricle during diastole
- If left untreated, can progress to left heart failure
- Patients have a wide pulse pressure (SBP – DBP)

Characteristics of the murmur

- High-pitched blowing early diastolic decrescendo murmur
- S1 intensity is decreased
- See the following figure to know where the murmur is best heard

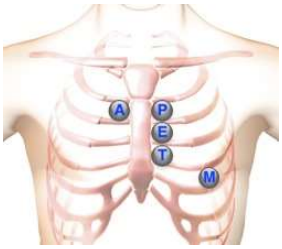


Figure 14: The aortic regurgitation murmur is heard at the right upper sternal border, also known as the aortic area. Source: First Aid 2018

Patent Ductus Arteriosus

- The ductus arteriosus might remain open after birth because:
    - It is an isolated occurrence where the DA failed to close
    - It has been kept open on purpose because the infant's life is dependent on mixing between venous and arterial blood because of a congenital heart defect
    - The latter is achieved by administering prostaglandins E_1 and E_2
    - Also seen in congenital rubella or premature babies

Characteristics of the murmur:

- Continuous machine-like murmur heard at the left infraclavicular area
- S2 is obscured. Murmur is loudest at S2
- See the following figure to know where the murmur is best heard

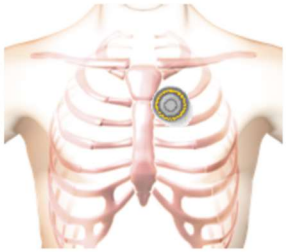


Figure 2: The PDA murmur is best heard at the infraclavicular area. Source: https://www.easyauscultation.com/cases-anatomy?coursecaseorder=2&courseid=29

Cardiac Conduction System

Myocardial Action Potential

The bundle of His and Purkinje fibers are capable of generating an action potential which is characterized by five different phases:

Phase 0:

- Rapid upstroke and depolarization
- Voltage-gated sodium channels open

Phase 1:

- Initial repolarization
- Voltage-gated sodium channels close
- Voltage-gated potassium channels begin to open

Phase 2:

- A plateau phase
- Calcium influx through voltage-gated calcium channels balance potassium efflux
- Calcium influx triggers release of calcium from sarcoplasmic reticulum → myocyte contraction

Phase 3:

- Rapid repolarization
- Massive potassium efflux
- Closure of voltage-gated calcium channels

Phase 4:

- Resting potential
- Increased potassium permeability via potassium channels

In Figure 1, you can see the different phases of myocardial action potential.

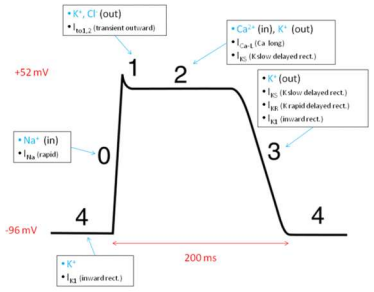


Figure 15: The different phases of the cardiac myocyte action potential and related channels. Source: https://commons.wikimedia.org/wiki/File:Action_potential_ventr_myocyte.gif

Pacemaker Action Potential

The SA and AV node show automaticity in generating impulses.

Phase 0:

- Upstroke
- Voltage-gated calcium channels open
- Voltage-gated sodium channels are permanently inactivated → delayed conduction velocity at AV node

The pacemakers of the heart do not have the phase 1 and 2 of the myocardial action potential.

Phase 3:

- Repolarization
- Calcium channels are inactivated
- Potassium channels are open → potassium efflux

Phase 4:

- Slow spontaneous diastolic depolarization
- Occurs due to I_f also known as funny current
- I_f channels allow for slow sodium and potassium influx
- Responsible for the automaticity of SA and AV nodes
- Slop of phase 4 is decreased when acetylcholine or adenosine are administered → bradycardia
- The slop is increased when the sympathetic tone is increased → faster depolarization → tachycardia

Figure 2 shows the action potential of a pacemaker.

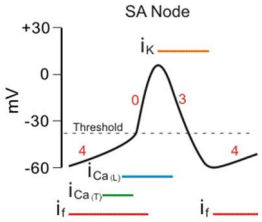


Figure 16: The different phases of a pacemaker action potential. Source: https://www.cvphysiology.com/Arrhythmias/A004

Anatomy of the Cardiac Conduction System:

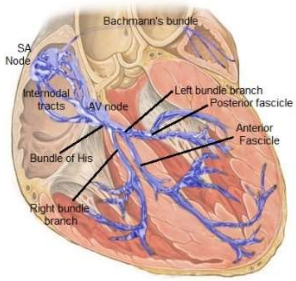


Figure 17: Anatomy of the cardiac conduction system. Source: https://commons.wikimedia.org/wiki/File:Cardiac_conduction_system.jpg

- SA node, near the entrance of the superior vena cava
  - Dominant pacemaker of the heart
- AV node, in the posteroinferior part of the interatrial septum
  - Blood supply through the PDA, which arises from the RCA in 80% of people
  - 100 msec delay → allows enough time for ventricular filling
- Bachmann bundle
- Bundle of His
- Left and right bundle branches
- Purkinje fibers

SA node has the highest pacemaker rate, followed by the AV node, bundle of His, and the slowest is from the Purkinje fibers and ventricles.

The Purkinje fibers have the highest speed of conduction followed by the atria, ventricles and slowest at the AV node.

Pathway of Conduction: Depolarization

The order of depolarization is as follows:

1. SA node
2. Atria → P-wave on ECG
3. AV node → PR interval on ECG
4. Bundle of His → Q from QRS complex
5. Right and left bundle branches → R from QRS complex
6. Purkinje fibers → S from QRS complex
7. Ventricles → ST segment which is isoelectric

Repolarization:

The order of repolarization is as follows:

1. The atrial repolarization occurs during the QRS complex, hence it is not seen on ECG
2. The ventricles undergo repolarization from outward to inward
3. Ventricular repolarization is responsible for the T-wave on ECG

Figure 4 shows the normal ECG.

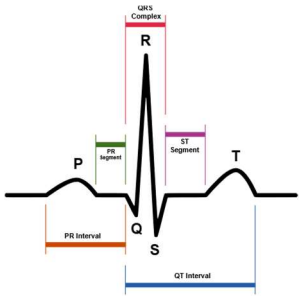


Figure 18: Normal ECG. Source: https://commons.wikimedia.org/wiki/File:SinusRhythmLabels.svg

Brugada Syndrome

Definition

Brugada syndrome is a rare inherited disease that predisposes the patient to ventricular fibrillation and sudden cardiac death without significant or identifiable ventricular structural abnormalities.

Epidemiology

The estimated prevalence of Brugada syndrome is 0.14%. Ethnic differences in incidence have been reported.

- Brugada syndrome is eight times more common in men
    - This is due to increased penetrance in men
    - The probability of inheriting a mutated gene is equal in both genders
- Age of onset is from 30 to 50 years, i.e. young men
- Age of sudden cardiac death as the presenting feature is 41 years in average
- Brugada syndrome puts the patient at an increased risk of polymorphic ventricular tachycardia which can evolve into ventricular fibrillation and cardiac arrest

Etiology and Pathophysiology

- Mutations in the SCN5A gene which encodes the voltage-gated sodium channel are reported in up to 30% of the cases
- Mutations in other genes that encode other protein channels involved with the myocyte action potential phases are reported in the remainder of the cases
- The mutations typically result in loss of function of the sodium channels, i.e. abnormal phase 0 and phase 1
- The loss of sodium voltage-gated channels is more pronounced in the right ventricle → right bundle branch block
- A repolarization gradient is present in patients with Brugada syndrome which is responsible for ST segment elevations on ECG

Clinical Findings

- Syncope
- Cardiac arrest
- Nightmares
- Family history of sudden cardiac death
- Cardiac arrest occurs during sleep or rest | cardiac arrest in HOCM occurs during exercise
- Physical examination is normal

Diagnosis:

- Laboratory testing is essential to exclude electrolyte abnormalities known to present with ST segment elevations
- Patients with symptoms of acute coronary syndrome should undergo CK-MB and troponin testing
- Genetic testing to look for mutations in SCN5A gene
- Electrocardiogram, which shoes three distinct types of ECG as depicted in Figure 1

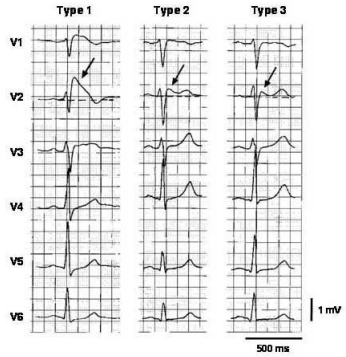


Figure 19: ECG in Brugada syndrome. Type 1: pronounced elevation of the J point, covered type ST elevation, and an inverted T-wave in leads V1 and V2. Type 2: saddleback ST-segment elevation. Type 3: ST segment elevation is less than 1 mm. Source: https://emedicine.medscape.com/article/163751-workup#c1

Treatment

- Placement of an implantable cardioverter defibrillator

How to read an ECG:

What is an ECG?

- The ECG (electrocardiogram) registers the heart's electrical activity
- The individual action potentials of the myocardial cells are average and a final vector is measured
- Therefore, the ECG is the average of billions of microscopic electrical signals
- The three important components of ECG are:
    - P-wave which is atrial depolarization
    - QRS complex which results from ventricular depolarization
    - T-wave which represents ventricular repolarization
- The three important intervals on ECG are:
    - PR interval which is due to AV node delay → prolonged in AV blocks
    - The ST segment which represents the isoelectric depolarized ventricles → important in MI and other conditions where it can be elevated or depressed
    - QT interval which can be prolonged in some conditions

Before Starting to Read the ECG

- You should always check the identification information on the top left of the ECG to make sure you have the right ECG for the right patient
- Check the ECG parameters which are standardized as the following:
- Paper speed: 25 mm/s → one small red square = 0.04 ms → one large red square = 0.2 ms
- Sensitivity: 10 mm/mV
- Filter frequency → 40 Hz
- The routine ECG should have six limb leads and six chest leads
- These important things are shown in Figure 1.

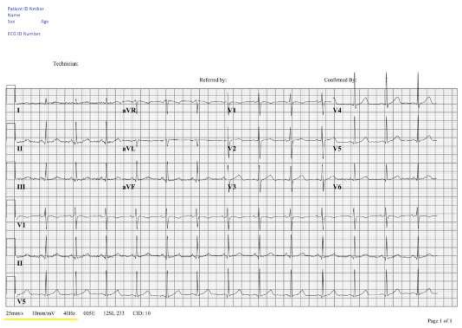


Figure 20: You should check the patient's identification information on top left in blue, the parameters of the ECG on the bottom left underlined with yellow and that there are six chest and six limb leads. In most cases, only limb lead II is given like a long trace. Source: https://nl.ecgpedia.org/images/7/76/Normaal_ecg.jpg

ECG Electrodes

- There are four extremity electrodes and six chest electrodes
- However, there are six limb leads and six chest leads on the ECG
- Extremity electrodes:
    - LA: left arm
    - RA: right arm
    - N: neutral and usually left leg
    - F: left foot
- The chest electrodes are electrodes V1 to V6

How do we have four extremity electrodes but six limb leads?

- It is easy to understand why we have six chest leads on the ECG
    - Each chest electrode is measuring the depolarization wave in one frontal plane
- Limb leads:

- I: observes from the right to the left arm
- II: observes from the right arm to the left leg
- III: observes from the left arm to the left leg
- AVL: points to left arm
- AVR: points to right arm
- AVF: points to the feet

- It is important to understand how an electrode is observing the heart to understand:
  - Whether measured depolarization will be a positive or a negative deflection
  - The determination of the heart axis as we will see later

Figure 2 shows the observation vectors of the six limb leads.

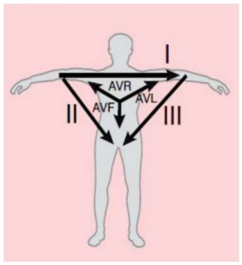


Figure 21: How the different limb leads observe "look at the heart". Source: https://nl.ecgpedia.org/images/8/8b/ECGafleidingen.jpg

The 7+2 Plan

In Figure 3, we see a normal ECG. In order for us to be familiar with the process of reading an ECG, we will refer to this figure in each step.

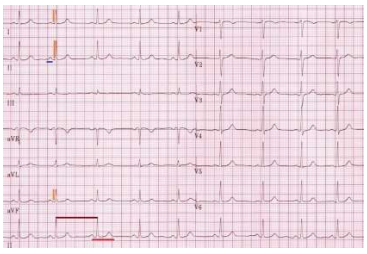


Figure 22: Blue underline: step 1, dark-red line: step 2, bright-red line: step 3, orange vertical lines: step 4. Steps 5 to 7+2 are explained in the text. Source: https://en.ecgpedia.org/images/8/82/Nsr.jpg

Step 1: Rhythm

- The goal of this step is to determine whether your patient has a sinus rhythm or not
- If there is a P-wave before every QRS complex, one can assume this is a sinus rhythm
- Refer to Figure 3, blue underline
  - This ECG shows a p-wave before every QRS complex and therefore has a sinus rhythm

Step 2: Rate

- Figure 3, dark-red line
- The next step is to determine the heart rate
- Method 1: counting the large red squares:
  - Use the sequence 300-150-100-75-60-50
  - Count the difference between two QRS complexes
  - Work best for regular rhythms
  - If the second QRS complex is between two lines, take the mean of the two corresponding numbers from the above sequence
  - Based on this method, the heart rate in Figure 3 is:

$$\frac{75+60}{2} = 68 \text{ beats/min}$$

- Method 2: counting small red squares and use the following equation:

$$\text{HR (beats/min)} = \frac{1500}{\text{number of small squares}}$$

  - HR from method 2 in our example will be 1500/22 = 68 beats/min

Step 3: Conduction

- In Figure 3, bright-red line, you see three important intervals that are used to assess the conduction on an ECG:
  - PR interval "from beginning of p-wave to start of QRS complex" which is indicative of how fast AP is transmitted via the AV node → normal PR: 0.12 to 0.20 seconds
  - QRS duration which indicates how fast the ventricles depolarize → should be really fast if depolarization occurs via the normal conduction pathway → < 0.1 seconds
    - Wide QRS complexes might be seen in LBBB, RBBB, or ventricular rhythms
  - QT interval which is indicative of how fast the ventricles are repolarized → < 0.45 seconds in men and 0.46 seconds in women

- In our example, we can find the three intervals to be as follows:
    - PR interval: 0.12 second
    - QRS duration: 0.08 second
    - QT interval: 0.36 second

Step 4: Heart Axis

- This is depicted by the orange lines in Figure 3
- Look at the QRS in leads I, II, and AVF.
- The normal heart axis is in the direction of leads I, II and aVF:
    - In our example, all of them are positive, hence the heart axis is normal
- Left heart axis deviation is when the heart axis is between -30 and -90 degrees:
    - Positive in lead I and negative in leads II and AVF
- Right heart axis deviation is when the heart axis is between 90 and 180 degrees:
    - Lead I is negative, whereas, lead AVF is positive

Step 5: P-wave Morphology

- Now we go back to the blue underline in Figure 3 to study the morphology of the p-wave
- The morphology is important as it can indicate right or left atrial enlargement
- A normal p-wave has the following characteristics:
    - Max height: 2.5 mm in leads II and III
    - Positive in leads II and AVF and biphasic in V1
    - P-wave duration < 0.12 seconds
- In our example, we can conclude that the p-wave is normal in morphology

Step 6: QRS Morphology

- The QRS complex should be narrow as described before
- Q-waves are minimal if present → if prominent, i.e. old MI
- Micro-voltage QRS is one that is less than 5 mm in height or depth in a chest lead
- R wave propagation is important. It should become larger from V1 to V5. R wave should be at its maximum height in lead V5
- In our example, the QRS morphology is normal

Step 7: ST Morphology

- The ST segment represents ventricular repolarization
- ST segment should be isoelectric as in our example
- Elevation of ST segment is indicative of acute ischemia, acute pericarditis, HOCM, PE, Brugada syndrome, LVH or acute myocardial infarction
- ST segment depression is seen in LVH with strain pattern, digoxin overdose, hypokalemia, and ischemia
- T-wave morphology is also checked in this step
- If you identify a T-wave abnormality such as a flat T-wave or a negative T-wave, it must be present in two consecutive leads to be considered as abnormal
- Our patient has normal T-wave morphology

Step 7+1: Compare to a Previous ECG

- Whenever examining an ECG, it is always advisable to compare the current ECG with a previous one
- You need to determine whether the patient has a new abnormality or an old one
- Treatment is different for acute versus chronic arrhythmias

Step 7+2: Conclusion

- This is perhaps the most difficult step of them all
- You need to show a concise and well-written conclusion that shows the results of the previously mentioned seven steps
- The conclusion in our example is as follows:
- “Normal sinus rhythm with HR of 68 beats/min, normal PR, QRS and QT intervals, normal heart axis, normal PR and QRS morphology, and no ST segment abnormality”

Wolff Parkinson White Syndrome

Definition

Wolff Parkinson White (WPW) syndrome is a medical condition characterized by the presence of one or more atrioventricular accessory pathways. These pathways are faster in conduction speed when compared to the AV node and put the patient at an increased risk of orthodromic re-entrant tachycardia and atrial fibrillation.

Epidemiology

- The estimated incidence of preexcitation syndrome in the United States is from 0.1 to 3 per 1000
- Preexcitation syndrome is the presence of a delta-wave on ECG without the other

abnormalities that are characteristic of WPW syndrome
- The incidence of confirmed WPW syndrome in the united states is 4 per 100,000 per year

Location of the accessory pathway from most common to least common:

- Left free wall
- Posteroseptal
- Right free wall
- Anteroseptal

Most patients with WPW syndrome will develop a reciprocating tachycardia. Up to 30% of them will also develop atrial fibrillation. Only 5% of WPW syndrome patients develop atrial flutter.

- There is a slight male to female predominance
- Onset is usually in infancy or early childhood
- The prognosis is excellent if the syndrome is recognized and treated

Etiology and Pathophysiology

- This is a congenital defect
- Abnormal fast accessory pathway allows for faster conduction from atria to ventricle via bundle of Kent
- The impulse bypasses the normal conduction pathway, the AV node
- Because the action potential will also be conducted through the AV node but with delay, you end up with the following characteristics on the ECG:
    - Delta-wave because the bundle of Kent is faster in conduction
    - Shorter PR interval
    - Widened QRS because the conduction was in part via the accessory pathway
- This can result in reentry tachycardia → supraventricular tachycardia

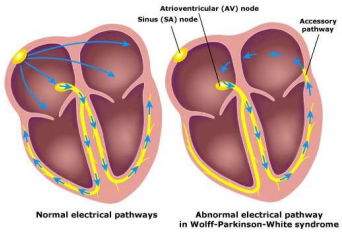


Figure 23: Failure of normal insulation of the ventricles and atria during embryogenesis result in the formation of the accessory pathway depicted here. This accessory pathway has a faster speed of conduction than AV node and does not have a delay period. Source: https://en.wikipedia.org/wiki/Wolff–Parkinson–White_syndrome#/media/File:WPW.jpeg

Clinical Findings

- Asymptomatic if the heart rate is normal
- When supraventricular tachycardia develops:
    - Palpitations
    - Dizziness
    - Dyspnea
    - Presyncope

Diagnosis

The ECG shows the characteristic delta-wave when in sinus rhythm. Patients with atrial fibrillation and WPW syndrome will have a rapid polymorphic wide-complex tachycardia that is irregular. This is a dangerous arrhythmia and most antiarrhythmics are contraindicated.

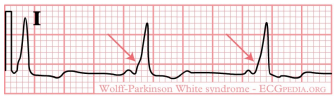


Figure 24: Delta-wave in a patient with WPW syndrome. Also notice the shortened PR interval. Source: https://en.ecgpedia.org/wiki/Ventricular_pre-excitation_(Wolff-Parkinson-White_pattern)

Treatment:

Patients with atrial fibrillation and WPW syndrome:

- Procainamide or amiodarone
- Avoid: adenosine, diltiazem, verapamil, or beta-blockers → block AV node and facilitate conduction via accessory pathway

Definition treatment:

- Radiofrequency catheter ablation

Atrial Fibrillation

Definition

Atrial fibrillation is a supraventricular tachycardia where there is uncoordinated activation of the atria that is irregular and does not originate from the SA node and is associated with rapid ventricular response. The rapid, irregular ventricular response can cause hemodynamic compromise.

Epidemiology

- Atrial fibrillation is the most common cardiac arrhythmia
- It is associated with a five-fold increase in the risk of embolic stroke

- It worsens the prognosis of heart failure and myocardial infarction
- The prevalence increases with age

Etiology and Pathophysiology

Common causes of atrial fibrillation:

- Cardiac causes:
  - Myocardial infarction or ischemia
  - Hypertension
  - Epicardial disease, myocarditis, or endocarditis
  - Heart failure
  - Iatrogenic: post ablation, catheterization, surgery, or device implantation
  - Atrial septal defect → atrial dilatation
  - Ebstein anomaly → atrial dilatation
  - Dilated cardiomyopathy and valvular disease → atrial dilatation
- Noncardiac causes:
  - Antiarrhythmics
  - Beta agonists → sympathomimetics
  - Drugs that increase QT interval
  - Electrolyte abnormalities
  - Sarcoidosis
  - COPD
  - Pneumonia
  - Pulmonary embolism
  - Obstructive sleep apnea
  - Hyperthyroidism

Pathophysiology:

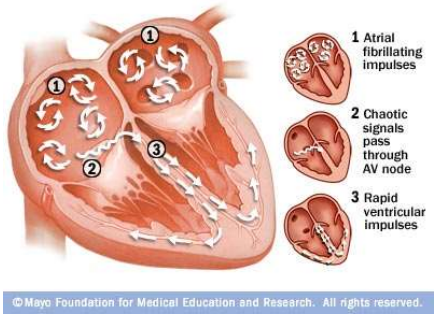


Figure 25: Mechanism of re-entry current in the pathogenesis of atrial fibrillation.

- Multiple micro-re-entry automatic areas or circuits are present in the atria
- Some of these APs are conducted via the AV node, others are blocked → chaotic rapid ventricular response
- Patients with such micro-circuits are more likely to develop atrial fibrillation when under sympathetic nervous system activation
- The atria no longer contract → blood stasis → clot formation

Clinical Findings

- Patients can be asymptomatic
- Most common symptom is palpitations
- Patients have an irregularly irregular tachycardia on palpation of the pulse
- Symptoms and signs suggestive of the etiology:
  - Heat intolerance, hypertension, agitation, tremors → hyperthyroidism
  - Angina → myocardial ischemia/infarction
- Symptoms or signs suggestive of embolic disease such as stroke
- Hypotension and syncope → hemodynamic compromise

Diagnosis

- Laboratory testing help in identifying the cause. Check electrolytes, troponins, CK-MB, thyroid function tests, and liver and kidney function tests
- Imaging of the heart with echocardiography to exclude structural heart disease, valvular disease, and intra-atrial thrombi
- ECG: using the 7+2 step plan:
  - Absent p-waves
  - Atrial rate: 400 to 600, ventricular rate is 75 to 175 beats/min
  - QRS duration is narrow → supraventricular tachycardia with AV nodal conduction
  - Heart axis might point to left or right depending on the cause → left ventricular hypertrophy → left axial deviation
  - QRS might show evidence of old MI, or LVH
  - ST segment could be depressed → ischemia, or elevated → infarction
  - T-wave inversion → acute myocardial infarction as the cause of atrial fibrillation

- Comparison to a previous ECG is important for categorization

Figure 26: ECG in atrial fibrillation. Source: https://en.wikipedia.org/wiki/Atrial_fibrillation#/media/File:Atrial_Fibrillation.png

The following table summarizes the categorization of atrial fibrillation:

Category of AF	Definition
First documented	First episode to be documented. No previous ECG or normal previous ECG
episode recurrent	Two or more episodes of AF that are separated in time
paroxysmal	If recurrent AF keeps converting to sinus rhythm without any intervention
persisting	An AF episode that lasts more than 7 days
permanent	An AF episode that persists despite electrical or chemical cardioversion

Treatment

Rate control treatment:

- Control rate without attempting to correct permanent AF
- Beta blockers and digoxin. Adenosine might be used
- Avoid beta blockers and calcium channel blockers in patients with AF and Wolff Parkinson White syndrome
- Target ventricular rate is < 100 beats/min

Rhythm control treatment:

- Converting the rhythm back to sinus rhythm
- Helpful in the other types of AF mentioned rather than permanent AF and in patients with hemodynamic compromise
- Restoration of sinus rhythm + intra-atrial thrombus without anticoagulation = arterial embolism
- Chemical cardioversion:
  - Amiodarone
  - Flecainide
- Electrical cardioversion
- Radiofrequency catheter ablation

Anticoagulation: see table below:

Item	Score	Total	% stroke per year	Recommendations
CHF	1	0	0	Aspirin
Hypertension	1	1	1.3	Aspirin + clopidogrel
Age ≥ 75 years	2	2	2.2	Warfarin: INR 2 to 3
DM	1	3	3.2	
Stroke or TIA	2	4	4	
MI or PAD	1	5	6.7	Or: Apixaban, dabigatran, edoxaban, rivaroxaban
Age 65 – 74 years	1	6	9.8	
Female	1	7	9.6	
		8	6.7	
		9	15.2	

CHA_2DS_2VASc score: C: CHF, H: Hypertension, A_2: age above or equal to 75 which takes two points, D: DM; S: stroke which takes two points, V: vascular disease such as MI or PAD, A: age from 65 to 74, and Sc: sex which is female to take one point.

Atrial Flutter

Definition

Atrial flutter is a supraventricular tachycardia that results when there is a reentry mechanism that involves the atrial tissue around the tricuspid area. If the AV node conduction is too fast, the patient's cardiac output will be diminished, and the patient can develop hemodynamic compromise.

Epidemiology

- Much less common than atrial fibrillation
- Represents 10% of supraventricular tachycardia
- 200,000 new cases of atrial flutter per year in the United States
- More common in men

Etiology and Pathophysiology

Cardiogenic causes such as coronary artery disease, congestive heart failure, and hypertension. Noncardiogenic causes include pulmonary embolism, electrolyte abnormalities, digitalis toxicity, and COPD.

Pathophysiology:

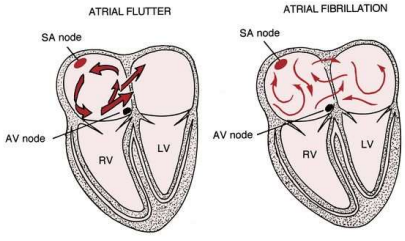


Figure 27: Mechanism of re-entry current in the pathogenesis of atrial flutter versus atrial fibrillation. Source: https://www.google.com/url?sa=i&rct=j&q=&esrc=s&source=images&cd=&cad=rja&uact=8&ved=2ahUKEwiX3bjokOPdAhVBSxoKHdR5AyAQjRx6BAgBEAU&url=ht

tps%3A%2F%2Fwww.pinterest.com%2Fpin%2F388294799112793734%2F&psig=AOvVaw1_10EIPyM05Wsj3Lrvf_lJ&ust=1538410744955803

- Can also lead to blood stasis in the atrium and might be associated with an increased risk of embolic events

Clinical Findings

- Patients can be asymptomatic
- Most common symptom is palpitations
- Symptoms and signs suggestive of the etiology:
  - Heat intolerance, hypertension, agitation, tremors → hyperthyroidism
  - Angina → myocardial ischemia/infarction
- Symptoms or signs suggestive of embolic disease such as stroke
- Hypotension and syncope → hemodynamic compromise

Diagnosis

- Laboratory testing and echocardiography to identify the cause of atrial flutter
- ECG: using the 7+2 step plan:
  - Sawtooth pattern p-waves
  - Atrial rate: up to 350, ventricular rate is dependent on AV conduction: 1:1 rare; 2:1 or 3:1 common. The slower the ventricular response, the more visible the sawtooth pattern
  - QRS duration is narrow → supraventricular tachycardia with AV nodal conduction
  - Normal heart axis or heart axis deviation
  - QRS might show evidence of old MI, or LVH
  - ST segment could be depressed → ischemia, or elevated → infarction
  - T-wave inversion → acute myocardial infarction as the cause of atrial fibrillation

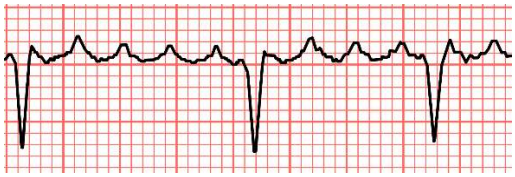


Figure 28: ECG in atrial flutter. Source: https://en.wikipedia.org/wiki/Atrial_flutter#/media/File:Atrial_flutter34.svg

Treatment:

Rate control treatment:

- This is more important here because 2:1 and 1:1 AV nodal conduction can result in hemodynamic compromise → decreased cardiac output
- Beta-blockers or calcium channel blockers
- Target ventricular rate is < 100 beats/min

Rhythm control treatment:

- Converting the rhythm back to sinus rhythm
- In patients with hemodynamic compromise
- Restoration of sinus rhythm + intra-atrial thrombus without anticoagulation = arterial embolism
- Chemical cardioversion:
  - Amiodarone
  - Flecainide
- Electrical cardioversion
- Radiofrequency catheter ablation more successful and is favorable → definitive treatment

Anticoagulation:

- Patients might benefit from anticoagulation treatment. Follow same recommendations as for atrial fibrillation

Atrioventricular Node Blocks

Definition

The conduction of the AP from the atria to the ventricles is via the atrioventricular (AV) node. When the AV node is disturbed, this conduction pathway becomes abnormal. The disruption of the conduction of AP at the AV node is known as an AV node block. The severity of such a block can be seen as incomplete or complete.

Incomplete AV block is defined as an AV block that delayed or transiently blocks the conduction from the atria to the ventricles. Complete AV block indicates that the atria and the ventricles are depolarizing independently from each other, i.e. dissociation between p-waves and QRS complexes.

First degree AV block

- Prolongation of the PR interval, i.e. > 0.20 sec
- Every P wave is followed by a QRS complex
- Prevalence in those older than 90 years is 16%
- Caused by degeneration of the conduction system
- Asymptomatic → no treatment is required

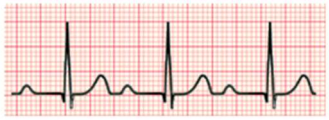


Figure 29: First degree AV block. PR interval is 0.36 sec. Source: https://en.wikipedia.org/wiki/Heart_block

Second degree AV block

- Two types
- Mobitz type I: "Wenckebach"
    - Progressive lengthening of the PR interval
    - One P wave is not conducted to the ventricles → not followed by a QRS complex
    - After the "dropped" beat, the pattern is repeated again
    - Because the PR interval is different, the rhythm is regularly irregular
    - The condition is benign and does not require treatment

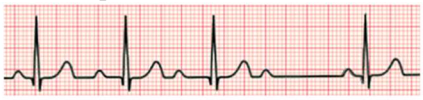


Figure 30: Second degree AV block Mobitz type I. Progressive lengthening of PR interval and one P wave is not followed by QRS complex. Source: https://en.wikipedia.org/wiki/Second-degree_atrioventricular_block

- Mobitz type II:
    - One of the P waves is suddenly not conducted to the ventricles "sudden somewhat random dropped beats"
    - The PR interval is constant and does not lengthen progressively
    - The condition is commonly associated with AV node ischemia
    - Can progress to complete third-degree AV block
    - Treatment is placement of a pacemaker

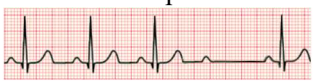


Figure 31: Second degree AV block Mobitz type II. Sudden drop of a QRS complex. Source: https://en.wikipedia.org/wiki/Second-degree_atrioventricular_block

Third degree AV block

- The AV node is not conducting atrial depolarization to the ventricles anymore
- The atria and ventricles beat independently of each other
- Complete dissociation between the p-waves and QRS complex
- The QRS complexes are still narrow because they tend to start from the bundle of His, however, they can be slightly variable in morphology between one beat and the other
- Atrial rate is faster than ventricular rate
- Ischemia and Lyme disease are possible causes
- Treated with a pacemaker

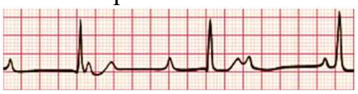


Figure 32: Third degree AV block. Complete dissociation between p-waves and QRS complexes. Source: https://en.wikipedia.org/wiki/Heart_block

Ventricular Fibrillation

Definition

Ventricular fibrillation (VF) is a cardiac arrest rhythm. There is chaotic depolarization of the ventricles and the heart is not contracting, i.e. in cardiac arrest. If untreated, the prognosis is immediate death.

Ventricular fibrillation in a conscious patient! Check for a technical problem, the patient is not in VF

ECG Findings

- Complete erratic arrhythmia without any identifiable waves or complexes

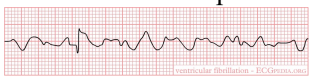


Figure 33: Ventricular fibrillation. Source: https://commons.wikimedia.org/wiki/File:De-Rhythm_ventricular_fibrillation_(CardioNetworks_ECGpedia).png

Treatment

- If the patient develops VF in front of you while on ECG monitoring, immediate defibrillate and start CPR
- If the patient is brought to you in cardiac arrest:
    - Check the pulse
    - Start CPR
    - Stop and check for rhythm, VF, defibrillate

- Check for pulse, if no pulse
- CPR again
- And repeat this algorithm

AVNRT and AVRT

AVNRT

Atrioventricular nodal re-entry tachycardia (AVNRT) is a type of a supraventricular arrhythmia, i.e. narrow QRS complex. This is a nodal rhythm.

- ANRT is the most common type of a regular non-sinus tachycardia
- More common in females

Etiology and Pathophysiology

- The patient has a normal pathway and an abnormal pathway within the AV node
- The normal pathway can undergo rapid depolarization, but normal speed of repolarization
- The abnormal pathway depolarizes slowly but can undergo repolarization very fast

- Impulse coming from SA node - Chooses the normal AV node pathway - AV node depolarizes fast - Impulse is passed down to the bundle of His - Conduction via the accessory pathway also happens at the same time - The fast depolarization via the normal pathway cancels the slow impulse coming from the accessary pathway - Normal ECG	
- An atrial premature beat occurs - The normal AV node pathway is still not fully repolarized - The abnormal pathway has fully repolarized - The impulse goes down this pathway - It takes long for the impulse to reach the bundle of His which is important for the next step in the pathogenesis	
- Because the impulse took enough time for the rest of the AV node to be fully repolarized, a re-entry current occurs - The impulse goes down the Bundle of His to depolarize the ventricles - But also goes up to the atria to depolarize them - An atrial echo, i.e. pseudo S-wave is seen on the ECG	
- The impulse that was sent to the atria is now back to repolarize the ventricles via the accessory pathway again - AVNRT develops	

Clinical Findings

Patients present with palpations due to tachycardia and dizziness. The heart rate is from 180 to 250 beats/min.

Diagnosis

ECG findings:

Atrial and ventricular rate of 180 to 250 beats per minute

Normal sinus rhythm → an atrial ectopic beat → AVNRT

Narrow QRS complexes

Pseudo S-wave which occurs because the atrial depolarization vector is in the opposite direction of the measuring lead

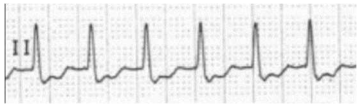


Figure 34: Regular narrow QRS complex tachycardia with pseudo S-waves. AVNRT. Source: https://nl.ecgpedia.org/images/1/12/Avnrt_ecg.jpg

Treatment

- Adenosine terminates the arrhythmia
- Carotid sinus massage

AVRT

- The pathophysiology is somewhat similar to AVNRT with few differences:
    - The accessory pathway is not in the AV node
    - The accessory pathway connects the atria and ventricles
    - Could be seen in patients with bundle of Kent
- Two patterns:
    - Retrograde conduction from the ventricles to the atria via the accessory pathway. Each QRS is preceded by a P-wave. Narrow QRS complex. Also known as orthodrome AVRT
    - Anterograde conduction from the atria to the ventricles via the accessory pathway. Wide QRS complexes. Retrograde p-waves after the QRS complex

Summary of SVTs

Figure 2 shows the origin of the different types of supraventricular tachycardias.

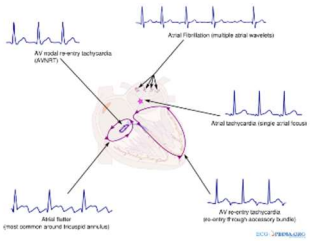


Figure 35: Summary of the different types of supraventricular tachycardias and their origin. Source: https://en.ecgpedia.org/index.php?title=File:SVT_overview.svg

Management of Supraventricular Tachycardias

Diagnosis Algorithm:

It is important to differentiate between supraventricular and ventricular tachycardias, and to further classify the supraventricular tachycardia into one of the following major types:

- Atrial fibrillation
- Atrial flutter
- AVNRT
- AVRT

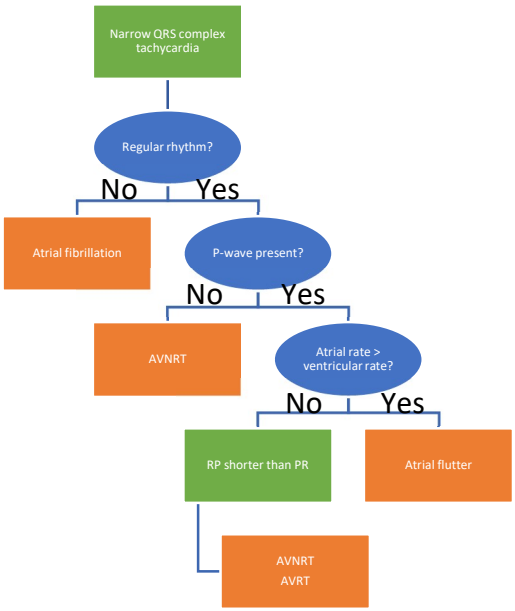


Figure 36: Diagnosis algorithm of SVTs. Orange boxes have the definitive diagnosis.

Treatment of Supraventricular Tachycardia with Hemodynamic

Compromise

- A very fast ventricular response rate in a patient with SVT → decreased cardiac output → hemodynamic compromise
- The following treatment options assume that you want to provide rhythm control in atrial fibrillation, or rate control and abolishing of arrhythmia in other SVTs
- If intravenous access is not established yet:
    - Synchronous DC shock at 1J per kg
    - Not converted to sinus rhythm? → synchronous DC shock at 2J per kg
    - Not converted to sinus rhythm? → amiodarone
- If intravenous access is established:
    - Adenosine 100 µg/kg → slows conduction at AV node
    - Wait for 2 minutes
    - No response? → adenosine 200 µg/kg and wait for 2 minutes
    - No response? → adenosine 300 µg/kg
    - No response? → synchronous DC shock or amiodarone

Treatment of Supraventricular Tachycardia without Hemodynamic Compromise

- Start with vagal nerve stimulation maneuvers:
  - Valsalva maneuver
  - Carotid sinus massage → glossopharyngeal afferent, vagal efferent
  - Immersion of head in cold water
- If the arrhythmia is not controlled:
  - Follow adenosine protocol as explained above 100, followed by 200, followed by 300 µg/kg
- If still not controlled:
  - Consider beta-blockers, calcium channel blockers such as verapamil, synchronous DC shock, or amiodarone

Treatment of Supraventricular Tachycardia with WPW Syndrome

- Accessory pathway in WPW syndrome is not blocked by CCBs, adenosine, and beta-blockers
- AV node is blocked by these drugs → if used, conduction via the accessory pathway will be enhanced → degeneration into ventricular tachycardia
- Accordingly, treat with amiodarone or procainamide to abolish the arrhythmia

Prevention of SVTs

- Most SVTs can be prevented by chronic beta-blockers or CCBs
- Digoxin in patients with atrial fibrillation
- Radiofrequency catheter ablation → definitive treatment

Classification of Congenital Heart Defects

Definition

- The embryogenic development of the heart is a complex phenomenon. Because of the normal connection between the right and left atria via the foramen ovale and ductus arteriosus in fetal circulation, most congenital heart defects cause problems to the baby after birth.
- Based on the type of defect, the presentation with cyanosis might be early in life, “blue babies”, or later in life, “blue kids”. In other cases, cyanosis might not be an important feature.

Classifications

- The classical classification of congenital heart defects into cyanotic and acyanotic defects is outdated, however it is still in use by many physicians and textbooks. Cyanotic heart defects result in cyanosis during infancy or short after birth, whereas, acyanotic defects may result in cyanosis later in life during childhood.
- The following classification of congenital heart defects is based on the direction of shunting of blood.

Right-to-left	**left-to-right**
Truncus arteriosus	Ventricular septal defects
Transposition of the great arteries	Atrial septal defects
Tricuspid atresia	Patent ductus arteriosus
Tetralogy of Fallot	Eisenmenger syndrome
Total anomalous pulmonary venous return	
Ebstein anomaly	

Others: coarctation of the aorta

A more recent classification is based on the clinical consequences and pathophysiology of the congenital heart defect is given below.

CHD with increased pulmonary flow	**CHD with decreased pulmonary flow**	**CHD with obstruction and no shunt**	**CHD incompatible with postnatal circulation**	**CHD silent until adulthood**
ASD	Tetralogy of Fallot	Aortic stenosis	Transposition of the great arteries	Bicuspid aortic valve
VSD	Tricuspid atresia	Coarctation of aorta	Total anomalous pulmonary venous return	Anomalies of coronary arteries
Truncus arteriosus PDA	Ebstein anomaly			WPW syndrome

This classification gives you an idea which congenital heart defects need to be corrected during neonatal period, which can be corrected during infancy, and which ones can wait until childhood.

Right to Left Shunt

- These typically present during infancy or neonatal period
- Cyanosis is marked
- Those that belong to “CHD incompatible with postnatal circulation” classification need to keep the PDA open and corrected urgently
- They can be diagnosed prenatally with recent advances in ultrasonography

Truncus arteriosus

- More of mixing of arterial and venous blood rather than a true right-to-left shunt
- Truncus arteriosus fails to divide into pulmonary trunk and aorta
- Lack of aorticopulmonary septum formation during organogenesis
- Associated with a VSD

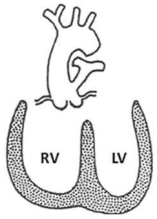


Figure 37: Persistent truncus arteriosus. Source: doi:10.1016/j.carpath.2010.02.006

Transposition of great vessels

- Belongs to "CHD incompatible with postnatal circulation"
- Shunting of blood is required for postnatal life → VSD, PDA or patent foramen ovale
- Aorta leaves RV, pulmonary trunk leaves LV
- Systemic and pulmonary circulations are separate
- Failure of aorticopulmonary septum to spiral
- Urgent corrective surgery

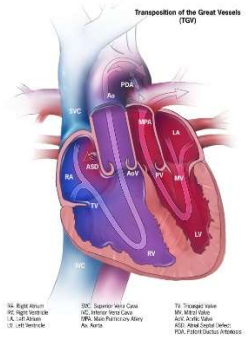


Figure 38: Transposition of the great vessels. Source: https://en.wikipedia.org/wiki/Transposition_of_the_great_vessels#/media/File:D-tga-575px.jpg

Tricuspid atresia

- Absence of the tricuspid valve
- Hypoplastic right ventricle
- ASD and VSD are both required

Tetralogy of Fallot

- Most common cause of early childhood cyanosis
- Pulmonary infundibular stenosis
- Right ventricular hypertrophy → boot-shaped heart on chest radiograph
- Ventricular septal defect
- Overriding aorta
- Pulmonary stenosis → right to left shunt through VSD → let spells during crying or exercise

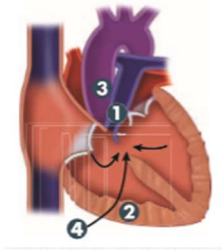


Figure 39: Tetralogy of Fallot. 1. Pulmonary atresia. 2. RVH. 3. Overriding aorta. 4. VSD

Total anomalous pulmonary venous return

- Belongs to "CHD incompatible with postnatal circulation"
- An ASD or a PDA is required to maintain life after birth
- The pulmonary veins drain into the superior vena cava instead of the left atrium
- Needs urgent corrective surgery

Ebstein anomaly

- Downward displacement of the tricuspid valve leaflets into the right ventricle
- Tricuspid regurgitation
- Usually associated with a patent foramen ovale → right to left shunt and cyanosis
- Associated with accessory conduction pathways
- Can lead to right-sided heart failure
- Risk factor: in-utero exposure to lithium

Left to Right Shunts

- These typically present during childhood
- Cyanosis is rare. Usually acyanotic at presentation
- Belong to "CHD with increased pulmonary flow" category

Ventricular septal defects

- Most common CHD
- Asymptomatic at birth

- Depending on size, may present within the first few weeks of life, or remain asymptomatic throughout life
- Large VSD → increased pulmonary blood flow → increased pulmonary venous return to the left atrium → LV volume overload → heart failure

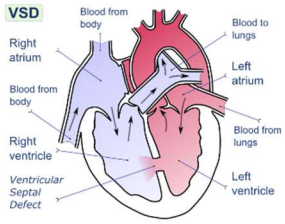


Figure 40: VSD. Source: https://en.wikipedia.org/wiki/Ventricular_septal_defect#/media/File:Ventricular_septal_defect-en.png

Atrial septal defects

- A defect in the interatrial septum
- Most common type is ostium secundum
  - Usually an isolated finding
- Ostium primum
  - Rare and occur with other CHDs
- Atrial septum is missing tissue
  - In patent foramen ovale, the ovale fails to close
- Can be symptomatic or result in heart failure in a mechanism similar to VSDs

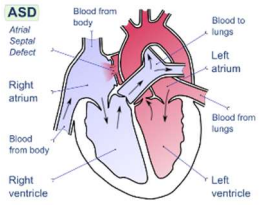


Figure 41: ASD. Source: First Aid 2018

Patent ductus arteriosus

- When a newborn takes his or her first breath: Decreased pulmonary vascular resistance → increased oxygen saturation → decrease in prostaglandins → closure of the ductus arteriosus between the aorta and pulmonary trunk
- If the above events do not lead to the closure of the DA, then a PDA becomes evident
- Left to right shunt because aortic pressure is higher than pulmonary pressure
- Right ventricular hypertrophy → right-sided heart failure
- Uncorrected → late cyanosis in lower extremities
- Indomethacin → closes PDA | prostaglandins E1 and E2 → keep PDA open

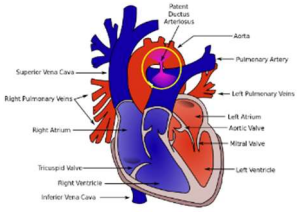


Figure 42: PDA. Source: https://en.wikipedia.org/wiki/Patent_ductus_arteriosus#/media/File:Patent_ductus_arteriosus.svg

Eisenmenger syndrome

- The previously mentioned left-to-right shunts are associated with increased pulmonary blood flow
- Increased pulmonary blood flow → pulmonary arteriolar remodeling and increased resistance → pulmonary arterial hypertension → right ventricular hypertrophy → RV pressure exceeds that of LV → right to left shunt → Eisenmenger syndrome
- Causes cyanosis and clubbing
- Associated with polycythemia

Coarctation of the Aorta

- Belongs to "CHD with obstruction to blood flow without shunt" category
- Most common site of narrowing is at the insertion of ductus arteriosus "juxtaductal"
- Associated with another CHD: bicuspid aortic valve
- Also associated with Turner syndrome
- Hypertension in upper extremities, weak delayed pulse in lower extremities
- If uncorrected → intercostal arteries enlarge → collateral circulation, → they erode ribs → ribs' notched appearance on chest radiograph
- Because afterload is increased → heart failure
- Increased risk of intracerebral hemorrhage due to berry aneurysm association
- Possible risk of endocarditis

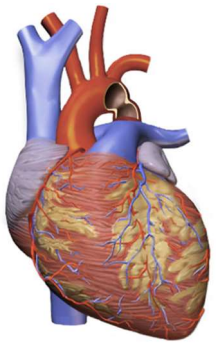


Figure 43: Coarctation of the aorta. Source: https://en.wikipedia.org/wiki/Coarctation_of_the_aorta#/media/File:Coarctation_Of_Aorta.png

Transposition of the Great Arteries

Cause

- The cause of this congenital heart defect is the failure of the aorticopulmonary septum to spiral around its vertical axis.

Description

- The aorta originates from the right ventricle
- The pulmonary artery originates from the left ventricle
- Considered as a form of vascular discordance with atrioventricular concordance

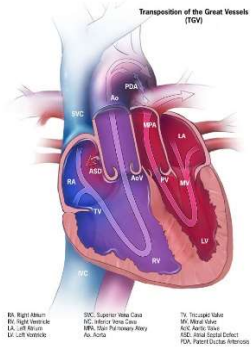


Figure 44: Transposition of the great arteries. Source: https://en.wikipedia.org/wiki/Transposition_of_the_great_vessels#/media/File:D-tga-575px.jpg

Pathophysiology

- Right to left shunt
- At birth, the systemic and pulmonary circulations will become parallel
- Deoxygenated systemic blood will be forwarded to the aorta
- Oxygenated pulmonary venous blood will be forwarded to the pulmonary artery
- A VSD or a PDA is required to be compatible with postnatal circulation
- The oxygenated blood is mixed with the deoxygenated blood to perfuse systemic circulation

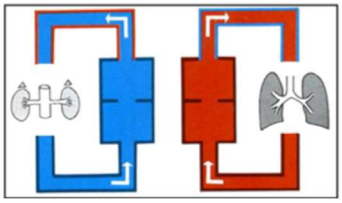


Figure 45: Schematic representation of the separation of the systemic and pulmonary circulations in complete transposition of the great arteries. Source: doi:10.1016/j.carpath.2010.02.006

Treatment

- Prostaglandins to maintain the patency of the ductus arteriosus
- Rashkind balloon atrial septostomy
- Urgent corrective surgery:
  - Right atrium is connected to the left ventricle
  - Left atrium is connected to the right ventricle

Ventricular Septal Defects

Cause

The ventricular septum, the wall that separates the left from the right ventricle, contain an opening. This might be caused by Down syndrome, incomplete looping of the heart, or mutations in NKX2.5 gene.

Description

- An opening exists between the right and left ventricles
- Five major types:
  - Subaortic
  - Membranous: most common CHD, and represent 70% of all VSDs
  - Inlet or an AV canal: associated with AV septal defect
  - Muscular: found in 20% of VSDs
  - Garbode: communication between left ventricle and right atrium → due to absence of AV septum

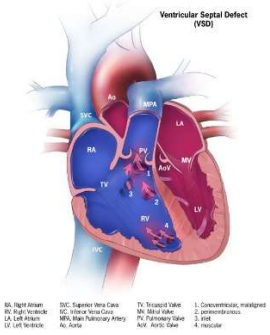


Figure 46: VSDs and their classification. Source: https://en.wikipedia.org/wiki/Ventricular_septal_defect#/media/File:Vsd_simple-lg.jpg

Pathophysiology

- Left to right shunt
- Systole → LV contraction → LV pressure exceeds RV → shunting of blood from LV to RV → increased pulmonary blood flow
- Eventually, more blood will be returning to the left ventricle → LV overload
    - Also, pulmonary hypertension if large VSD and uncorrected
- If pulmonary arterial hypertension is severe → reversal of the shunt to become right to left → Eisenmenger syndrome
- Patients can be asymptomatic, develop symptoms in neonatal period, infancy, childhood, or remain asymptomatic throughout life

Cardiac Auscultation

- Holosystolic murmur at left lower sternal border
- Palpable thrill
- Normal heart sounds

Treatment

- No treatment is required, unless:
    - Development of heart failure
    - VSD with pulmonic stenosis
    - Large VSD that has caused pulmonary hypertension
    - VSD with aortic regurgitation
- If the patient meets any of these criteria, surgical intervention is required
- Infants who are symptomatic should receive digoxin, loop diuretics, and ACE inhibitors to prevent cardiac remodeling and decrease preload

Atrial Septal Defects

Cause

There is missing tissue in the septum that separates the left and right atria. It is associated with the following diseases:

- Down syndrome
- Ebstein anomaly
- Fetal alcohol syndrome
- Lutembacher syndrome
- Holt-Oram syndrome

Description

- An opening exists between the right and left atria
- Four major types:
    - Ostium secundum ASD: most common type of ASD, 10% of all CHDs
        - Enlarged foramen ovale, limited growth of septum secundum, or excessive resorption of septum primum
        - If combined with mitral valve stenosis → Lutembacher syndrome
        - Symptomatic after 40 years of age
        - Can result in pulmonary hypertension in 50% of those > 40 years
    - Patent foramen ovale:
        - Asymptomatic
        - Can be associated with a paradoxical embolism
        - Associated with migraine
    - Ostium primum ASD: Less common that ostium secundum:
        - Associated with an AV septal defect
        - Associated with Down syndrome
    - Sinus venosus ASD: rarest type of ASDs

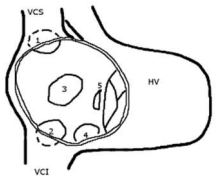


Figure 47: ASD types: 1. And 2. Sinus venosus ASD, 3. Ostium secundum ASD, 4. ASD involving coronary sinus, 5. Ostium primum ASD. Source: https://en.wikipedia.org/wiki/Atrial_septal_defect#/media

/File:Schematic_drawing_of_various_types_of_atrial_septal_defect.png

Pathophysiology

- Left to right shunt
- ASD > 9 mm → blood shunts from LA to RA → RV overload → RVH → right-sided heart failure
- Coronary artery disease in late 40s → increased stiffness of LV → increased filling pressure of left ventricle during diastole → increased left to right shunt through ASD
- Both mechanisms lead to increased pulmonary blood flow → and if severe enough pulmonary hypertension
- Can result in Eisenmenger's syndrome
- Dilated right atrium → atrial fibrillation
- The diagnosis is confirmed by transesophageal echocardiogram

Cardiac Auscultation

- Fixed splitting of S2
- Systolic ejection murmur at pulmonic area due to increased flow of blood through the valve

Patent Ductus Arteriosus:

Cause

The ductus arteriosus is normally present during fetal life. After birth, it is supposed to close. If it fails to close, then the term patent ductus arteriosus is used to describe the anomaly. The cause can be unknown in some cases. Risk factors include:

- Preterm birth
- Congenital rubella
- Down syndrome
- Other genetic disorders such as CHARGE syndrome and Loeys-Dietz syndrome

Description

- The normal communication between the aorta and pulmonary trunk fails to close after birth
- The ductus arteriosus connects the aorta and the pulmonary artery bifurcation area

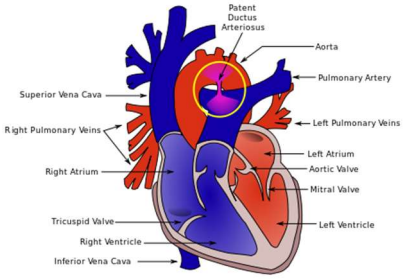


Figure 48: PDA. Source: https://en.wikipedia.org/wiki/Patent_ductus_arteriosus#/media/File:Patent_ductus_arteriosus.svg

Pathophysiology

- Left to right shunt
- Oxygenated blood from the aorta escapes to the pulmonary artery
- If the PDA is large, pulmonary blood flow increases significantly → pulmonary arterial hypertension during neonatal period → congestive heart failure
- In patients with transposition of the great arteries, a PDA is required for compatibility with postnatal physiology
- The infant can develop tachycardia, dyspnea, cardiomegaly due to ventricular dilation, a widened pulse pressure, and an increased cardiac output

Cardiac Auscultation

- S1 and S2 are obscured by the loud machinery-like continuous murmur
- Murmur best heard at the left infraclavicular area

Treatment:

- NSAIDs such as indomethacin promotes the closure of PDA

Eisenmenger's Syndrome

Definition

Eisenmenger's syndrome is a process in which a long-standing left to right shunt caused by a congenital heart defect causes severe pulmonary hypertension and reversal of the shunt into a cyanotic right to left shunt.

Etiology

- Any left to right shunt congenital heart defect that causes increased pulmonary blood flow can lead to Eisenmenger's syndrome
- Examples include atrial septal and ventricular septal defects, and patent ductus arteriosus

Pathophysiology

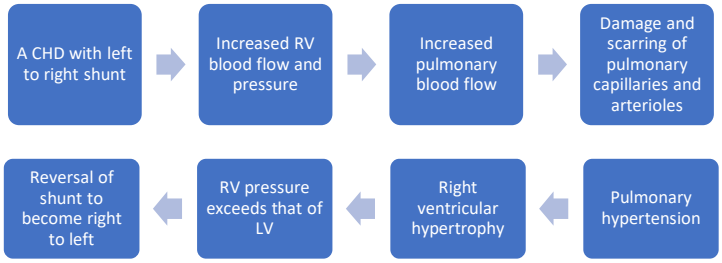


Figure 49: Pathogenesis of Eisenmenger's syndrome.

Clinical Findings

- Cyanosis
- Polycythemia
- Nail clubbing see Figure 2
- Syncope
- Heart failure
- Ventricular and atrial arrhythmias

Figure 50: Nail clubbing of fingers in a patient with Eisenmenger's syndrome. Source: https://en.wikipedia.org/wiki/Eisenmenger%27s_syndrome#/media/File:ClubbingFingers1.jpg

Diagnosis

- Echocardiography confirms the reversal of the shunt
- Catheterization can be used to confirm the diagnosis of pulmonary hypertension

Treatment

- The only curative treatment for this complication of acyanotic CHDs is heart-lung transplantation
- Accordingly, the current recommendation is to correct any acyanotic CHD that does not close by itself and is large enough to cause future issues by age of 2 years

Eisenmenger's Syndrome and Pregnancy

- Maternal mortality can be as high as 60% in those with Eisenmenger's syndrome
- Most deaths occur during or within the first week after delivery
- If a woman with Eisenmenger's syndrome becomes pregnant and the termination of pregnancy is not accepted:
- Hospitalization after the 20th week of gestation until delivery

Coarctation of the Aorta

Definition

Coarctation of the aorta is a congenital malformation where the aorta is narrowed around the area of insertion of the ductus arteriosus.

Pathophysiology

Classification of coarctation of the aorta is given in the table below.

	location of narrowing	**notes**
Preductal	Proximal to DA insertion	- Blood flow distal to the narrowing is dependent on PDA - Closure of PDA at birth → symptoms during neonatal period - Hypoplastic development of the aorta
ductal	At the site of DA insertion	
postductal	Distal to DA insertion	- Most common type in adults - Associated with notching of ribs - HTN in upper limbs, weak pulses in lower limbs

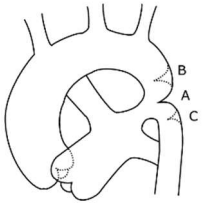


Figure 51: A. Ductal CoA, B. Preductal CoA, C. Postductal CoA. Source: https://en.wikipedia.org/wiki/Coarctation_of_the_aorta#/media/File:Coarctation_and_PDA.png

- In preductal CoA:
  - Blood pressure might show discrepancy between right and left arms if the coarctation is very proximal
- In postductal CoA:
  - Hypertension in upper extremities
  - Weak pulses in lower extremities
  - Collaterals enlarge → dilated intercostal arteries → ribs' notching on chest radiograph
- Coarctation of the aorta is more common in boys and in girls
- Girls with Turner syndrome are at an increased risk
- The condition is often associated with bicuspid aortic valve, in 50% of the cases

Clinical Findings

- In mild cases, symptoms and signs might occur only in late childhood or during adulthood
    - Dyspnea
    - Dizziness
    - Fatigue
    - Cold legs and feet
    - Legs intermittent claudication
    - Upper extremity hypertension
    - Weak pulses in lower limbs
- In severe cases, symptoms might be present soon after birth:
    - Upper limbs hypertension and lower limbs hypotension
- If the coarctation occurs before the left subclavian artery:
    - Normal pulses and blood pressure in the right arm
    - Weak pulses and decreased BP in left arm
    - Weak and delayed pulses in the legs

Diagnosis

- Chest radiograph reveals notching of ribs in adults
- Magnetic resonance imaging angiography can confirm the diagnosis
- Catheterization can reveal the narrowing or show a bicuspid aortic valve
- Measurement of BP in upper and lower extremities

Treatment

- Adults who are asymptomatic should receive conservative treatment
- Patients with arterial hypertension should undergo surgical resection of the narrowed part
- Angioplasty with stent graft to dilate the narrowed artery
- Prognosis is good, however, there is a risk of re-stenosis at the site of a previous coarctation

CHDs and their Associations

Mechanism of Association

There are different environmental factors, exposures, and certain genetic or chromosomal disorders that are known to increase the risk of congenital heart defects (CHDs) by interfering with the processes of embryogenesis, organogenesis, or sequential chamber localization such as the spiral rotation of the great blood vessels.

Fetal Alcohol Syndrome

Diagnostic criteria:

- Minor facial anomalies such as short palpebral fissures, thin vermilion border of upper lip, or smooth philtrum
- Prenatal or postnatal growth deficiency
- Head circumference at 10th percentile or smaller, structural brain anomalies, recurrent nonfebrile seizures
- Neurobehavioral impairment
- Alcohol exposure during pregnancy

Associated CHDs:

- VSD
- PDA
- ASD
- Tetralogy of Fallot

Congenital Rubella Syndrome

Clinical features:

- Sensorineural hearing loss
- Ocular abnormalities such as cataract or infantile glaucoma
- History of maternal exposure to rubella virus

Associated CHDs:

- PDA
- Pulmonary artery stenosis

Down Syndrome

Neonatal features:

- Excess neck skin
- Hypotonia
- Flat faces
- Dysplastic ears
- Epicanthic fold
- Increased gap between first and second toes
- Protruding tongue

Chromosome 21 trisomy

Associated CHDs:

- AV septal defects
- VSD
- ASD

Maternal DM

Congenital malformations associated with maternal DM:

- Caudal regression syndrome
- Holoprosencephaly

- Neural tube defects

Associated CHDs:

- Transposition of the great arteries
- VSD

Marfan Syndrome:

Clinical features:

- Large ear lobes
- Enophthalmos
- Micrognathia
- High palate

Associated CHDs:

- Mitral valve prolapse
- Thoracic aortic aneurysm/dissection
- Aortic regurgitation due to aortic root dilatation

Prenatal lithium Exposure:

Associated CHDs:

- Ebstein anomaly

Turner Syndrome:

Neonatal features:

- Webbed neck
- Low hair line
- Prominent ears

Single X chromosome (XO)

Associated CHDs:

- Coarctation of the aorta – neonatal presentation
- Bicuspid aortic valve

Williams Syndrome:

Clinical features:

- Mild to moderate intellectual disability
- Broad forehead
- Short nose
- Full cheeks
- Wide mouth with full lips

Deletion of a segment on chromosome 7

Associated CHDs:

- Supra-valvular aortic stenosis

22q11 Syndromes

Clinical features:

- Cleft palate, bifid uvula
- Learning difficulties
- Immune deficiency
- Hearing loss

DiGeorge (21q11.2 deletion) syndrome

Associated CHDs:

- Truncus arteriosus
- Tetralogy of Fallot

Regulation of BP and Blood Flow to Organs: Baroreceptors

The regulation of the blood pressure is made possible by two mechanisms:

- Fast mechanism which involves neural pathways and the baroreceptors
- Slower mechanism that involves hormonal changes among other changes

Location of the receptors:

- The aortic arch which transmits pressure information via the vagus nerve to the solitary nucleus of medulla
- The carotid sinus at the region of common carotid bifurcation which transmits information via the glossopharyngeal nerve (Herring's nerve) also to the solitary nucleus of medulla

Mechanism of BP regulation:

- A decreased blood pressure decreases the stretch on the baroreceptor
- This decreases afferent baroreceptor firing to the solitary nucleus
- This is an inhibitory pathway → decreased firing = loss of inhibition on the sympathetic pathway
- Increased efferent sympathetic firing and decreased efferent parasympathetic stimulation
- Vasoconstriction → blood pressure is elevated
- The activation of the sympathetic nervous system also has an effect on the SA node → increased automaticity due to faster diastolic depolarization of SA node → increased heart rate

Carotid massage:

- The carotid sinus baroreceptors can be massaged to increased the parasympathetic tone and decrease the sympathetic tone temporarily
- Increased pressure on the carotid sinus leads to increased stretch
- Increased afferent baroreceptor firing
- Increased parasympathetic stimulation at the AV node
- Slower heart rate

Cushing reflex:

- Patients with increased intracranial pressure might have a triad of hypertension, bradycardia, and respiratory depression
- It might seem unreasonable how hypertension is combined with bradycardia in this triad
- The following mechanism explains this observation:
  Increased ICP → pressure on cerebral arterioles → cerebral ischemia → increased brain pCO_2 → activation of central reflex sympathetic system to increased brain perfusion (remember CPP = mean arterial pressure – intracranial pressure) → hypertension

  The elevated blood pressure put more stretch on the peripheral baroreceptors → increased afferent baroreceptor firing → increased parasympathetic stimulation of the AV node → bradycardia

Chemoreceptors

- When the Cushing reflex was explained, we mentioned central receptors that were concerned with the PCO_2 of brain interstitial fluid.
- These are central chemoreceptors and they are also capable of responding to pH of brain interstitial fluid and arterial CO_2 but do not respond to PO_2
- The peripheral chemoreceptors are found in the carotid and aortic bodies
  - They are stimulated by hypoxia (PO_2 < 60 mmHg), hypercapnia and acidemia

Normal Cardiac Pressures

The following Figure 1 shows the normal pressures, in mm Hg, of the different cardiac chambers and major blood vessels. Different types of heart failure are related to changes in these pressures.

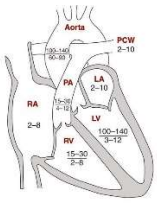


Figure 1: Normal cardiac and major blood vessel pressures in mmHg. Notice: blood pressures in the ventricles and the aorta or pulmonary artery have a systolic and a diastolic value. Source: https://www.pinterest.com/pin/14496030029159021/?lp=true

Autoregulation

- Changes in blood pressure can be large
- Accordingly, there are local organ-specific mechanisms that allow for autoregulation of blood flow to that organ
- The goal is for blood flow to remain constant over a range of perfusion pressure

The table below summarizes the different mechanisms of autoregulation of blood flow in different body organs.

Organ	Autoregulation mechanisms
Lungs	- Hypoxia → vasoconstriction - The lungs are unique in that they are the only organ where hypoxia causes vasoconstriction - Blood is shifted away from hypo-ventilated areas
Heart	- NO, CO_2 and hypoxia → vasodilation
Brain	- CO_2 and low pH → vasodilation
Skeletal muscle	- CO_2, low pH, adenosine, lactate, and increased potassium → vasodilation
Kidneys	- Myogenic and tubuloglomerual feedback
Skin	- Sympathetic stimulation → temperature control

Mean Arterial Pressure

The mean arterial pressure as was explained before is important in determining cerebral perfusion pressure. The following equation is used to calculate the mean arterial pressure.

$$\text{MAP} = \frac{2\,\text{DBP} + \text{SBP}}{3} \sim 93.33\ \text{mm Hg in healthy people}$$

Where MAP: mean arterial pressure, DBP: diastolic blood pressure, and SBP: systolic blood pressure

Hypertension

Definition

Hypertension can be defined as a persistent systolic blood pressure of 140 mmHg or more; and/or a diastolic blood pressure of 90 mmHg or more; on two different occasions.

Essential Hypertension

Up to 90% of hypertensive patients have essential hypertension where a cause is not identifiable.

The most likely mechanism is unexplained increased cardiac output or increased total peripheral resistance

Most cases of essential hypertension are responsive to current antihypertensive treatments

Therefore, if the patient is diagnosed with resistant hypertension, the possibility of secondary hypertension becomes high

Secondary Hypertension

When a cause such as renovascular, renal, or endocrine disorder, is identified, the patient will be diagnosed with secondary hypertension.

- Up to 10% of hypertensive patients have secondary hypertension
- 85% of those with resistant hypertension have secondary hypertension
- Resistant hypertension: failure to achieve a target arterial pressure despite optimum dose of antihypertensive medications

Chronic Kidney Disease

- Approximately, 5% of all hypertensive patients
- 10% of resistant hypertension cases
- Two important pathogenic mechanisms:
    - Renal failure → intravascular volume overload → hypertension
    - The activation of the renin-angiotensin system
- Patients with CKD also have:
    - Increased sympathetic nervous system tone
    - Endothelial dysfunction
    - Reduced concentration of NO which is responsible for vasodilation
    - Increased thickening of arterial wall
    - These changes lead to vasoconstriction → hypertension
- Treatment options either block the renin-angiotensin system, decrease the sympathetic tone “beta-blockers”, or decrease volume overload “diuretics”
- Potassium sparing diuretics are contraindicated

Renovascular Disease

- Approximately, 5% of all hypertensive patients
- 20% of resistant hypertension cases
- Atherosclerosis (90%) and fibromuscular dysplasia (10%) with the latter being more common in younger patients
- Fibromuscular dysplasia → string of beads
- Same pathogenesis like CKD

The diagnosis of renovascular hypertension is suspected when the patient has:

- Severe hypertension with DBP > 120 mmHg
- Resistant hypertension
- Hum on the auscultation of the abdomen
- A difference in the size of the kidneys on ultrasonography
- Or hypertension with an increase in serum creatinine after a trial of ACE inhibitors

Primary Hyperaldosteronism

- Approximately 1 to 3% of hypertensive patients
- Adrenal gland adenoma and idiopathic bilateral adrenal gland hyperplasia → increased secretion of aldosterone
- Patients with resistant hypertension and hypokalemia should be screen for hyperaldosteronism especially if younger than 40 years of age
- Aldosterone → sodium and water retention → volume overload → hypertension

Pheochromocytoma

- 0.1 to 0.5% of all hypertensive patients
- An adrenal gland medulla tumor of chromaffin cells → overproduction of catecholamines → hypertension
- Can be also para-aortic in location
- 5 Ps:
    - Paroxysmal hypertension
    - Palpitation
    - Perspiration
    - Pale
    - Pulsating headache

Cushing’s Syndrome

- 0.5% of all hypertensive patients
- Increased cortisol production which can be due to excessive pituitary production of ACTH, ectopic secretion of ACTH, or adrenal gland adenoma/cancer
- Pathogenesis of hypertension:
    - Mineralocorticosteroid activity of cortisol → water and sodium retention

- Activation of renin-angiotensin-aldosterone system
- Increased reactivity to catecholamines and vasopressin
- Reduced activity of NO synthase, and the kallikrein-kinin system which produce endogenous vasodilators

Hyperthyroidism

- Overproduction of T3 and T4
- Activation of the sympathetic nervous system and increased sensitivity to catecholamines → hypertension

Medications

- Decongestants that contain sympathomimetics such as ephedrine or pseudoephedrine can elevate the blood pressure

Other causes of secondary hypertension include coarctation of the aorta in patients younger than 30 years of age, and illicit drug use such as cocaine.

Pathophysiology

- Elevated blood pressure → increased pressure on arterial walls → smooth muscle cell proliferation and stenosis of blood vessels → decreased diameter of blood vessel → further elevation in blood pressure
- Increased shear forces on endothelium → endothelial dysfunction → cholesterol deposition in injured blood vessels' walls → further vasoconstriction → elevated blood pressure
- Eventually, all of the above leads to increased afterload → left ventricle needs to work harder → left ventricular hypertrophy → heart remodeling → heart failure

Risk Factors

While an exact cause of essential hypertension is not found, certain risk factors are known to increase the risk of hypertension:

- Advanced age
- Obesity
- Diabetes mellitus
- Sedentary lifestyle
- Tobacco smoking
- Excessive salt intake
- Excessive alcohol intake
- Family history
- Ethnicity:
  - African American more often than Caucasian
  - Least common in Asian

Complications

Coronary artery disease:

- Elevated blood pressure results in endothelial dysfunction which increases the risk of coronary artery disease and myocardial infarction

Left ventricular hypertrophy:

- This occurs because of the increased afterload
- Can result in heart failure

Stroke:

- Increased risk of hemorrhagic stroke, ischemic stroke, and lacunar infarcts

Aortic dissection:

- Elevated blood pressure damages the intima of the major blood vessels including the aorta → aortic dissection

Peripheral vascular disease:

- Same pathogenesis of coronary artery disease

Ocular complications:

- In hypertensive emergency → papilledema can be seen
- Chronic hypertension can lead to hypertensive retinopathy.
  Discussed in detail in Neurology – Visual Disorders – Retinal Disorders – Hypertensive Retinopathy

Renal disease:

- Chronic hypertension leads to afferent and efferent arteriolar stenosis which is known as hypertensive nephrosclerosis
- The glomerular filtration rate will decrease
- Activation of the renin-angiotensin system in essential hypertension
- Development of chronic kidney disease and eventually renal failure

Hypertensive Crises:

Definitions:

Hypertension can be defined as a persistent systolic blood pressure of 140 mmHg or more; and/or a diastolic blood pressure of 90 mmHg or more; on two different occasions.

Hypertensive urgency is a SBP ≥ 180 mmHg and/or a DBP ≥ 120 mmHg without end-organ damage.
Hypertensive emergency is a SBP ≥ 180 mmHg and/or a DBP ≥ 120 mmHg with evidence of end-organ damage.

Etiology:

- Most patients with hypertensive crises have an established diagnosis of hypertension
- Noncompliance is a common cause
- Use of sympathomimetics such as decongestants or illicit drugs

Epidemiology:

- 1 to 2% of those diagnosis with hypertension will have a hypertensive emergency or urgency in their lifetime
- The most common types of hypertensive emergency are:
- Acute pulmonary edema
- Cardiac ischemia
- Neurologic emergencies

Pathophysiology:

- End-organ damage in hypertensive emergencies occur by the following mechanism: Mechanical stress on vascular walls → endothelial damage and release of pro-inflammatory mediators → increased vascular permeability and activation of coagulation cascade in the microvasculature → micro-clots and hypoperfusion to the target organ

Specific Types of End-Organ Damage in Hypertensive Emergencies:

Acute aortic dissection:

- Clinical findings include tearing mid-sternal chest pain
- Intravenous esmolol is indicated.
- Lower SBP < 120 mmHg in 5 to 10 minutes!

Acute pulmonary edema:

- Patients present with dyspnea and basal crackles
- Intravenous nitroglycerin, clevidipine, or nitroprusside
- Lower by 25% of presenting BP within first hour, then more gradually
- Beta-blockers are contraindicated

Acute myocardial infarction:

- Symptoms and signs suggestive of MI
- ECG findings suggestive of MI
- Lower BP with esmolol
- Target BP < 140/90 mmHg
- Maintain DBP > 60 mmHg for adequate coronary perfusion

Acute renal failure:

- Symptoms and signs of acute renal failure such as decreased urinary output
- Administer intravenous clevidipine, fenoldopam, or nicardipine

Eclampsia or pre-eclampsia:

- Pregnant woman with pregnancy induced hypertension or chronic hypertension
- Eclampsia → delivery
- Pre-eclampsia: BP can be lowered with hydralazine, labetalol, or nicardipine
- ACEi, angiotensin receptor blockers, and nitroprusside are contraindicated

Emergency caused by pheochromocytoma or use of sympathomimetics:

- Intravenous clevidipine, nicardipine, or phentolamine

Acute intracerebral hemorrhage:

- Focal neurological deficits, headache, fever, meningism
- Adequate brain imaging with non-contrast CT scan
- Intravenous hypertensives to lower SBP < 140 mmHg within 1st hour
- Nicardipine or labetalol are first-line treatments

Acute ischemic stroke:

- Not recommended to lower BP unless:
  - > 220/120 mmHg
  - > 180/110 mmHg in patients undergoing fibrinolytic therapy
- If meet the above criteria, intravenous labetalol is indicated
- Over correction of BP → decreased cerebral pressure perfusion → worsen ischemia

Diagnosis and Treatment of Hypertension

Diagnosis

The diagnosis of hypertension is confirmed when two separate readings show stage 1 or stage 2 hypertension in two separate occasions.

Classification

	SBP mmHg		DBP mmHg
Normal	< 120	and	< 80
Elevated	120 to 129	and	< 80
HTN stage 1	130 to 139	or	80 to 89
HTN stage 2	≥ 140	or	≥ 90

This classification is based on the most recently published guidelines, where the threshold for the diagnosis of hypertension was lowered.

Treatment Option per Classification

	recommendations
normal	Promote healthy lifestyle
elevated	Nonpharmacologic therapy
htn stage 1	Nonpharmacologic therapy, and Pharmacology therapy with one antihypertensive
HTN stage 2	Nonpharmacologic therapy, and one or two antihypertensives

Lifestyle Modifications

Known as nonpharmacologic therapy of hypertension in the most recent guidelines.

Nonpharmacologic intervention	effect on sbp in hypertensive patients
weight loss	- 5 mmHg
dash diety pattern	- 11 mmHg
dietary sodium < 1,500 mg/day	- 5 mmHg
aerobic exercise 90 t0 150 min/week	- 5 mmHg
resistance training	- 5 to 9 mmHg
reduced alcohol ≤ 2 per day drinks for men ≤ 1 per day drink for women	- 4 mmHg

Antihypertensives

First-line agents

Thiazide diuretics:

- Blocks sodium/chloride reabsorption → sodium is excreted in urine → drags water with it → decreases intravascular volume
- Hydrochlorothiazide
- Very effective in African American patients
- Can cause hyponatremia and hypokalemia
- Use with caution in gout
- Hypercalcemia

ACE inhibitors:

- Inhibit ACE which decreases the production of angiotensin II → decreased vasoconstriction and decreased production of aldosterone → decreased sodium reabsorption and retention of water
- Also dilate the efferent arterioles in the glomerulus → blood flows faster so that proteins including albumin are not filtered → less kidney damage → renal protective especially in diabetes mellitus
- The above mechanism decreases GFR → therefore, ACE inhibitors are contraindicated in renovascular hypertension "patients with hypertension secondary to renal artery stenosis"
- Drugs end with "pril"
- Side effects: hyperkalemia, angioedema, dry cough, avoid in pregnancy

ARBs:

- Angiotensin II receptor blockers → vasodilation → decreased afterload
- Do not cause dry cough or angioedema
- Do not combine with an ACE inhibitor

CCBs:

- Vasodilators
- Nifedipine and amlodipine

Second-line agents

Beta-blockers:

- Blocks cardiac beta-receptors → effect on AV node → decreased CO
- Blocks vascular beta-receptors → vasodilation of arteries and veins → decreased afterload and preload respectively
- Blocks sympathetic stimulation of renin production by the kidneys → less aldosterone → less sodium reabsorption → diuresis
- Metoprolol
- Side effects: bronchospasm, bradycardia, fatigue, hypertriglyceridemia, low HDL, sedation, hypoglycemia, mask hypoglycemic symptoms in diabetic patients

Vasodilators:

- Hydralazine in pregnant women with hypertension
- Vasodilation → reflex tachycardia
- Can be associated with drug-induced lupus-like syndrome

Target BP

Important principles in treating hypertension:

- The new guidelines state that all HTN patients regardless of comorbidities should have a BP ≤ 130/80 mmHg
- Once pharmacologic treatment is started, it is for lifetime

- Beta-blockers and thiazide diuretics decrease mortality
- ACE inhibitors are first-line treatment of hypertension in diabetics
- Always try to start with a thiazide diuretic, unless diabetic then start with ACEi
    - If not controlled, consider adding another different class such as a beta-blocker
    - If not controlled, consider adding a third antihypertensive such as calcium channel blockers “nifedipine” or “amlodipine”

Atherosclerosis

Definition

Atherosclerosis is a term used to describe a vascular pathology that is characterized by thickening of the intimal layer of the arteries and the accumulation of fat. The fatty material is found in the central core of the atherosclerotic plaque.

The word “atherosclerosis” summarizes the pathogenesis of the disease. Atherosis refers to the accumulation of fat and macrophages, whereas sclerosis is used to describe the formation of a fibrosis layer of smooth muscle cells, leukocytes, and collagen deposition.

Epidemiology

It is difficult to estimate the incidence or prevalence of atherosclerosis itself; however most epidemiological studies focus on the incidence of coronary and peripheral arterial disease as an indicator of atherosclerosis incidence.

- More than 400,000 Americans die each year because of coronary artery disease
- Approximately, 785,000 Americans develop an initial MI each year
- More 470,000 Americans develop a recurrent MI each year
- Ischemic heart disease is the leading cause of death in the Western world
- In North American and Europe, 27 million individuals are affected with peripheral arterial disease

Risk Factors

- Dyslipidemia:
    - Hypercholesteremia
    - Elevated LDL
    - Low HDL
    - Elevated triglycerides
- Hypertension
- Lifestyle:
    - Smoking
    - Overweight or obesity
    - Sedentary lifestyle
    - Unhealthy diet
    - Alcohol
    - Stress
- Nonmodifiable risk factors:
    - Older age
    - Family history of early heart disease
- Metabolic:
    - Diabetes mellitus
    - Inflammation disorders

Pathophysiology

Three important processes:

- Fatty streaks formation
- Atheroma formation
- Atherosclerotic plaques formation

Fatty streaks formation: sequential stages

1. Chronic endothelial injury by hyperlipidemia, hypertension, smoking, or other factors
2. Endothelial dysfunction characterized by increased permeability, enhanced leukocyte adhesion, and migration of monocytes
3. Smooth muscle cell emigration from the media to the intima and the activation of the macrophages which release inflammatory mediators
4. Engulfment of fat by macrophages → formation of fatty streaks

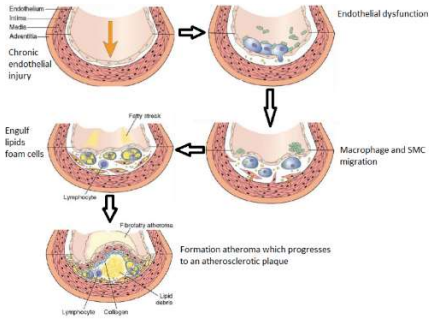
Atheroma formation: happens after stage 4 of fatty streaks formation

5. Smooth muscle cell proliferation, deposition of collagen, deposition of extracellular lipids

Atherosclerotic plaque formation happens after atheroma formation process

6. The plaque consists of a vascular epithelium, arterial smooth muscle cells, lymphocytes and a core of: cell lesions, foam cells, calcium, cholesterol, and other fatty substances
7. The plaque is pale-yellow in color due to the deposition of carotenoid pigments

The following figure summarizes the different processes involved in atherosclerosis.



Clinical Findings

The major arteries are affected in this order:

- The aorta, especially abdominal part
- Coronary arteries
- Popliteal arteries
- The carotid arteries

Symptoms include:

- Angina → coronary artery disease
- Claudication → peripheral arterial disease
- Symptoms of hyperlipidemia:
    - Xanthomas: nodules of lipid-laden histiocytes in the eyelids
    - Lipid deposition in tendons → tendinous xanthoma
    - Lipid deposition in cornea → corneal arcus
- Ischemic stroke or TIA
- Or the patient might be asymptomatic

Complications: could also be the presentation of the disease

- Aneurysms
- Ischemic stroke or ischemic heart disease
- Myocardial infarction
- Carotid artery stenosis secondary to thrombosis
- Embolic disease

Diagnosis

- The diagnostic approach is dependent on the presenting symptoms and signs of the patient
- For example, a patient presenting with symptoms suggestive of coronary artery disease will need:
    - ECG
    - Imaging studies such as CTA, MRA, or imaging studies of the heart to assess cardiac function such as echocardiography
    - Catheterization of the coronary arteries

Treatment

- Lipid lowering drugs such as statins
- Control of modifiable risk factors such as hypertension, diabetes, smoking, hyperlipidemia, obesity, and sedentary lifestyle

The goals of treatment are:

- Lower the risk of thrombosis
- Prevent atherosclerotic complications
- Reduce modifiable risk factors to slow the progression of the process
- Symptomatic relief for example for anginal pain
- Direct widening of a stenotic artery or removal of the diseased part such as carotid artery endarterectomy

Abdominal Aortic Aneurysm

Definition

An aneurysm is the dilation of a blood vessel in respect to the original artery. An abdominal aortic aneurysm (AAA) is an aortic diameter at least 1.5 times the normal diameter at the level of the renal arteries. The normal diameter at that level is 2.0 cm, accordingly, a segment of the abdominal aorta that is 3.0 cm or more is an aneurysm. Most common site is infrarenal.

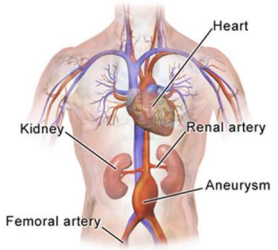


Figure 52: An abdominal aortic aneurysm illustration. Source: https://en.wikipedia.org/wiki/Abdominal_aortic_aneurysm

Epidemiology

- AAA is the 14th leading cause of death in the United States
- AAA rupture is responsible for 4500 deaths each year in the United States
- AAA is more common in those 65 years or older
- The condition is four times more common in men
- Equal incidence in white and black people

Risk Factors

- Nonmodifiable:

    - Age:
        - 1% of those aged 55 to 64 years | increase by 3% each decade after 64 years
    - Male gender:
        - Four times more common in males
        - 10 years earlier in onset in males
    - Positive family history increases the risk by four times
    - Genetic disorders such as Marfan syndrome, and Ehlers-Dantos syndrome
- Modifiable:
    - Smoking is more important than all the above risk factors
    - Atherosclerosis
    - Hypertension
    - Less common in patients with diabetes mellitus

Risk of rupture of AAA:

- Three important factors: size of AAA, expansion rate, and sex of the patient
- AAA size: diameter in cm | annual risk of rupture
    - < 4 | 0%
    - 5 – 7.9 | 3 – 40%
    - ≥ 8 | up to 50%
- A AAA that expands 0.5 cm or more over six months → high risk of rupture
    - Most important risk factor for rapid expansion is smoking
- Uncontrolled hypertension

Pathogenesis

- Atherosclerotic changes in the abdominal aortic wall
- Degradation of the tunica media by a proteolytic process
- Increased activity of matrix metalloproteinases
- Elimination of elastin → aortic arterial wall is more amenable to high blood pressure induced injury

Clinical Findings

- Most patients are asymptomatic
- An incidental finding on ultrasonography, abdominal CT or MRI
- Most remain silent until they rupture
- If symptomatic before rupture, they can present with:
    - Abdominal pain and tenderness
    - Evidence of embolic disease
    - A pulsatile mass in the abdomen

Ruptured aneurysm:

- Sudden death in 5% of the patients
- Shooting abdominal pain or back pain
- A pulsatile abdominal mass
- Severe hypotension and hemodynamic compromise
- 50% of the patients remain alive by the time they arrive to the hospital
- 50% of those survival the urgent repair procedure

Diagnosis

- It is important to confirm the diagnosis before AAA rupture
- A physical examination that reveals a pulsatile, expansile mass should raise the suspicion of an AAA
- Abdominal ultrasonography, CT or MRI performed for other purposes can detect an AAA
- Abdominal ultrasonography is the screening modality of choice for AAA
- CT angiography has a 100% sensitivity for AAA detection – only in hemodynamically stable patients
- Smoking Men aged between 65 to 75 years who are asymptomatic should be screened once by abdominal ultrasonography

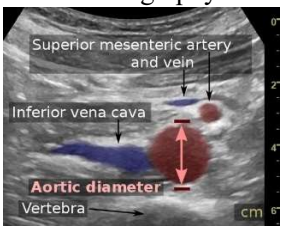


Figure 53: Measurement of abdominal aortic diameter by ultrasonography. Source: https://en.wikipedia.org/wiki/Abdominal_aortic_aneurysm#/media/File:Ultrasonographic_measurement_of_aortic_diameter_at_the_navel.svg

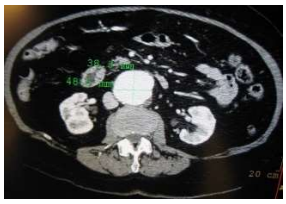


Figure 54: A contrast-enhanced abdominal CT scan showing an abdominal aortic aneurysm that is 4.8 cm in diameter. Source: https://en.wikipedia.org/wiki/Abdominal_aortic_aneurysm#/media/File:Contrast-enhanced_CT_scan_demonstrating_abdominal_aortic_aneurysm.jpg

Treatment

Nonsurgical treatment:

- Cessation of smoking
- Beta-blockers → reduce expansion rate
- Modification of risk factors such as atherosclerosis and hypertension
- Only for AAAs that are less than 5.5 cm in diameter

AAA with diameter between 3.0 to 4.0 cm:

- Imaging surveillance every two to three years (ultrasonography)

AAA with diameter between 4.0 to 5.4 cm:

- Imaging surveillance very six to twelve months (ultrasonography)

Surgical repair indications in unruptured AAA:

- AAA ≥ 5.5 cm in diameter
- Any AAA that expands by 0.5 cm or more in six months
- Some surgeons consider 5.0 cm to be the threshold for indication of surgical repair

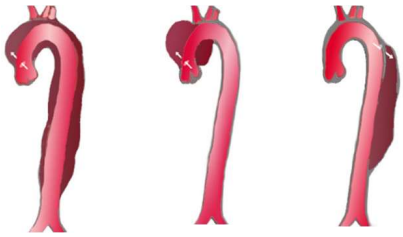
Invasive interventions:

- Surgical repair, via transabdominal route
- Endovascular repair: insertion of an endograft into the lumen of the AAA

Aortic Dissection

Definition

Aortic dissection is an injury to the innermost layer of the aorta where blood starts to flow between the layers of the aortic wall.



Debakey classification	Type I	Type II	Type III
stanford classifical	Type A		Type B
Percentage	70%		30%

Figure 55: An illustration of the different types of aortic dissection. Source: https://en.wikipedia.org/wiki/Aortic_dissection

Epidemiology

- Incidence 30 per one million per year
- Mortality rate in type A aortic dissection if untreated is 50% by the 3rd day
- Mortality rate in type B aortic dissection if untreated is 10% at 30 days

Risk Factors

- Nonmodifiable:
  - Age 60 to 70 years
  - Male gender
  - Bicuspid aortic valve
  - History of Marfan syndrome (could be younger than 40 years)
- Modifiable:
  - Hypertension (most important risk factor)
  - Smoking

Note: One of the hypertensive emergencies that can be encountered in clinical practice is aortic dissection with severe hypertension

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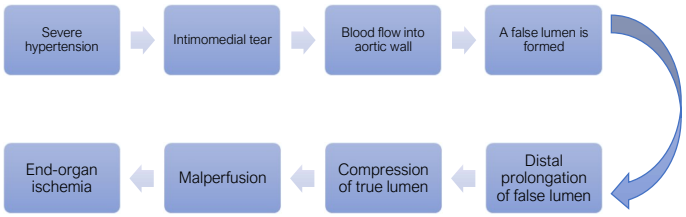
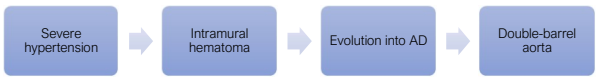
Pathogenesis

Different pathogenesis mechanisms can lead to aortic dissection. The most straightforward mechanism is depicted below.



The other mechanism of an aortic dissection does not involve an intimomedial tear and is depicted below.



The mechanism of aortic dissection in atherosclerosis is the following:

- Atherosclerotic degeneration of the descending thoracic aorta → ulceration of the intima and medial layers of the aorta → the formation of an intramural hematoma → evolution into an aortic dissection
- This is common in older patients with severe atherosclerosis

Clinical Findings

- Tearing, sudden-onset chest pain radiating to the back
- Unequal BP in arms
- Severe hypertension → this is a hypertensive emergency
- Hemodynamic compromise or shock in few patients

Diagnosis

- Chest radiograph shows mediastinal widening. If you suspect an aortic dissection, do not waste your time with this imaging test
- CT angiography

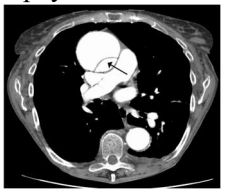


Figure 2: A contrast-enhanced CT scan showing an aortic dissection in the ascending aorta, Stanford type A aortic dissection. Source: https://en.wikipedia.org/wiki/Aortic_dissection#/media/File:DissectionCT.png

Treatment

In any patient with aortic dissection:

- IV Esmolol to lower blood pressure to SBP < 120 mmHg in 5 to 10 minutes
- Sodium nitroprusside

Stanford type A:

- Open heart surgery

Stanford type B:

- Medical treatment with beta-blockers
- Control of hypertension and other risk factors
- Thoracic endovascular aortic repair (TEVAR) in complicated cases only

Complicated type B aortic dissection:

- Evidence of thoracic aortic rupture, mal perfusion to end organs, or rapid expansion
- Candidates for TEVAR

Ischemic Heart Disease

Definition

Ischemic heart disease is an inclusive term that refers to acute coronary syndromes (ACS), coronary artery disease (CAD), and coronary heart disease (CHD). While CAD and CHD are used interchangeably, they are two different terms from a pathological point of view. CHD is the consequence of CAD.

Epidemiology

- Leading cause of death and disability in the world
- Responsible for one in every six deaths in the Western world
- CHD prevalence in those older than 20 years is 6.4%
- Prevalence in men older than 20 years is 8%, whereas the prevalence in women is 5% (1.5:1 male to female ratio)
- The prevalence of myocardial infarction in that age group is 3%, with a 2:1 male to female ratio

Risk Factors:

- Family history of early heart disease
- Age > 45 in men, 55 in women
- Hypertension
- Smoking
- Male gender
- Diabetes mellitus

- Atherosclerosis – PAD, CAD, or other forms of atherosclerosis-related diseases

Pathogenesis:

The pathogenesis of CHD consists of two main processes:

- Decreased oxygen delivery
- Increased oxygen demand

Therefore, an imbalance between coronary perfusion (CAD) and the oxygen demand of the heart muscle is the main drive for CHD. The mechanism of CAD is the same of atherosclerosis in other arteries and is given in Figure 1.

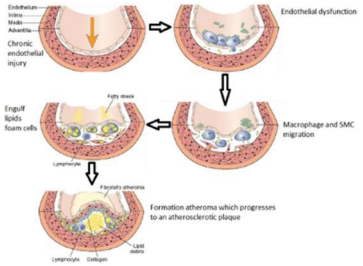


Figure 56: Pathogenesis of CAD.

As it has been shown above, CHD is the consequence of CAD. As the blood supply is compromised from one step to the next in the pathogenesis of CAD, certain effects happen in the cardiomyocytes. Figure 2 shows the pathogenesis of CHD.

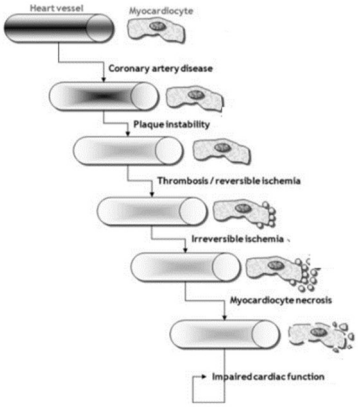


Figure 57: Pathogenesis of CHD. Source: http://dx.doi.org/ 10.1055/s-0032-1333543.

Oxygen demand increases in these patients because of the following reasons:

- Left ventricular hypertrophy induced by chronic hypertension
- Increased sympathetic nervous system tone

Clinical Findings:

- Chest pain – anginal type, substernal with possible radiation to the jaw or arms
- Exertion dyspnea or chest pain
- Stable angina occurs when there is ≥ 70% occlusion of a coronary artery
- Pain resolves with rest within 1 to 5 minutes
- Physical examination is mostly normal, except for signs suggestive of hypertension, hyperlipidemia or other risk factors
- Nitroglycerin relieves the pain very quickly by inducing venous vasodilation, decreasing preload

Diagnosis:

- ECG can be normal when patients are not in an anginal attack
- Cardiac enzymes such as troponins and CK-MB are normal
- Echocardiography to assess regional and global cardiac function

Stress tests:

- Exercise ECG:
  - Treadmill is used
  - Maximum heart rate should be 220 – age
  - Look for chest pain, hypotension, arrhythmias, and other ECG abnormalities
    - ST segment depression
  - Neither specific nor sensitive for CHD
- Stress echocardiography or myocardial perfusion tests are more sensitive and specific for CHD → regional myocardial wall motion
- If positive in any of these tests, go for cardiac catheterization to confirm the diagnosis of CAD and CHD

Pharmacologic stress test:

- Can be used after exercise testing or when the patient cannot do an exercise stress test
- Adenosine, dipyridamole
  - They cause coronary artery vasodilation → increased blood flow rate and velocity in normal vessels but not in stenotic vessels → a steal of flow pattern on perfusion nuclear studies of the heart or ST-segment changes
- Dobutamine
  - A cardiac inotrope → increases oxygen demand → similar to exercise

Treatment:

Nonpharmacological therapy:

- Same as nonpharmacological therapy of hypertension:
  - Weight loss
  - Smoking cessation
  - Decrease salt intake
  - Avoid sedentary lifestyle
  - DASH diet

Risk modification therapy:

- Statins:
  - Lipid lowering drugs
  - Increase HDL and decrease LDL
  - Anti-inflammatory properties
- Pharmacological treatment of hypertension and diabetes mellitus

Specific treatments of CHD:

- Aspirin
  - Secondary prevention of arterial thrombosis
- Cardiac-specific beta-blockers such as metoprolol
  - Decrease oxygen demand by decreasing HR
- Nitrates such as nitroglycerin
  - Decreases preload

Revascularization:

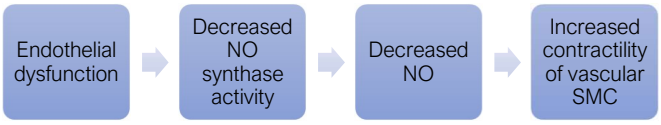
- If the patient still has symptoms of CHD despite medical treatment, then revascularization should be considered
- Perform a coronary angiography
- Choose the appropriate method: CABG versus PTCA
- PTCA:
  - Moderate-sized viable myocardium vulnerable to severe ischemia on noninvasive
  - Angiographic evidence of a major blood vessel occlusion supplying that area that is > 1.5 mm in diameter
- CABG:
  - Complex CAD
  - 3-vessel disease
  - 2-vessel disease with LAD artery disease
  - Avoid in 1-vessel disease without LAD disease

Prinzmetal's "Variant" Angina

Definition:

This is a special type of angina that occurs at rest or even during sleep. It is caused by vasospasm of an already narrowed coronary artery due to the contraction of smooth muscle cells. The condition could also occur in healthy coronary arteries. The symptoms are very brief when compared to typical angina pectoris.

Pathogenesis



- Endothelial dysfunction occurs because these coronary arteries are more often already undergoing atherosclerotic changes
- Decreased NO synthase activity leads to decreased production of NO. NO is a vasodilator
- The absence of NO increases the sensitivity of smooth muscle cell (SMC)
- Moreover, endothelial damage results in exposure of subendothelial collagen to circulating platelets
- The activation of platelets and coagulation cascade results in the release of thromboxane A2, serotonin, and histamine. These are vasoconstrictors → increase contractility of SMC

Why vasospasm occurs at rest or during sleep?

- At rest, the parasympathetic nervous system is activated
- Acetylcholine is released:
  - Direct vasoconstrictor of the coronary arteries
  - Also activates the production of NO by NO synthase → eventual effect in normal people is vasodilation
  - Because NO synthase activity is decreased in patients with variant angina → rest and the release of acetylcholine result in unopposed sudden vasospasm

Diagnosis

- ECG if performed during the attack can reveal ST-segment elevation. This is transient
  - Occurs secondary to transmural ischemia not infarction

- Coronary catheterization:
    - Most definitive test
    - IV ergonovine → vasospasm → confirms the diagnosis

Treatment:

- Calcium channel blockers → blocks contractility of vascular smooth muscle cells → vasodilation
- Nitrates

Acute Coronary Syndrome

Definition:

Acute coronary syndrome is an inclusive term that includes unstable angina, non-ST elevation myocardial infarction, and ST-elevation myocardial infarction. These conditions can be seen as a continuous spectrum where unstable angina can progress to NSTEMI and NSTEMI may progress to STEMI.

Pathogenesis

- ACS is most commonly caused by atherosclerosis
- The pathogenesis of unstable angina, NSTEMI, and STEMI is similar with slight differences
- ACS in unstable angina occurs by the following mechanism:
  An atherosclerotic plaque in a narrowed coronary artery ruptures → stimulation of platelet aggregation and thrombus formation → severe occlusion of the coronary artery, however it does not reach 100% → decreased oxygen delivery to myocardial cells → decreased contractility and electrical stability due to failure of production of ATP by myocardiocytes
- NSTEMI occurs by the following mechanism:
  Infarction of the innermost layers of the heart due to prolonged decreased perfusion
- STEMI occurs when there is a transmural infarction
- ACS is a problem of decreased oxygen delivery with unchanged oxygen demand

Clinical Findings

Unstable angina:

- Patients report new-onset angina or a change in the character of their previous angina
- Pain occurs at rest, increases in intensity, and may last longer than 10 to 15 minutes
- Other anginal pain characteristics are also present:
    - Radiation to arm, neck, or jaw
    - Associated with dyspnea
- Patients have diaphoresis, nausea, dizziness, and can be tachycardic or hypotensive
- Other patients might have severe hypertensive → this is one form of hypertensive emergency
- Decreased peripheral oxygen saturation

NSTEMI:

- Same as unstable angina, but the pain is longer in duration and is more severe
- This happens because unstable angina is known to progress to NSTEMI after 20 minutes if coronary perfusion is not restored spontaneously or by an intervention

STEMI has a similar clinical presentation to NSTEMI.

Diagnosis

Unstable angina:

- ECG: ST-segment depression or T-wave inversion
- Cardiac biomarkers must not be elevated

NSTEMI:

- ECG: Same as unstable angina
- Cardiac biomarkers are elevated: troponins

STEMI:

- ECG: ST-segment elevation or new left bundle branch block
- Cardiac biomarkers are elevated: troponins or CK-MB based on the evolution of the MI

The Thrombosis in Myocardial Infarction (TIMI) Risk Score for Unstable Angina and NSTEMI:

1 point for each risk factor	**Notes and interpretation**
age ≥ 65 **3 cad risk factors:** - **family history** - **htn** - **dm** - **smoking** - **hypercholestorelmia** **prior documented coronary stenosis ≥ 50%** **2 anginal events in last 24 hours** **use of aspirin in last 7 days** **elevated cardiac enzymes**	TIMI score is used to estimate the rate of end-point adverse events such as mortality, recurrent MI, or requiring urgent revascularization in the next 14 days TIMI score of 1 has a 4.7% rate of such complications, whereas a TIMI score of 6 or more has a 40.9% of developing an adverse event in the next 14 days Patients who score high might be candidates for PCI

Treatment:

Treatment of unstable angina and NSTEMI:

Aspirin 162 to 325 mg

Acute anti-ischemic treatment (MONA):

- Morphine
- Supplemental oxygen
- Nitroglycerin
- ACE inhibitors or ARBs
- Recently, beta-blockers and statins were added to this group

Conservative treatment:

- Low and moderate risk patients
- Start clopidogrel
- Initiate anticoagulation with unfractionated heparin, enoxaparin, or fondaparinux

Invasive treatment:

- Initiate a second antiplatelet such as clopidogrel with or without an IV GP IIb/IIIa inhibitor
- Consider a $P2Y_{12}$ receptor inhibitor in patients undergoing PCI
- Perform PCI → implant a stent in some patients
- Initiate anticoagulation

Long-term treatment:

- Lifestyle modifications
- Aspirin
- $P2Y_{12}$ receptor inhibitor for one year
- Statins regardless of LDL level
- Beta-blockers
- ACE inhibitors or ARB
- Aldosterone antagonists

Treatment of STEMI:

- PCI is recommended in all patients
- CABG in selected patients
- Fibrinolytic therapy which has its own indications and contraindications
- Long-term treatment is similar to that of other types of ACS

Evolution of Myocardial Infarction

Definition:

Myocardial infarction occurs when coronary artery perfusion is disrupted for a long period, usually over 20 minutes. This occurs secondary to rupture of a coronary artery atherosclerotic plaque and subsequent thrombosis. Thrombosis can result in near-complete or complete occlusion of the affected coronary artery. Because there is irreversible damage to the myocardium, cardiac enzymes such as CK-MB and troponins will be elevated.

Types:

- The two types of acute coronary syndrome that are related to myocardial infarction are ST-segment elevation MI and non-ST-segment elevation MI (STEMI versus NSTEMI)
- STEMI: Figure 1A
  - Complete sudden occlusion of a coronary artery
  - Transmural infarction – involves the full thickness of the myocardial wall
  - ST-segment elevation or new LBBB on ECG. Q-waves
- NSTEMI: Figure 1B
  - Near-complete, prolonged occlusion of a coronary artery
  - Subendocardial infarction
  - Inner third of the sub-endocardium is known to be vulnerable to ischemia
  - ST-segment depression on ECG
- Both have elevation in cardiac biomarkers, unlike unstable angina

A B

Figure 1: A. STEMI. B. NSTEMI. Source: https://www.123rf.com/photo_55067905_stock-vector-ecg-of-non-st-elevation-myocardial-infarction-nstemi-and-detail-of-ecg-p-wave-pr-segment-pr-interval.html and https://www.123rf.com/photo_55067904_stock-vector-ecg-of-st-elevation-myocardial-infarction-stemi-and-detail-of-ecg-p-wave-pr-segment-pr-interval-qrs-.html

- The coronary arteries are affected more commonly in this order: LAD > RCA > circumflex

Clinical Findings:

- Severe retrosternal pain – can be silent in a patient with diabetes mellitus
- Diaphoresis
- Nausea
- Vomiting
- Pain in left arm or jaw
- Dyspnea
- Fatigue

Note: The diagnosis of acute MI is confirmed when the patient has characteristic ST-segment deviations and an elevation in cardiac biomarkers.

Evolution over Time:

0 to 24 hours:

Gross:

- The heart is grossly normal. It might have a pale discoloration if tetrazolium stain is used

Light microscopy:

- Early coagulative necrosis
- Release of necrotic cell contents into blood stream → elevated cardiac biomarkers
- Microscopic hemorrhages, edema, and wavy fibers
- Neutrophils
- Reperfusion injury:
  - In some cases, reperfusion might result in hypercontraction of myofibrils
  - This occurs due to the generation of free radicals and increased calcium influx

Possible complications:

- During this period, ventricular arrhythmias can occur
- This occurs because of conduction abnormalities secondary to failure of ATP generation due to hypoxia
- Heart failure
- Cardiogenic shock

1st to 3rd day:

Gross:

- Hyperemia is prominent

Light microscopy:

- Extensive coagulative necrosis
- Acute inflammatory response with neutrophils abundance

Possible complications:

- Post-infarction fibrinous pericarditis

3rd to 14th day:

Gross:

- Hyperemic border
- Central yellow-brown soft tissue in the affected area

Light microscopy:

- Macrophages are found at this stage
- Granulation tissue formation starts

Possible complications:

- Ventricular wall rupture → tamponade
- Papillary muscle rupture → mitral regurgitation
- Interventricular septal rupture
- Left ventricular pseudoaneurysm which increases risk of rupture

14th day to several months:

Gross:

- The affected artery undergoes recanalization
- The affected myocardial area is gray white

Light microscopy:

- A contracted scar tissue

Possible complications:

- Dressler syndrome
  - Might be immune-mediated
  - Associated with high levels of antimyocardial antibodies
  - Symptoms occur fever, malaise, pleuritic chest pain, and decreased appetite
  - Diagnosed by echocardiography
  - Treatment: NSAIDs over four to six weeks
- Heart failure
- Arrhythmias
- True ventricular aneurysm → blood stasis → mural thrombus formation

Acute Myocardial Infarction

Definition:

Acute myocardial infarction occurs when there is acute myocardial injury with clinical evidence of myocardial ischemia and a rise or a fall in cardiac biomarkers in temporal relation to the onset of symptoms plus one of the following:

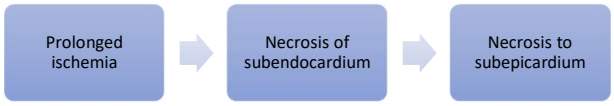
- Symptoms of MI
- Diagnostic ECG findings
- Development of pathological Q-waves on ECG

- Direct visualization of the thrombus on angiography

Epidemiology

- Prevalence of acute MI in adults is 3%
- MI is two times more common in males
- Mortality is estimated to be around 40%

Pathology



- The rupture of an atherosclerotic plaque results in acute thrombus formation
- This, if not resolved, can lead to prolonged ischemia
- Necrosis of the sub-endocardium precedes that of the sub-epicardium by few hours
- If the patient has chronic coronary heart disease, it can take longer than usual to develop a transmural infarct
- Patients with recurrent intermittent occlusion "recurrent unstable angina" tend to have a longer period before they develop a transmural infarct
- Longer period in the above two scenarios is in terms of hours, not days

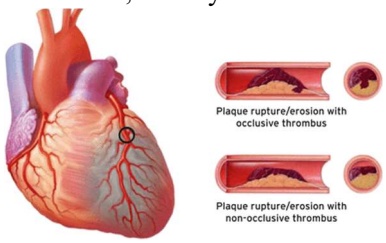


Figure 58: Pathogenesis of MI "occlusive thrombus" and unstable angina which can progress to MI "non-occlusive thrombus". Source: DOI: 10.1016/j.jacc.2018.08.1038

Clinical Findings

- Retrosternal chest pain that radiates to upper extremities, jaw, or epigastric region
- Dyspnea and fatigue
- Diaphoresis, nausea and vomiting
- Palpitations secondary to arrhythmias
- Cardiogenic shock and hypotension
- Severe hypertension might be also seen → hypertensive emergency

Cardiac Biomarkers

CK-MB:

- Rises after 6 to 12 hours of acute MI
- Peaks at 16 to 24 hours
- Not specific to cardiac muscle – also found in skeletal muscle
- Return to normal after 48 hours → useful in detecting a re-infarction
- Because it takes too long to be elevated, it is not the recommended biomarker in the confirmation of the diagnosis of acute MI

Troponins:

- Cardiac troponin I is specific to the heart → it is elevated only in cardiac injury
- Rises after 4 hours of acute injury
- Peaks at 24 hours
- Return to normal in 7 to 10 days → appropriate for detection of late presentation MI. Not appropriate for confirmation of a re-infarction detection
- The most recent definition of acute MI only takes troponins into account

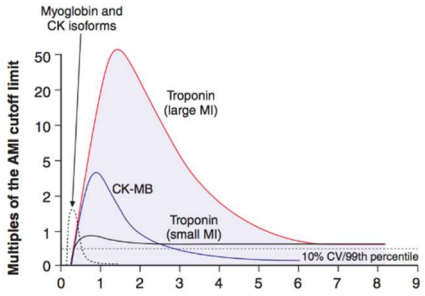


Figure 59: Changes in troponin I and CK-MB after MI onset over time. Source: https://www.grepmed.com/images/1921/ami-biomarkers-enzymes-peaks-trends-ckmb-cardiology

Electrocardiographic Detection

- Gold standard diagnostic test in the first six hours of MI
- ST-segment elevation in STEMI and T-wave changes or ST-segment depression in NSTEMI, see table below
- New left bundle branch block

ECG Finding	Notes

ST elevation	- ≥ 1 mm in leads specific to the infarcted area except in V_2 and V_3
	- Men with ST elevation V_2 and V_3:
	  ○ ≥ 2 mm
	- Women with ST elevation in V_2 and V_3:
	  ○ ≥ 1.5 mm

ST depression	- ≥ 0.5 mm in two consecutive leads
t-wave changes	- Hyperacute: peaked T-waves - T-wave inversion in two consecutive leads
Other findings	- New LBBB - Pathologic Q-waves

- Poor R wave progression → evolving or old transmural infarct

Table: ECG findings in acute MI. Source: DOI: 10.1016/j.jacc.2018.08.1038

- ST-segment deviation is determined by comparing the point of onset of the Q-wave to the point of onset of the ST-segment "J-point", see Figure 3

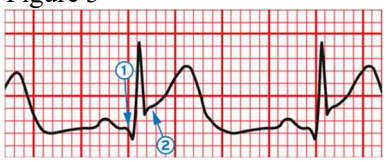


Figure 60: Point 1 is the onset of the Q-wave, point 2 is "J-point". Source: DOI: 10.1016/j.jacc.2018.08.1038

The following table summarizes the ECG findings in STEMI based on the infarct location.

Infarct location	Occluded artery	leads with st elevation
anteroseptal	LAD	V_1 and V_2
anteroapical	Distal LAD	V_3 and V_4
anterolateral	LAD OR CircumflexHo	V_5 and V_6
lateral	Circumflex	Limb leads I and AVL
inferior	RCA	Limb leads II, III, and AVF V_1 to V_3 ST depression
posterior	PDA	Supplementary leads V_7 to V_9 show ST elevation

Treatment

Aspirin 325 mg

Acute anti-ischemic treatment (MONA):

- Morphine
- Supplemental oxygen
- Nitroglycerin
- ACE inhibitors or ARBs → decrease afterload → decrease mortality
- Beta-blockers → decrease oxygen demand by decreasing HR and afterload
- Statins
- Anticoagulation

Reperfusion therapy:

- Recommended in all patients with STEMI of ≤ 12 hours duration
- PCI is first-line if the patient meets the following timeframe:
    - Max time from first medical contact to ECG diagnosis ≤ 10 min
    - Max delay from STEMI diagnosis to PCI ≤ 120 minutes
        - If not, consider fibrinolysis
- PCI in NSTEMI:
    - Hemodynamically unstable patients or cardiogenic shock
    - Chest pain refractory to MONA
    - Life-threatening arrhythmias
    - Acute mechanical complications of MI
    - Acute heart failure
- Fibrinolytic therapy in patients who are not candidates for PCI
    - Streptokinase, alteplase, reteplase, or tenecteplase
    - If you consider the patient a candidate for fibrinolysis, start fibrinolysis as soon as STEMI is diagnosed, preferably at the prehospital setting

Absolute contraindications to fibrinolytic therapy:

- Previous ICH
- Ischemic stroke 6 months ago
- CNS neoplasms or AVM
- Major trauma, head injury, or surgery one month ago
- GI bleeding one month ago
- Bleeding disorder
- Aortic dissection
- Liver biopsy or LP 24 hours ago

- Relative contraindications to fibrinolytic therapy:
    - TIA 6 months ago
    - Oral anticoagulant therapy
    - Pregnancy
    - SBP > 180 mmHg and/or DBP > 110 mmHg
    - Advanced liver disease
    - Infective endocarditis
    - Active peptic ulcer disease

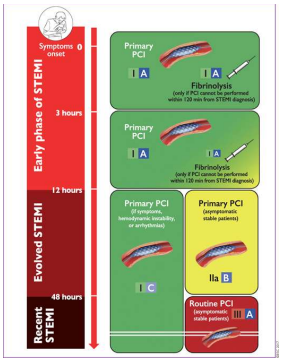


Figure 61: PCI versus Fibrinolysis for STEMI. Recommendations based on the timeframe. Source: https://doi.org/10.1093/eurheartj/ehx393

Long-term treatment:

- Lifestyle modifications
- Aspirin
- $P2Y_{12}$ receptor inhibitor
- Statins
- In selected patients:
    - Beta-blockers
    - ACE inhibitors, ARBs, or aldosterone antagonists

Complications of MI

Overview

- Acute MI patients need to be admitted to an intensive care unit or a cardiac intensive care unit for close monitoring
- Reperfusion therapy is the main preventive measure against mechanical complications of MI
- The adequate and early recognition of these complications is life-saving

Classification

Category	Examples
Mechanical	- Cardiogenic shock - Rupture complications - Acute mitral regurgitation - Pseudo/true ventricular aneurysm
electrical	- Bradyarrhythmias: AV block, sinus bradycardia, asystole - Tachyarrhythmias: atrial fibrillation, PVC, ventricular tachycardia, ventricular fibrillation - Bundle branch blocks
inflammatory	- Post-infarction pericarditis - Dressler syndrome
embolic	- Mural thrombus in true ventricular aneurysm
ischemic	- Re-infarction

Congestive Heart Failure and Cardiogenic Shock

- Reperfusion therapy decreases the risk in the acute setting
- Congestive heart failure might develop:
    - Loss of ability to contract of the left ventricle
    - Decreased cardiac output
    - End-organ hypoperfusion in cardiogenic shock
- Treatment:
    - ACE inhibitors to decrease afterload
    - Aldosterone antagonists
    - Diuretics

Arrhythmias

Sinus arrhythmias:

- Sinus tachycardia or bradycardia is corrected by identifying the cause
- Tachycardia might be caused by sympathetic nervous system activation, or secondary to hypotension
- Bradycardia secondary to sinus node ischemia

Atrial fibrillation:

- Dilation of the left ventricle → mitral regurgitation → left atrial dilation → development of atrial fibrillation
- Or secondary to atrial ischemia
- The patient has an irregularly irregular pulse
- Treatment consists of:
    - Rhythm control in hemodynamically unstable patients with amiodarone or synchronized DC cardioversion
    - Rate control with beta-blockers if not contraindicated
    - Anticoagulation

PVC:

- The ischemic myocardium is more prone to generation of premature ventricular complexes
- These PVCs can degenerate into ventricular tachycardia or ventricular fibrillation

Ventricular fibrillation:

- The conduction system becomes dysfunctional in ischemic myocardium
- Ventricular fibrillation is a cardiac arrest rhythm
- Treatment is immediate defibrillation

- Patients with recurrent ventricular fibrillation might need an implantable defibrillator
- Ventricular tachycardia is treated with amiodarone

AV blocks:

- Occurs secondary to AV node ischemia
- AV blocks types IIb and III "complete AV block" are dangerous
- Treatment is the implantation of a pacemaker

Asystole:

- This can occur in massive myocardial infarction
- Exclude other causes of cardiac arrest such as hypoxia, hypothermia, electrolyte imbalances, hemorrhage
- Non-shockable rhythm
- Treatment: follow BLS and ACLS algorithms

Rupture Complications

Free wall rupture:

- Occurs in 0.2% after the introduction of PCI in routine practice
- Responsible for 15% of all MI-related deaths
- Peak time is in the 3rd to 5th day post MI
- Older, women, with totally occluded LAD and Q-waves on ECG are more likely to develop a free wall rupture
- Patients develop recurrent chest pain, hypotension secondary to tamponade, or sudden death
- Echocardiography confirms the diagnosis
- Treatment: IV fluids to increase preload, followed by pericardiocentesis

Interventricular septal rupture

- 0.3% of MI patients
- Responsible for 5% of all MI-related deaths
- Occurs within the first week post-MI
- Hypotension is pronounced
- Treatment: emergency surgery to fix the ventricular septum

Papillary muscle rupture

- 0.3% of MI patients
- Occur within the first week post-MI
- Patients develop shortness of breath, pulmonary edema, and hypotension
- Soft-holosystolic murmur due to mitral regurgitation
- Treatment: mitral valve replacement, and reduce the afterload by administrating sodium nitroprusside

True ventricular aneurysm

- Rare in the era of PCI
- If it occurs, there is blood stasis within the aneurysm → mural thrombosis → increase risk of embolic phenomena
- Treatment: anticoagulation

Pericarditis:

- Immune-mediated
- Early onset post-MI pericarditis
- Later-onset Dressler Syndrome
- Treatment: NSAIDs, especially aspirin

Re-infarction:

- Recurrence of MI symptoms
- Rise in CK-MB; troponins are not very useful because they remain elevated from the first MI for up to 10 days
- Consider reperfusion therapy: PCI

Cardiomyopathies

Definition

Cardiomyopathies are diseases that affect the myocardium and result in structural or functional abnormalities. While the pathogenesis of these conditions is different, they share a similar clinical presentation and are identified by the same diagnostic approach. The main four types are: dilated, hypertrophic, restrictive, and arrhythmogenic right ventricular cardiomyopathy.

Dilated Cardiomyopathy

- Most common type, representing 60% of cardiomyopathies
- Characterized by a dilated and poorly functioning left, or both, ventricles
- Can be classified into primary and secondary disease
- While hypertension, valvular disease, and ischemic heart disease can cause a dilated left ventricle, the condition is not recognized as a dilated cardiomyopathy
- More common in men
- Annual incidence is 0.54 per 100,000 in children
- Annual incidence in adults is 7 per 100,000
- The prevalence of dilated cardiomyopathy in the United States is 36 per 100,000

Etiology:

- Beriberi
- Familial or genetic dilated cardiomyopathy
- Myocarditis induced dilated cardiomyopathy
- Peripartum cardiomyopathy
- Stress-induced cardiomyopathy
- Drug-induced cardiomyopathy:
    - Anthracyclines – doxorubicin
    - Cyclophosphamide
    - Cocaine
    - Alcoholic cardiomyopathy

Pathology:

- Dilated thin ventricles
- Normal or non-occlusive atherosclerotic plaques in coronary arteries
- Histopathological findings:
    - Interstitial and perivascular fibrosis
    - Myocardial necrosis at the sub-endocardium

Clinical findings:

- Symptoms and signs of congestive heart failure
- Cardiomegaly on radiological examination in an asymptomatic patient
- Abnormal ECG findings in an asymptomatic patient
- Chest discomfort that is not relieved by nitroglycerin
- Peripheral edema occurs late in the disease
- Mainly systolic dysfunction
- In case of viral-induced cardiomyopathy, the patient might describe flu-like illness prior to the onset of cardiac symptoms:
    - Myocarditis
    - Coxsackievirus B
- Patients might develop ventricular arrhythmias
- S3 gallop on auscultation
- Severely reduced ejection fraction on echocardiography
- Murmur of mitral regurgitation

ECG findings:

- T-wave or ST segment changes
- Pathological Q waves
- Wide QRS complexes
- Type 1 AV block
- None of these findings are specific or sensitive

Echocardiography:

- Diagnostic
- M-mode shows LV dilation and hypokinetic walls

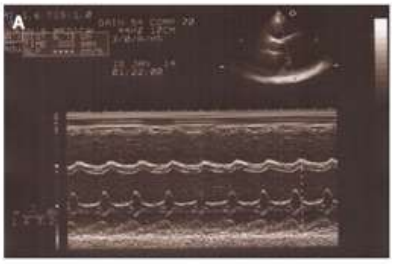


Figure 62: M-mode echocardiography showing a dilated left ventricle and diffuse hypokinetic walls. Source: DOI: 10.4330/wjc.v6.i6.478

Catheterization:

- To measure cardiac pressures
- To exclude coronary artery disease as the possible cause

Treatment:

- Beta-blockers – decrease mortality
- ACE inhibitors – decrease mortality
- Spironolactone
- Patients with ventricular or supraventricular arrhythmias respond to beta-blockers and amiodarone – no effect on mortality
- Diuretics – no effect on mortality
- ICD is indicated in selected patients to prevent sudden cardiac death

Specific Types of Dilated Cardiomyopathy

Myocarditis and dilated cardiomyopathy:

- A possible long-term complication of viral myocarditis is inflammatory dilated cardiomyopathy
- Also characterized by fibrosis similar to idiopathic dilated cardiomyopathy
- Histopathological examination of a biopsy is needed to confirm the diagnosis
- PCR can be used to confirm the presence of coxsackievirus B

Peripartum cardiomyopathy:

- Life-threatening condition
- Last month of pregnancy up to 6 months postpartum

- Unknown mechanism → possible role of prolactin
- A diagnosis of exclusion
- A systolic form of heart failure
- Treatment is challengeable because most pharmacological treatments of heart failure are contraindicated during pregnancy

Stress-induced cardiomyopathy:

- Also known as Takotsubo cardiomyopathy
- History of intense emotional or physical stress followed by LV contractile dysfunction
- ST-segment elevation on ECG
- Cardiomyopathy is transient and reversible

Drug-induced cardiomyopathies:

- Anthracyclines are antineoplastic drugs
- Highly effective in different cancers
- Can cause cardiac dysfunction
    - Acute or subacute cardiotoxicity
    - Chronic cardiotoxicity
    - Late-onset cardiotoxicity decades after discontinuing anthracyclines
- Echocardiography for screening of patients on antineoplastic therapy
- Treated with ACE inhibitors, beta-blockers and spironolactone
- Dexrazoxane is a cardioprotective agent used in patients receiving anthracycline chemotherapy

Alcoholic cardiomyopathy:

- One of the most common types of dilated cardiomyopathies
- Related to duration and dose of alcohol consumption
- Good prognosis if the patient discontinue alcohol consumption

Arrhythmogenic cardiomyopathy:

- Right ventricular dysplasia
- Genetic form of dilated cardiomyopathy
- Fibrosis and fatty infiltration of the right ventricle
- Ventricular tachycardia and ventricular fibrillation

Chagas disease:

- A parasitic infection that affects multiple organ systems
- Caused by Trypanosoma cruzi infection
- Significant fibrosis in the left ventricular myocardium in some patients → ventricular dilation → chronic heart failure
- Fibrosis can affect the SA and AV nodes → arrhythmias and sudden death
- If the immune response was adequate → fibrosis of the myocardium with indeterminate clinical significance
- Also associated with mega-colon, dilated esophagus, achalasia

Hypertrophic Cardiomyopathy

- A heterogenous group of different inherited cardiomyopathies

Pathology:

- An autosomal dominant genetic disorder
- Mutations in approximately 10 different genes for sarcoplasmic proteins
- Mutations in beta-myosin heavy chains and other myosin binding proteins account for up to 80% of the cases
- Asymmetrical or symmetrical hypertrophy of the left ventricle
- Left free ventricular wall hypertrophy plus interventricular septal hypertrophy → left ventricle outflow tract obstruction
- Histopathological findings:
    - Cardiomyocyte hypertrophy
    - Disarray and enlarged nuclei
    - Hyperchromasia
    - Increased content of interstitial collagen
- Diastolic dysfunction due to impaired filling

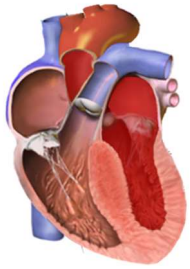


Figure 63: Septal and left-ventricular hypertrophy in hypertrophy cardiomyopathy. Source: https://en.wikipedia.org/wiki/Hypertrophic_cardiomyopathy#/media/File:Hypertrophic_obstructive_cardiomyopathy.png

Clinical findings:

- Syncope during exercise

Mechanism: asymmetric septal hypertrophy → systolic anterior motion of the mitral valve → outflow obstruction → possible syncope
- Sudden cardiac death in a young athlete
- S4 secondary to a stiff left ventricle during late diastole
- Systolic murmur
- Diagnosis is confirmed by echocardiography and ECG findings of LVH and septal hypertrophy

Treatment:

- Beta-blockers are first-line therapy
  - Negative inotropes
  - Improved ventricular relaxation → increased diastolic filling → increased stroke volume → increased CO
- Calcium channel blockers have also some role
- The goal is to decrease the left ventricular outflow tract gradient to less than 50 mmHg
- Definitive treatments include alcohol septal ablation, and septal myectomy

Restrictive Cardiomyopathy

- Impaired ventricular filling and reduced diastolic volume
- Normal or near-normal systolic function
- Changes in restrictive cardiomyopathy are functional, not structural
- 5% of all pediatric cardiomyopathies

Pathology:

- Infiltrative conditions of the myocardium result in impaired ventricular filling
- Can be primary diseases such as in Loffler's endocarditis and idiopathic restrictive cardiomyopathy
- Infiltrative diseases that can cause secondary restrictive cardiomyopathy include:
  - Hemochromatosis
  - Sarcoidosis
  - Glycogen storage disorders
  - Fabry's disease
  - Amyloidosis

Clinical findings:

- Signs and symptoms of congestive heart failure
- Distended jugular veins

Amyloid heart disease:

- Near-normal LV dimensions
- Increased myocardial wall thickness
- Infiltrative cardiomyopathy
- Low-voltage QRS complexes
- No treatment and poor prognosis

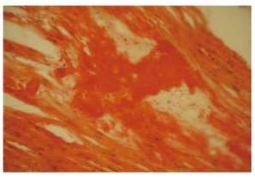


Figure 64: Amyloid deposits in a patient with secondary amyloidosis due to familial Mediterranean fever. Source: DOI: 10.4330/wjc.v6.i6.478

Hemochromatosis:

- Iron overload and deposition in sarcoplasmic reticulum of the heart
- Autosomal recessive disorder
- Multi-system manifestations
- Treatment is by repeated phlebotomy

Sarcoidosis:

- Systemic infiltrate disease
- Noncaseating granulomas infiltrate the myocardium
- Restrictive cardiomyopathy → can progress to dilated cardiomyopathy
- Associated with ventricular tachycardia and AV block type 3
- Steroids improve symptoms but do not prevent sudden death
- Patients who develop a complete AV block should be treated with a permanent pacemaker

Heart Failure:

Definition

Heart failure results when there are structural or functional abnormalities of the ventricles that impair their filling or ejection of blood. Patients with heart failure present with dyspnea, fatigue, limited exercise tolerance, and fluid retention.

Systolic HF:

- Heart failure with reduced ejection fraction
- LVEF $\leq$ 40%
- Increased end-diastolic volume
- Decreased contractility
- Patients with systolic HF tend to have diastolic HF elements too
- Most common cause is CAD

Diastolic HF:

- Heart failure with preserved ejection fracture
- LVEF ≥ 50%
- Normal end-diastolic volume
- Increased end-diastolic pressure
- Seen in patients with HCM

Classification:

ACC/AHA stages of hf		nyha functional classification	
A	High risk of HF | No structural heart disease | No symptoms of HF	None	
B	Structural heart disease | No symptoms or signs of HF	I	No limitation of physical activity
C	Structural heart disease with prior or current symptoms of HF	I	No limitation of physical activity
		II	Slight limitation of physical activity
		III	Marked limitation of physical activity
		IV	Unable to carry out any physical activity
D	Refractory HF	IV	Unable to carry out any physical activity

Epidemiology:

- Lifetime risk of HF is 20% of those 40 years or older
- 650,000 new HF cases per year in the US
- Incidence is 20 per 1000 in those aged 65 to 69 years
- African Americans have a higher incidence of HF
- Mortality remains 50% within 5 years of diagnosis

Risk Factors:

- Hypertension is the most important modifiable risk factor for HF
- Obesity, insulin resistance and diabetes mellitus
- Metabolic syndrome
- Atherosclerotic disease

Pathophysiology:

- The pathophysiology of systolic HF is summarized here:
  Decreased LV contractility → decreased cardiac output → activation of renin-angiotensin-aldosterone system and sympathetic nervous system → increased sodium and water retention → increased preload → increased cardiac output if compensated HF

  Decreased LV contractility → pulmonary venous congestion → impaired gas exchange, pulmonary edema, and decreased right ventricular output → increased systemic venous pressure → peripheral edema

Clinical Findings:

General symptoms:

- Pitting edema
- Fatigue
- Dyspnea
- Jugular venous distension
- S3 heart sound

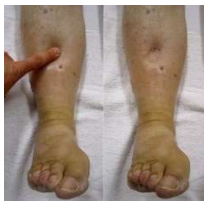


Figure 65: Pitting edema in HF. Source: https://commons.wikimedia.org/wiki/File:Pitting_Edema.jpg

Left heart failure:

- Orthopnea
  Increased venous return when supine → increased pulmonary vascular congestion
- Paroxysmal nocturnal dyspnea
- Pulmonary edema
  Increased pulmonary venous pressure → pulmonary venous distention → transudation of fluid in the lungs. Hemosiderin-laden macrophages in the lungs

Right heart failure:

- Hepatomegaly
  Increased central venous pressure → increased resistance to portal flow
- Jugular venous distention
- Peripheral edema
  Increased peripheral venous pressure → fluid transudation

Diagnosis:

- Echocardiography for the classification of HF into systolic, diastolic, and combined
- Measurement of ejection fraction by echocardiography
- BNP levels are elevated in HF and it is a good biomarker

- Other diagnostic testing based on etiology for instance MRA, CTA, and angiography is the cause is ischemic heart disease

Treatment:

AHA Stage A:

- Goals are to prevent vascular and CAD, and prevent LV structural abnormalities
- Promote healthy lifestyle modifications
- ACE inhibitors or ARB especially in DM patients
- Statins as appropriate

AHA Stage B:

- Goal is to prevent HF symptoms and prevent further cardiac remodelling
- ACE inhibitors or ARB
- Beta-blockers
- In selected patients, ICD or revascularization treatment

AHA Stage C:

- Goal is to control HF symptoms, prevent hospitalization, and prevent mortality
- Patients with systolic HF:
    - Diuretics to treat fluid retention
    - ACE inhibitors or ARBs
    - Beta-blockers
    - Aldosterone antagonists
    - In selected patients: hydralazine, digitalis, CRT, ICD, or revascularization
- Patients with diastolic HF:
    - Diuretics
    - Treatment of comorbidities such as HTN, CAD or DM

AHA Stage D:

- Control symptoms
- Heart transplantation

Treatments that reduce mortality:

- ACE inhibitors and ARBs
- Beta-blockers except in decompensated HF
- Spironolactone
- Hydralazine and nitrate therapy in selected patients

Treatments used only for symptomatic relief:

- Thiazide and loop diuretics

Shock Basics:

Definition:

The current definition of shock considers tissue hypoperfusion/decreased oxygen delivery to be the definition of shock without relying on blood pressure alone. Accordingly, shock state is present when cellular hypoxia develops which leads to organ dysfunction and failure.

Classification:

	Causes
Hypovolemic	- Hemorrhage - Third-space losses - Vomiting and diarrhea
obstructive	- Tamponade - Massive PE - Tension pneumothorax
cardiogenic	- Acute MI - Myocarditis or cardiomyopathies - Valvular heart disease
distributive	- Septic shock - Neurogenic shock - Adrenal crisis
cytotoxic	- Cyanide poisoning - CO poisoning

Pathophysiology:

- Decreased end-organ perfusion → hypoxic injury
- Decreased kidney perfusion can result in acute kidney failure
- Hypoperfusion can be secondary to hypotension
- Lactic acidosis:
  In absence of oxygen, pyruvate is converted to lactate
- Oliguria
- CNS dysfunction

Important Parameters in Shock:

Cardiac output:

- This is dependent on the stroke volume and heart rate
- It is decreased in cardiogenic shock

Systemic vascular resistance:

- The arterioles and arteries have smooth muscle cells
- These can constrict when the sympathetic nervous system is activated as in shock
- When this happens, the systemic vascular resistance is increased
- In some types of shock, the systemic vascular resistance will be decreased

Pulmonary capillary wedge pressure:

- A pulmonary catheter is wedged into a small pulmonary arterial branch and inflated
- The pressure is measured
- It is an estimate of left atrial pressure

Common Symptoms and Signs:

- Hypotension
- Oliguria
- Tachycardia
- Altered mental status

Note: The symptoms of shock come from our understanding of the pathophysiology, i.e. end-organ dysfunction secondary to hypoperfusion

---

Treatment Principles:

Patient presents with signs of hypoperfusion:

- ABC
- Intravenous access
- CBC, renal function, electrolytes, lactate
- ABG, ECG, chest radiograph depending on the presenting symptoms
- Cardiac enzymes or echocardiogram if you suspect cardiogenic shock

Assess volume status:

- Classify patients into three main categories
- Hypovolemic, cold extremities
- Hypovolemic, warm extremities and signs of infection
- Hypervolemic, history of cardiovascular event

Hypovolemic patients with cold peripheries:

- Control ongoing losses
- Replace volume loss
- Consider transfusion
- Consider vasopressors only in unresponsive cases

Hypovolemic patients with warm peripheries and signs of infection:

- Septic shock
- Replace volume loss
- Antibiotics
- Consider vasopressors early in the disease
- If unresponsive, consider inotropes, activated protein C, and corticosteroids
- Vasopressin in refractory cases

Hypervolemic shock with history of cardiac disease:

- Cardiogenic shock
- Correct volume status
- Reverse ischemia by PCI or fibrinolysis as indicated
- If unresponsive, consider vasodilators and inotropes

Cardiogenic and Obstructive Shock

Definition:

Cardiogenic shock is a state of tissue hypoperfusion secondary to ventricular damage. Cardiac pump function is impaired.

Obstructive shock is characterized by impaired ventricular filling. It occurs because of cardiac compression or severe obstruction to the ventricular outflow or inflow.

Epidemiology:

Cardiogenic shock:

- Number one cause of death in CAD
- Incidence is 8% in ACS
- Mainly left ventricular failure (75% of the cases)
- Reperfusion therapy reduces mortality

Obstructive shock:

- 2% of cardiogenic shock is obstructive, i.e. cardiac tamponade

Pathophysiology:

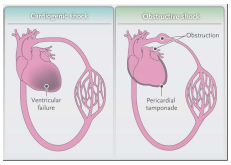


Figure 66: Cardiogenic and obstructive shock are characterized by decreased cardiac output with hypervolemia. Peripheral vascular resistance is usually unchanged. Source: https://www.nejm.org/doi/full/10.1056/nejmra1208943

Cardiogenic shock:

- Myocardial damage → impaired cardiac pump function → decreased stroke volume → decreased cardiac output → cardiogenic shock

- Decreased cardiac output also leads to coronary artery hypoperfusion and exacerbate myocardial ischemia
- Heart rate and afterload are increased because of the release of catecholamines → increased myocardial oxygen demand → worsen myocardial ischemia
- Tachycardia → no enough time for diastolic filling of the heart → diastolic dysfunction on top of systolic dysfunction
- Activation of RAAS system → fluid retention by the kidneys → further increase in preload → pulmonary congestion

Obstructive shock:

- Inadequate ventricular filling secondary to cardiac compression or severe obstruction to ventricular inflow or outflow
- Cardiac tamponade → decreased ventricular filling → decreased stroke volume → decreased cardiac output and hypotension → reflex vasoconstriction and increased intracardiac pressures
- A massive pulmonary embolism → obstruction of pulmonary vessels → increased right-sided pressures and low cardiac output → right ventricular failure

Hemodynamic Profile:

Type/etiology	CO	Preload	Afterload	Contractility
cardiogenic	Decreased	Increased	Increased	Decreased
pe	Decreased	Decreased	Increased	Normal
tamponade	Decreased	Decreased	Increased	Normal

Clinical Findings:

- Symptoms and signs of tissue hypoperfusion such as AMS, oliguria, and pulmonary edema
- Symptoms and signs suggestive of acute coronary syndrome or MI
- History of other cardiac disease such as myocarditis, cardiomyopathies, valvular heart disease
- S3
- Symptoms and signs suggestive of cardiac tamponade:
  Recent MI → ventricular free wall rupture → sudden death or shock state = cardiac tamponade
- Symptoms of DVT and chest pain → pulmonary embolism
- Upper extremities hypertension with weak pulses in the lower limbs → coarctation of the aorta
- History of trauma, dyspnea, and shock → tension pneumothorax

Diagnosis:

- Hypotension
- Estimate cardiac output, which should be low
- Measure central venous pressure, which will be high
- Perform echocardiography:
  - In cardiogenic, expect to see large poorly contracting ventricles
  - In cardiac tamponade: pericardial effusion, small ventricles, dilated IVA
  - In massive PE: dilated right ventricle, small left ventricle
- ECG:
  - STEMI or NSTEMI
  - Decreased voltage in tamponade

Treatment:

Cardiogenic shock:

- Early revascularization
- Intra-aortic balloon pump
- Left ventricular assist device

Obstructive shock:

- Needle or catheter drainage of tamponade
- Fluid and vasoactive drugs while awaiting decompression
  - Dopamine increases renal perfusion
  - Dobutamine increases cardiac output
  - Norepinephrine
- Massive PE is an indication for thrombolytic therapy

Unresponsive patients with cardiogenic shock:

- If early revascularization does not improve the hemodynamic profile, other treatments might be considered
- Inotropes
- Vasodilators only if the patient is not severely hypotensive

Hypovolemic Shock:

Definition:

Hypovolemic shock is a state of end-organ hypoperfusion due to loss of circulating volume. Hypotension is seen in patients with hypovolemic shock which activates the sympathetic nervous system to raise blood pressure by cardiac and vascular mechanisms.

Epidemiology:

- A major cause of death in trauma
- A complication of surgery
- Also seen in patients with gastrointestinal losses or burn patients
- Trauma patients tend to have a mixed picture of hypovolemic, neurogenic and obstructive shock
- Trauma-related mortality and morbidity are related to the occurrence of hypovolemic shock

Pathophysiology

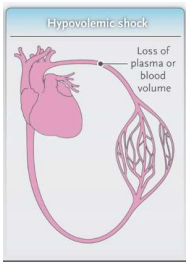


Figure 67: Hypovolemic shock is characterized by a decreased circulating volume and increased peripheral vascular resistance. Source: https://www.nejm.org/doi/full/10.1056/nejmra1208943

- Loss of circulating volume → hypotension and pain due to tissue injury → activation of the sympathetic nervous system → increased heart rate, cardiac contractility, and peripheral vascular resistance → beneficial in early stages of shock
- Prolonged activation of the sympathetic nervous system → hypermetabolic state in end-organs → worsen local ischemia
- These compensatory mechanisms fail when volume loss is > 25%
- When volume loss is ≥ 40% → if not corrected within 2 hours → activation of systemic inflammatory cascade → irreversible tissue damage and increased risk of reperfusion injury
  Because of this, early correction of severe hypovolemic shock is mandatory

Hemodynamic Profile

Type/etiology	CO	Preload	Afterload	Contractility
Hypovolemic	Decreased	Decreased	Increased	Normal

Clinical Findings:

- Symptoms and signs of tissue hypoperfusion such as AMS, oliguria, and pulmonary edema
- Symptoms and signs suggestive of the mechanism of volume loss:
  - Concealed or open hemorrhage
  - Major trauma
  - Vomiting or diarrhea
  - Third-space losses
  - Dehydration
- Hypotension when > 30% circulating volume is lost
- Tachycardia when > 15% circulating volume is lost
- Narrow pulse pressure

Diagnosis:

- Hypotension
- Lactic acidosis
- Decreased central venous pressure

The table below shows the stages of hypovolemic shock.

Stage	Volume loss	BP	HR	Other
I	< 15% 750 ml	Normal	Normal	- Pallor
II	15 – 30% 750 – 1500 ml	Increased DBP Narrow pulse pressure	Normal or slightly elevated	- Increased RR - Sweating
III	30 – 40% 1500 – 2000 ml	SBP ≤ 100 mmHg	Tachycardia	- Marked tachypnea
IV	> 40% > 2000 ml	SBP ≤ 70 mmHg	Extreme tachycardia	- Severe tachypnea

Treatment

- ABC
- Control ongoing losses
- Start volume replacement with crystalloids
- Consider blood transfusion in hemorrhagic patients
- Avoid vasopressors if possible

Septic Shock

Definitions:

The conventional understanding of sepsis and other related pathologies lead to the definition of four important conditions, or stages.

SIRS:

Systemic inflammatory response syndrome is characterized by the presence of at least two of the following:

- Temperature < 36C or > 38.3 C
- HR > 90 beats/min
- RR > 20 per minute or $PaCO_2$ < 32 mmHg
- WBC count < 4000 per mm^3 or > 12,000 per mm^3

Sepsis:

Presence of two SIRS criteria plus a known or suspected source of infection.

Severe sepsis:

- Hypotension:
  - SBP < 90 mmHg, MAP < 70 mmHg, or a reduction in SBP of 40 mmHg from baseline
- Serum lactate > 2 mmol/L
- Signs of organ dysfunction

Septic shock:

Any sepsis-induced hypotension that does not respond to fluid replacement therapy and requires vasopressors to maintain end-organ perfusion.

Note: Recent definitions of sepsis and septic shock have removed the definitions of SIRS and severe sepsis in light of recent advances in the understanding of septic shock pathogenesis.
Sepsis is defined as a life-threatening end-organ dysfunction secondary to a dysregulated patient response to infection.
Septic shock is seen in patients with sepsis who develop hypotension that needs vasopressors to be maintain MAP ≥ 65 mmHg and have a serum lactate of ≥ 2 mmol/L despite adequate volume replacement therapy.

Epidemiology:

- Because of recent changes in the definitions of sepsis and septic shock, it is difficult to know the incidence of sepsis
- Septic shock has a mortality rate > 40%
- Gram-negative bacteria cause 38% of the cases
- Gram-positive bacteria are responsible for 52% of the cases
- Fungi are becoming a more common cause of sepsis and septic shock

Pathophysiology:

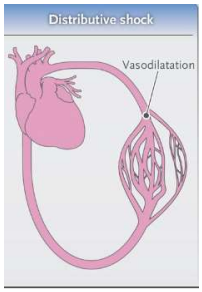


Figure 68: Septic shock is characterized by marked vasodilation and decreased peripheral vascular resistance. Source: https://www.nejm.org/doi/full/10.1056/nejmra1208943

- Release of TNF-α and IL-1 in septic shock is believed to play a major role
- TNF- α is produced by activated macrophages in response to microbial antigens
- Increase in TNF- α → increase in IL1-beta, IL-6, IL-8, thromboxane, and eicosanoids → activation of the coagulation and complement systems → decreased myocardial contractility
- Activation of NO synthase → increased NO production → vasodilation → decreased peripheral vascular resistance
- Patients also have inability to extract oxygen from the blood → lactic acidosis despite normal venous oxygen saturation

Hemodynamic Profile:

Type/etiology	CO	Preload	Afterload	Contractility
Septic – before IV fluids	Decreased	Decreased	Decreased	Decreased
Septic – After IV fluids	Increased	Normal	Decreased	Decreased

- Notice that despite adequate fluid replacement, patients still have a decreased afterload "hypotension" and decreased contractility of the heart
- This is characteristic of septic shock
- Lactic acidosis does not resolve after fluid replacement therapy because peripheral tissues are unable to extract oxygen from the blood

Clinical Findings:

- Symptoms and signs of tissue hypoperfusion such as AMS, and oliguria
- Symptoms and signs of SIRS
- Symptoms and signs suggestive of the source of infection

- Hypotensive despite adequate fluid replacement therapy
- Lactic acidosis despite fluid replacement therapy

Complications of septic shock:

- Acute respiratory distress syndrome
- Disseminated intravascular coagulation
- Acute tubular necrosis
- Multi-organ dysfunction syndrome
- Death

Diagnosis:

- Hypotension
- Lactic acidosis

Sequential organ failure assessment score:

Parameter	interpretation of results
PaO_2:FiO_2 < 300 mmhg	
platelets < 100,000 per mm^3	
hypotention requiring vasopressors	Patients who meet 2 or more of these criteria have a high risk of development of multi-organ failure, poor outcome, and possibly death
gcs ≤ 12	
bilirubin ≥ 2 mg/dl	
creatinine ≥ 2 mg/dl, or urine output < 500 ml/day	

Treatment:

- ABC
- Initial resuscitation with IV fluids
- Identification of the source of the infection
- IV antimicrobials to cover gram-negative, gram-positive and fungal organisms implicated in sepsis and septic shock

Vasoactive medications:

- IV fluid replacement therapy will not correct the hypotension in patients with septic shock
- Norepinephrine is the vasopressor of choice in septic shock
- Patients with low risk of tachyarrhythmias can receive high dose dopamine
- Low-dose dopamine is indicated in all patients → renal protection by improving perfusion
- Dobutamine only in patients who do not respond to norepinephrine and dopamine

Neurogenic Shock:

Definition:

A distributive shock with hypotension and bradycardia secondary to acute spinal cord injury with disruption of the sympathetic nervous system pathways.

Pathophysiology:

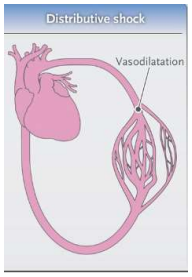


Figure 69: Neurogenic shock is caused by an acute spinal cord injury and characterized by unopposed vagal tone "vasodilation" due to disruption of the sympathetic nervous system pathways. Source: https://www.nejm.org/doi/full/10.1056/nejmra1208943

- Brain, cervical or high-thoracic spinal cord injury → loss of sympathetic stimulation to the blood vessels → unopposed vagal tone → vasodilation → decreased peripheral vascular resistance
- The level of spinal cord injury must be above the 6^{th} thoracic vertebra
- Bradycardia or no reflex tachycardia

Hemodynamic Profile:

Type/etiology	CO	Preload	Afterload	Contractility
Neurogenic	Decreased	Decreased	Decreased	Decreased

Clinical Findings:

- Symptoms and signs of tissue hypoperfusion such as AMS, and oliguria
- Severe hypotension with bradycardia
- Hypotension is sudden

Respiratory consequences of spinal cord injuries:

- Injuries at C5 or below → paralysis of intercostal muscles → diaphragmatic breathing
- Injuries above C3 → paralysis of the diaphragm → immediate respiratory arrest

Patients will also have history of trauma and focal neurological deficits based on the level of injury.

Diagnosis:

- Sudden severe hypotension with bradycardia in a spinal cord injury patient is diagnostic
- Spinal cord MRI can detect the injury, even if small

Treatment:

- ABC
- Initial resuscitation with IV fluids

Vasoactive drugs:

- Dopamine
- Atropine in patients with bradycardia
- Other vasopressors such as norepinephrine and ephedrine if dopamine fails to improve the hemodynamic profile
- Vasopressin

Infective Endocarditis:

Definition:

- Infective endocarditis is a life-threatening disease where there is damage to the endocardium that attracts microorganisms to colonize the damaged part. Infective endocarditis is a multisystem disease that is usually of a bacterial etiology.

Epidemiology:

- Annual incidence is from 1.5 to 11.6 per 100,000
- Untreated → 100% mortality rate
- Treated → 25% mortality rate
- Most patients are older than 50 years of age in the developed world
- Two thirds of patients are males

Risk factors:

- Rheumatic valvular heart disease
- Prosthetic valves or other cardiac devices
- Congenital heart disease such as mitral valve prolapse
- Injection drug use
- Human immunodeficiency virus infection
- Most cases (80%) are attributed to streptococcus and staphylococcus infections
    - Staphylococcus aureus
    - Streptococcus viridans
- Enterococci species are also reported in infective endocarditis

Pathophysiology:

- This mechanism explains how the involvement of the endocardium occurs in patients with infective endocarditis
- Patients also have involvement of other organs
- The main mechanism is dislodgement of infected vegetations → embolism to distant organs

Systemic pathology in infective endocarditis:

- Embolization to the brain → embolic stroke with conversion to hemorrhagic stroke or pyogenic brain abscess
- Embolization to the lungs → septic pulmonary foci
- Embolization to the spleen → splenic infarcts
- Activation of the immune system and the formation of immune complexes → deposition of immune complexes in the retinal blood vessels → Roth spots
- Peripheral finger infarcts
- Petechiae, cutaneous infarcts, and Osler's nodes are immune-mediated

Osler's nodes:

- Arteriolar intimal proliferation
- Diffuse perivascular infiltration by neutrophils
- Immune complexes

Janeway lesions:

- Septic emboli
- Presence of bacteria, neutrophils, necrosis and subcutaneous hemorrhage

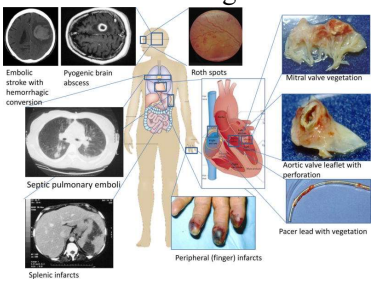


Figure 70: Systemic pathology in infective endocarditis. Source: DOI: 10.1038/nrdp.2016.59

Causative organisms:

- Native valves:
    - Streptococcus viridans
    - HACEK group
- Prosthetic valves:
    - Streptococcus epidermis if less than 60 days post-surgery
    - Other streptococci if > 60 days post-surgery

Diagnosis:

Blood culture and identification of causative organisms:

- Patients who present with symptoms and signs suggestive of infective endocarditis should get

blood cultures withdrawn before starting antimicrobial treatment
- Patients with negative blood cultures can undergo the following tests to identify the causative organism:
    - Serology testing
    - Histopathology
    - PCR
    - Immunohistology

Echocardiography:

- This is the second most important diagnostic test in infective endocarditis
- Should be performed in all patients suspected to have infective endocarditis
- Transthoracic and transesophageal echocardiography
- Identification of vegetations among other findings

Diagnostic Criteria

Modified Duke Criteria for IE:

Major clinical criteria:

A. Blood culture positivity for typical microorganisms or persistent bacteremia
B. Echocardiographic evidence of valvular vegetation or new valvular regurgitation
C. Serology: positive for C. burnetii

Minor clinical criteria:

A. Predisposing condition such as intravenous drug use or cardiac lesion
B. Arterial embolism
C. Septic pulmonary emboli
D. Mycotic aneurysm
E. Intracranial hemorrhage
F. Subconjunctival hemorrhage
G. Janeway's lesions

Interpretations of the results:

Definite IE:

- Proven IE by histopathology, or
- Two major criteria, one major and three minor criteria, or five minor criteria

Possible IE:

- One major and one minor criterion, or
- Three minor clinical criteria

Rejected IE:

- Established other diagnosis, or
- Resolution of IE symptoms with antibiotics in 4 days or less, or
- No pathologic evidence of IE at surgery
- Does not meet the criteria of possible IE

Treatment:

- Antimicrobial treatment
    - Streptococcus viridans and bovis:
        - Penicillin
        - Ceftriaxone
        - For four weeks, or two weeks if combined with gentamicin
    - Enterococci:
        - Ampicillin + gentamicin
        - For six weeks
    - Staphylococci:
        - Nafcillin
        - Cefazolin
        - Vancomycin
        - Nafcillin + gentamicin + rifampin for prosthetic valve IE
    - HACEK:
        - Ceftriaxone
        - Ampicillin
        - Ciprofloxacin
    - Fungi:
        - Amphotericin
        - Long-term suppressive therapy
- Surgery in selected patients

Acute Rheumatic Fever and Rheumatic Heart Disease

Definition:

Acute rheumatic fever is a systemic autoimmune response to pharyngitis caused by streptococcus pyogenes "group A streptococcus bacteria". Rheumatic heart disease is the long-term sequalae of cardiac damage caused by acute rheumatic fever.

Epidemiology:

- The incidence of acute rheumatic fever and rheumatic heart disease in the developed world is low
- The incidence is quite high among low-income and middle-income countries, i.e. 155 per 100,000 per year in children aged 5 to 14 years

Risk factors:

- Acute rheumatic fever is more common in children aged 5 to 14 years

- Rheumatic heart disease is more common in adults in their 20s or 30s
- Acute rheumatic fever has equal frequency in males and females
- Rheumatic heart disease is more common in women
- Increased exposure to streptococcus pyogenes, i.e. living in crowded places, appears to be a risk factor.

Pathophysiology:

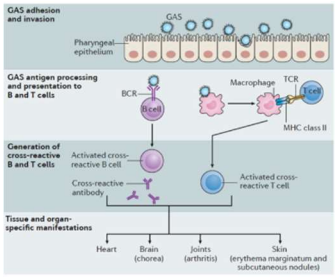


Figure 71: Pathogenesis of acute rheumatic fever. Source: https://www.ncbi.nlm.nih.gov/books/NBK425394/pdf/Bookshelf_NBK425394.pdf

Acute rheumatic fever:

- Colonization, adhesion, and invasion of the pharyngeal epithelium by group A beta-hemolytic streptococcus (GAS)
- Macrophages process GAS antigens and present them to B and T cells
- Generation of cross-reactive B and T cells which recognize self-antigens and attack them
- Activated cross-reactive B-cells secrete cross-reactive antibodies, whereas activated cross-reactive T-cells result in cellular-mediated immune responses
- Damage to the heart, brain (chorea), joints (arthritis) and skin (erythema marginatum and subcutaneous nodules)

Carditis mechanism in acute rheumatic fever:

- Cross-reactive antibodies and activated T-cells bind to laminin and glycoproteins on the valve surface, or VCAM1 respectively
- This leads to tissue damage and an inflammatory response characterized by the recruitment of macrophages
- The consequences of carditis are as follows:
    - Elongation and fusion of chordae tendinea
    - Valvular thickening and calcification
    - Collagen deposition
    - Dilation of the annular rings
- These changes can eventually result in valvular stenosis or regurgitation
- Mitral > aortic >> tricuspid valve
- Regurgitation is the early lesion. Stenosis in late presentation

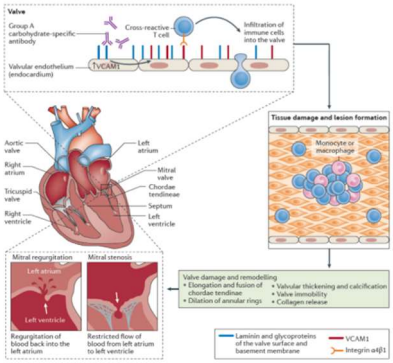


Figure 72: Mechanism of carditis in acute rheumatic fever. Source: https://www.ncbi.nlm.nih.gov/books/NBK425394/pdf/Bookshelf_NBK425394.pdf

Clinical Findings

Acute rheumatic fever:

- Arthritis:
    - Mainly large joints
    - Knees, ankles, elbows and wrists
    - Multiple joints are affected, sequentially or at the same time
    - Migratory polyarthritis
    - Rapid response to anti-inflammatory response (NSAIDs or glucocorticoids)
    - Sterile synovial fluid with lymphocytosis
- Carditis:
    - Can result in pancarditis
    - Most often endocarditis with valvular disease (mitral regurgitation)
    - MR findings on auscultation:
        - Pansystolic murmur
    - Cardiomegaly secondary to atrial dilation
- Chorea:
    - Sydenham's chorea
    - Also known as St. Vitus's dance
    - 30% of acute rheumatic fever cases

    - Involuntary non-rhythmic purposeless movements of trunk and limbs
    - Usually more pronounced on one side
- Erythema marginatum and subcutaneous nodules:
    - 10% of patients have skin manifestations
    - Erythema margination: bright pink, blanching, non-pruritic macules on the trunk and proximal limbs
    - Subcutaneous nodules: painless small nodules that develop over bony prominences (elbows) or extensor tendons
    - Patients usually have three to four nodules at time of presentation
- Fever
- Arthralgia without arthritis
- Elevated acute phase reactants
- Prolonged PR interval on ECG

Diagnosis:

Based on Jones criteria for the diagnosis of acute rheumatic fever. Chronic rheumatic valvular disease is discussed in the lectures titled: mitral regurgitation, mitral stenosis, aortic regurgitation, and aortic stenosis.

Category	criteria
Major	
carditis	- Clinical or subclinical
arthritis	- Polyarthritis - Chorea - Erythema marginatum - Subcutaneous nodules
minor	
carditis	- Prolonged PR interval
arthralgia	- Polyarthralgia
Fever	- ≥ 38.5
markers of inflammation	- ESR ≥ 60 mm - CRP ≥ 3 mg/dL
Evidence of preceding streptococcal infection	- Increased or rising anti-streptolysin O titer - Anti-DNASE B - Positive culture of group A B-hemolytic streptococci - Positive rapid group A streptococcal carbohydrate antigen test

- The diagnosis is confirmed when there is documentation of preceding streptococcal infection plus:
    - Two major, or
    - One major and one minor, or
    - Three minor
- Evidence of carditis is taken from echocardiography and ECG
- Biopsy might reveal Aschoff bodies:
    - Granuloma with giant cells
    - Enlarged macrophages with ovoid, wavy rod-like nucleus
    - Known as Anitschkow cells

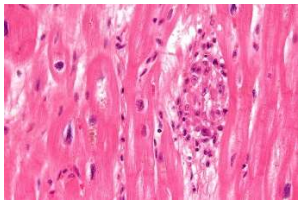


Figure 73: Aschoff bodies. Source: https://en.wikipedia.org/wiki/Aschoff_body#/media/File:Rheumatic_heart_disease_-_3b_-_very_high_mag.jpg

Treatment:

- Penicillin for the eradication of GAS infection
- Prophylaxis against acute rheumatic fever

Acute Pericarditis

Definition

Acute pericarditis is an inflammatory condition of the pericardium.

Epidemiology

- 0.1% of patients hospitalized because of chest pain
- 5% of patients admitted to emergency department for chest pain not caused by MI
- More often in men
- Most patients are 20 to 50 years old
- Low mortality, but can be associated with high morbidity
- 30% recurrence

Predictors of high morbidity in acute pericarditis:

- Fever > 38 C
- Subacute onset
- Cardiac tamponade
- Large pericardial effusion
- Unresponsiveness to NSAIDs

Pathophysiology

Etiology:

- Viral:
    - Adenovirus
    - Coxsackievirus A and B
    - Echovirus
    - Epstein-Barr virus
    - Hepatitis
    - HIV

    - Mumps
- Bacterial:
    - Hemophilus
    - Legionella
    - Meningococcus
    - Neisseria
- Fungal
- Parasitic
- Noninfectious:
    - Idiopathic
    - Post-MI
    - Dressler syndrome
    - Neoplastic
    - Drug-induced: hydralazine, isoniazid, procainamide
    - Rheumatic fever
    - Inflammatory conditions
    - Collagen vascular diseases
    - Uremia and Gout

Pericardial inflammation → increased pericardial fluid → pericardial effusion

Clinical Findings

- Chest pain:
    - Retrosternal
    - Duration of hours to days
    - Sharp and stabbing in nature
    - Worse when supine, improved when sitting up
    - Worsened with inspiration
    - Radiation to jaw, neck, and arms
    - No response to nitroglycerin
- Friction rub in 85% of patients
- Fever

Diagnosis

- Pleuritic chest pain plus friction rub plus characteristic ECG findings and a pericardial effusion on echocardiography is diagnostic of pericarditis

ECG findings:

- Stage I: diffuse concave ST-segment elevation
- Stage II: normalization of ST-segment, PR-segment depression, flat T-waves
- Stage III: symmetric diffuse T-wave inversions
- Stage IV: normal ECG

Treatment

- NSAIDs for pain and inflammation control
- Resolves within 2 to 6 weeks
- Corticosteroids only in patients who do not respond to NSAIDs

Cardiac Tamponade

Definition

Cardiac tamponade is characterized by the accumulation of fluid in the pericardial space, which results in reduced ventricular filling and hemodynamic compromise. The condition can result in pulmonary edema, shock and death.

Epidemiology

- Incidence is 2 cases per 10,000
- 2% of penetrating injuries to the chest
- Male to female ratio is 7:3 in children
- Slight male predominance in adults
- Medical emergency
- Prognosis:
    - 1-year mortality in malignancy-related cardiac tamponade is 76.5%
    - 1-year mortality in non-malignancy cardiac tamponade is 13.3%

Pathophysiology

Etiology:

	% of cases
malignant diseases	30 – 60
uremia	10 – 15
idiopathic pericarditis	5 – 15
Infectious diseases	5 – 10
coagulopathy	5 – 10
Connective tissue diseases	2 – 6

Anatomy:

- The pericardium is a two-layer structure surrounding the heart
- The normal pericardial fluid volume is 20 to 50 mL

Phases of hemodynamic changes in cardiac tamponade:

- Phase I:
  Impaired relaxation of the ventricles → impaired diastolic filling of the ventricles → the intraventricular filling pressures are still higher than the intrapericardial pressure
- Phase II:
  Further accumulation of fluid in the pericardium → intrapericardial pressure exceeds intraventricular filling pressures → reduced cardiac output

- Phase III:
  Further decrease in cardiac output → equilibration of pericardial and left ventricular pressures

Pathophysiology:

- Systemic venous return is decreased because of the compression of the heart → impaired venous return to the right atrium → right atrium and ventricle collapse
- Accumulation of blood in the pulmonary venous network → pulmonary venous congestion and reduced cardiac output because of decreased return to the left atrium
- Rapid accumulation of 150 mL can severely decrease cardiac output
- Slow accumulation of up to 1000 mL will result in minimum hemodynamic changes and insignificant effect on diastolic filling of the ventricles
  - Adaptive stretching of the pericardium

Clinical Findings

- Symptoms and signs of obstructive shock and end-organ hypoperfusion:
  - Dyspnea
  - Decreased urine output
  - Altered mental status
  - Cold and clammy extremities
- Physical findings:
  - Elevated jugular venous pressure
  - Tachycardia and tachypnea
  - Hepatomegaly
  - Diminished heart sounds
- Beck triad:
  - Increased jugular venous pressure
  - Hypotension
  - Diminished heart sounds
  - Seen in patients with acute cardiac tamponade
- Pulsus paradoxus:
  More than 12 mmHg drop in blood pressure during inspiration
- Kussmaul sign:
  Paradoxical increase in jugular venous pressure during inspiration
- Ewart sign:
  Dullness to percussion, bronchial breathing sounds, and bronchophony below the angle of the left scapula

Diagnosis

Imaging:

- Chest radiography shows cardiomegaly
- Bowed catheter sign on chest radiography after the insertion of a central venous catheter in children
- Cardiac tamponade is a clinical diagnosis, but echocardiography can provide some valuable information:
  - Massive pleural effusion
  - Early diastolic collapse of the right ventricular free wall
  - Swinging of the heart in the pericardial sac
  - Inferior vena cava plethora

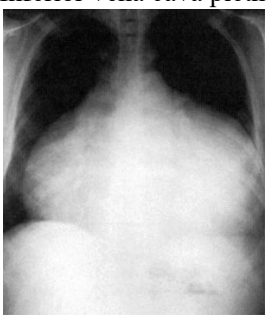


Figure 74: Massive, bottle-shaped heart in a patient with cardiac tamponade. Source: Chest 1996: 109:825

Laboratory testing:

- Indicated for the etiological diagnosis
- For instance, troponins might be elevated in patients with cardiac tamponade secondary to myocardial infarction or cardiac trauma
- PT and PTT might be abnormal
- ESR, RF, and antinuclear antibodies are indicated in patients with connective tissue disorders
- Renal profile might be abnormal in patients with uremic pericarditis

ECG:

- Sinus tachycardia
- Low-voltage QRS complexes
- Electrical alternans
  An alteration in the QRS complex voltage. It is caused by the movement of the heart, i.e. swinging, in the pericardial space. Can be also seen in patients with myocardial ischemia or acute pulmonary embolism.

- PR segment depression

Swan-Ganz catheterization:

- Insert the catheter into a major vein
- In patients with cardiac tamponade, you will find the following pressures to be near equalization:
    - Right atrial pressure
    - Right ventricular diastolic pressure
    - Pulmonary arterial diastolic pressure
    - Pulmonary capillary wedge pressure which is indicative of the left atrial pressure

Treatment

- Pericardial drainage is indicated in all cases of cardiac tamponade
- If the patient is hemodynamically stage, drainage can be delayed up to 24 hours from diagnosis
- Indications for urgent surgical drainage of the pericardium in cardiac tamponade:
    - Type A aortic dissection
    - Ventricular free wall rupture in acute MI
    - Trauma
    - Purulent cardiac tamponade

Pericardiocentesis:

General principles:

- Do not drain more than 1 L of fluid
- If there is still fluid accumulation after withdrawing 1 L, place a prolonged catheter for drainage
- Delayed pericardiocentesis should be performed within 12 to 24 hours from diagnosis

Urgent pericardiocentesis:

- A scoring system is used to determine which patients need urgent pericardiocentesis
- The following features score high on this scoring system:
    - Malignant disease or tuberculosis as the cause of cardiac tamponade
    - Orthopnea or pulses paradoxus
    - Rapid worsening of symptoms
    - Left atrial collapse on echocardiography
- The scoring system is too complex for the USMLE Step 1, but you should be aware of the above high-risk features of cardiac tamponade
- This is to determine who needs urgent pericardiocentesis, the indications of urgent surgical drainage are described above
- Patients who score 6 or more on this scoring system need urgent or immediate pericardiocentesis

Primary Cardiac Tumors

Myxoma

A benign primary tumor of the heart mainly affecting left atrium.

Epidemiology

- 50 to 70% of primary cardiac tumors
- Middle aged women
- 10% of primary cardiac tumors in children
- 90% of the cases are sporadic
- Can be seen in some genetic diseases such as:
    - Carney syndrome: cardiac and cutaneous myxomas, endocrine hyperfunction, and hyperpigmentation
    - Caused by a mutation in the tumor suppressor gene PRKAR1A on chromosome 17q22-24
    - Peak incidence in the thirties

Gross Pathology

- 75% in the left atrium and 18% in the right atrium
- Pedunculated growths
- The left atrial cavity might be filled with the tumor in extreme cases
- Most tumors arise at the area of the fossa ovalis
- Average diameter of 5 to 6 cm
- Soft consistency with a smooth thrombotic surface

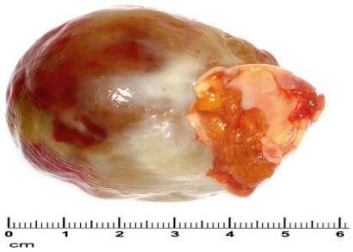


Figure 75: Gross appearance of a myxoma. Source: DOI: 10.3238/arztebl.2014.0205

Histopathology

- Multipotent mesenchymal cells
- Myxoma cells:
    - Multi-nucleated cells
    - Eosinophilic cytoplasm
    - Surrounded by a myxoid stroma

- Cystic formation
- Hemorrhages and fibrosis
- Calcifications
- Gland formation

Rhabdomyoma

The most common primary cardiac tumor in children.

Epidemiology

- Up to 60% of primary cardiac tumors in children
- Associated with tuberous sclerosis and congenital heart defects
- Spontaneous regression in 50% of the cases

Gross Pathology

- Single or multiple tumors
- Circumscribed
- Whitish
- Few centimeters in size
- Most commonly occur in the left ventricle or in the interventricular septum

Histopathology

- Focal hamartomatous accumulation of striated cardiomyocytes
- Not a true neoplasm

Clinical Findings

- Weight loss, fever and other constitutional symptoms
- Blockage of the mitral or tricuspid valves resulting in a stenosis-like syndrome
- Intermittent heart failure
- Embolic phenomena especially with myxomas

Diagnosis

- Echocardiography is the first diagnostic test in a patient suspected to have a primary cardiac tumor
- Transesophageal echocardiography has better sensitivity and specificity than transthoracic echocardiography

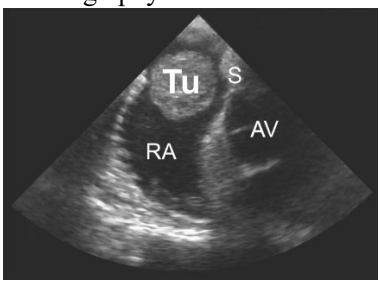


Figure 76: A right atrial tumor, most likely a myxoma. Source: DOI: 10.3238/arztebl.2014.0205

Treatment

- Despite being benign tumors, tumor resection must be performed as soon as possible
- Simple tumor resection:
  - Gentle handling of the tumor to avoid dislodging and breaking
  - The tumor should be removed with its root in toto
  - The defect in the heart is closed with patch material
- Curative

Vasculitis

Definition

These are immune-mediated inflammatory diseases that affect the arteries. They are classified based on the size of the affected blood vessels. They are systemic diseases.

Large Vessel Vasculitis

Assessment:

- Palpation of peripheral pulses
- Bilateral blood pressure assessment
- Auscultation for bruits over major arteries
- Temporal artery biopsy in giant cell arteritis
- MRI

Giant cell arteritis:

<u>Definition:</u>

A granulomatous arteritis of the aorta, carotid, and major carotid branches such as the temporal artery. Usually occurs in women older than 50 years.

<u>Clinical findings:</u>

- Jaw claudication
- Diplopia
- Temporal artery beading
- Tenderness on palpation of the temporal artery
- Can lead to irreversible blindness → ophthalmic artery occlusion
- Associated with polymyalgia rheumatica

<u>Diagnosis:</u>

- Focal granulomatous inflammation on biopsy
- Increased ESR

<u>Treatment:</u>

- High-dose corticosteroids
- Started before temporal artery biopsy
- Prevent blindness

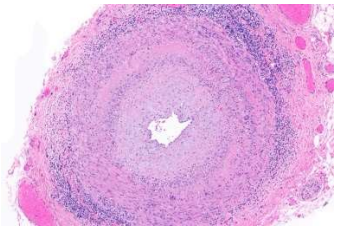


Figure 77: Granulomatous changes on temporal artery biopsy in a patient with giant cell arteritis. Source: https://commons.wikimedia.org/wiki/File:Giant_cell_arteritis_--_low_mag.jpg

Takayasu arteritis

Definition:

A granulomatous arteritis of the aorta and its branches. Occurs in patients younger than 40 years.

Clinical findings:

- Asian women
- Weak upper extremity pulses
- Fever
- Night sweats
- Arthritis, myalgia
- Skin nodules
- Ocular disturbances

Diagnosis:

- Granulomatous thickening and narrowing of the aortic arch
- Elevated ESR

Treatment:

- High-dose corticosteroids

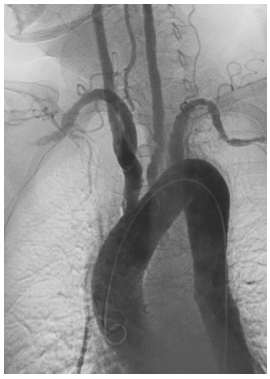


Figure 78: Narrowing of the right subclavian artery in a patient with Takayasu arteritis. Source: https://pt.m.wikipedia.org/wiki/Ficheiro:Takayasu_Arteritis.jpg

Medium-Sized Vessel Vasculitis

Assessment:

- Myalgia
- Arthritis
- Fever
- Weight loss
- Cutaneous, cardiovascular, mucous membranes, renal, ENT, nervous system, chest

Polyarteritis nodosa:

Definition:

Transmural inflammation of middle-sized arteries. Involves renal and visceral arteries but does not involve pulmonary arteries. Occurs in middle-aged men. Up to one third of the patients have hepatitis B.

Clinical findings:

- Fever
- Weight loss
- Malaise
- Headache
- Abdominal pain and melena
- Hypertension secondary to renal artery stenosis
- Neurologic dysfunction such as seizures and stroke
- Cutaneous eruptions
- Chronic kidney disease

Diagnosis:

- Biopsy reveals transmural inflammation of the arterial wall with fibrinoid necrosis
- Different stages of inflammation
- Renal microaneurysms

Treatment:

- High-dose corticosteroids
- Cyclophosphamide

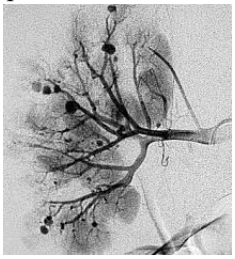


Figure 3: Multiple microaneurysms in a patient with polyangiitis nodosa. Source:

https://ucsfmed.wordpress.com/2017/01/25/polyarteritis-nodosa/

Buerger disease:

Definition:

Also known as thrombo-angiitis obliterans. Occurs in young (< 40 years) heavy-smoker men. Affects middle sized arteries, veins and nerves.

Clinical findings:

- Intermittent claudication
- Gangrene
- Autoamputation of digits
- Superficial nodular phlebitis
- Raynaud phenomenon

Diagnosis:

- Biopsy reveals segmental thrombosing vasculitis

Treatment:

- Smoking cessation

Small-Sized Vessel Vasculitis

Wegener's granulomatosis:

Definition:

A focal necrotizing vasculitis that affects the lungs, upper airways, and kidneys.

Clinical findings:

- Perforation of nasal septum, chronic sinusitis, otitis media and mastoiditis
- Hemoptysis
- Cough
- Dyspnea
- Hematuria
- Red cell casts

Diagnosis:

- Biopsy reveals necrotizing granulomatous vasculitis of the lungs and upper airway. Necrotizing glomerulonephritis
- Elevated levels of PR3-ANCA also known as c-ANCA
- Chest radiography shows large nodules

Treatment:

- Cyclophosphamide
- Corticosteroids

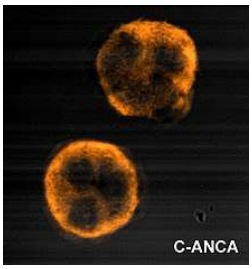


Figure 4: c-ANCA in a patient with Wegener's granulomatosis. Source: https://en.wikipedia.org/wiki/C-ANCA

Churg-Strauss syndrome:

Definition:

A necrotizing vasculitis affecting small to medium-sized vessels. Often associated with asthma and eosinophilia. Also known as eosinophilic granulomatosis with polyangiitis.

Clinical findings:

- Asthma
- Sinusitis
- Purpura and skin nodules
- Peripheral neuropathy such as foot drop
- Symptoms of affected systemic organs
- Can cause pauci-immune glomerulonephritis

Diagnosis:

- Biopsy reveals granulomatous necrotizing vasculitis with eosinophilia
- Elevated levels of MPO-ANCA also known as p-ANCA
- Elevated IgE levels

Treatment:

- Cyclophosphamide
- Corticosteroids

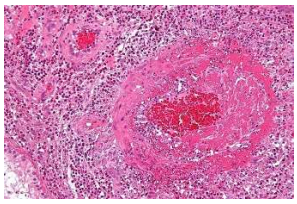


Figure 5: Granulomatous eosinophilic necrosis in a patient with Churg-Strauss syndrome. Source: https://en.wikipedia.org/wiki/Eosinophilic_granulomatosis_with_polyangiitis#/media/File:Churg-Strauss_syndrome_-_high_mag.jpg

Microscopic polyangiitis

Definition:

A necrotizing vasculitis affecting small to medium-sized vessels. Involvement of the pulmonary capillaries. Can affect the lung, kidneys, and skin

Clinical findings:

- Palpable purpura
- Symptoms and signs related to affected organs
- Can cause pauci-immune glomerulonephritis

Diagnosis:

- Biopsy reveals necrosis without granuloma formation
- Elevated levels of MPO-ANCA also known as p-ANCA

Treatment:

- Cyclophosphamide
- Corticosteroids

Figure 6: p-ANCA in a patient with microscopic polyangiitis or Churg-Strauss syndrome. The difference is that the latter will also have granulomas on histopathological examination. Source: https://en.wikipedia.org/wiki/P-ANCA#/media/File:P_anca.jpg

Henoch-Schoenlein purpura

Definition:

Vasculitis with immunoglobulin-A deposits in small vessels. This is the most common childhood systemic vasculitis and is often preceded by an upper respiratory tract infection.

Clinical findings:

- Triad of:
  - Palpable purpura on the legs and buttocks
  - Arthralgia or arthritis
  - Abdominal pain due to GI involvement. Can lead to intussusception

Diagnosis:

- Biopsy reveals IgA immune complex deposition and IgA nephropathy

Treatment:

- Resolves spontaneously
- Selected patients might benefit from steroids

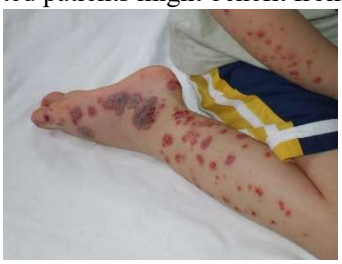


Figure 7: Palpable purpura in a child with Henoch-Schoenlein purpura. Source: https://commons.wikimedia.org/wiki/File:Purpura2.JPG

Behçet syndrome

Definition:

A small-vessel vasculitis that is more common in Turkish and eastern Mediterranean individuals.

Clinical findings:

- Recurrent aphthous ulcers
- Genital ulcers
- Uveitis
- Erythema nodosum
- Can be preceded by history of HSV or parvovirus infection
- Attacks can last up to four weeks

Diagnosis:

- Immune complex depositions
- Association with HLA-B51

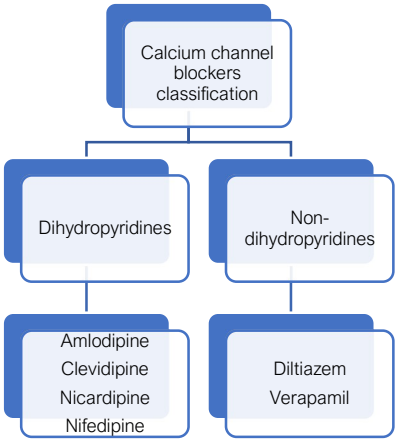
Ca channel blockers

Mechanism of action

- Block L-type Ca2+ channels in heart and blood vessels
- Act on vascular smooth muscle, reduce contraction of the arteries cause vasodilation
- Act on cardiac muscles (Myocardium), they reduce the force of the contraction of the heart (Negative inotropic)

Calcium channel blockers classification

- Dihydropyridines acts on vascular smooth muscle
- Non-dihydropyridines act on the heart



Clinical uses

1-Hypertension

- Directly dilates peripheral resistance arterioles, leading to a reduction in total peripheral vascular resistance & reduced arterial blood pressure

2-Arrhythmias- Atrial fibrillation

3-Classical angina

- Dilate peripheral arterioles which reduce afterload

4-Prinzmetal angina

- Drug used Diltiazam or Verapamil
- Dilate the main coronary arteries
- Potent inhibitor of coronary artery spasm

- Prinzmetal's variant angina (PVA) is due to vasospasm of coronary artery and characterized by recurrent episodes of chest pain (angina) that usually occur when a person is at rest, between midnight and early morning.

5-Raynaud's phenomenon

- Dihydropyridines except Nimodipine used to treat Raynaud's phenomenon since it works on vascular smooth muscle

Side effects

Dihydropyridines

- **Flushing**
- **Dizziness**
- **Peripheral edema**

Non-Dihydropyridines

- cardiac depression
- AV block
- Hyperprolactinemia
- Constipation
- Gingival hyperplasia

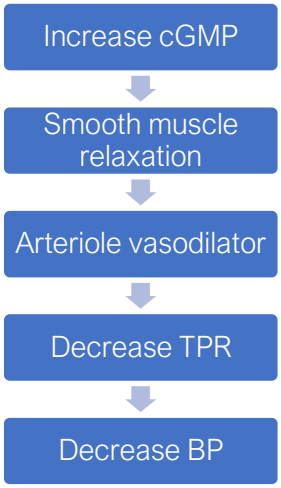
Drug interaction

- Cimetidine (80% increase in nifedipine plasma levels)

Vasodilators

Hydralazine

MOA



Clinical uses

- Congestive heart failure
- Hypertension (sever cases in hospitals)
- Hypertension during pregnancy (since it's not teratogenic)

Side effects

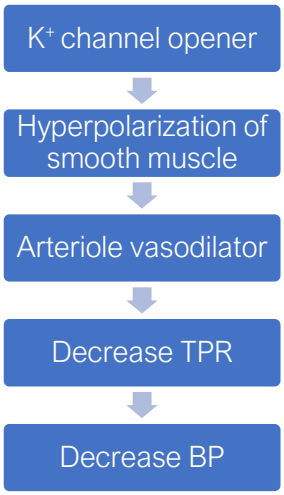
- Hypotension
- Reflux tachycardia
- Peripheral edema
- Lupus like symptoms (hydralazine and procainamide)

Contraindications

- Angina or coronary artery disease because reflex tachycardia might increase myocardial oxygen consumption

Minoxidil, Diazoxide

MOA



Clinical uses

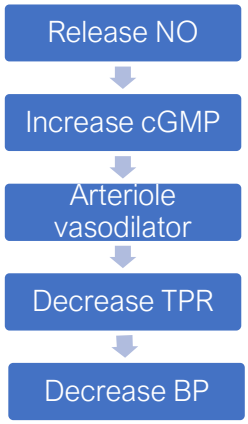
- Severe hypertension cases
- Baldness (Topical minoxidil)
- Insulinoma (Diazoxide)

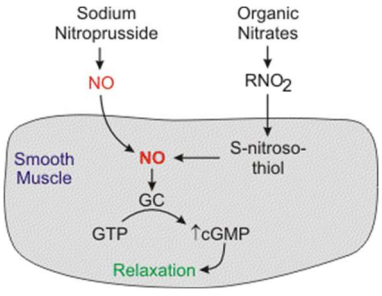
Side effects

- Hypertrichosis (Excess hair)-Minoxidil
- Peri cardiac effusion -Minoxidil
- Hypotension
- Reflex tachycardia
- Hyperglycemia (Block insulin release)

Sodium Nitroprusside

MOA





Clinical uses

- Hypertensive emergency
- Angina
- CHF

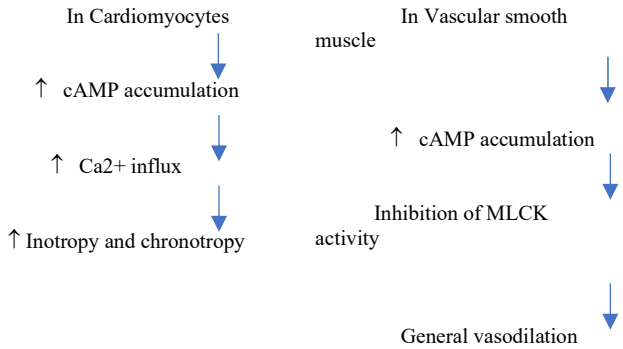
Side effects

- Cyanide toxicity
- Hypotension

Milrinone

Mechanism of action

- Inhibits cAMP phosphodiesterase activity in myocardium and vascular smooth muscle



- Decreases blood viscosity by reducing plasma fibrinogen concentrations and increasing fibrinolytic activity.

Clinical uses

- Congestive heart failure
- Short term use in decompensated heart failure

Adverse effects

- Arrhythmias
- Hypotension

Statins

LDL and atherosclerosis

- LDL and atherosclerosis
- When patient present high levels of LDL- LDL could be oxidized by free radicals leading to deposit on the endothelial basemen membrane
- The macrophages will engulf the oxidized LDL and degrade it forming foam cells
- As the fatty streak enlarges over time, necrotic tissue and free lipid accumulates, surrounded by epithelioid cells and eventually smooth muscle cells, an advanced plaque with a fibrous cap.
- The plaque eventually begins to occlude the blood vessel, causing ischemia and infarction in the heart, brain, or extremities.

- By time the plaque becomes unstable leading to rupture and thrombosis causes:
  - Myocardial infarction
  - Acute ischemic stroke
  - Mesenteric ischemia
  - Claudication

Pathophysiology

- Atherosclerosis = Unhealthy blood cholesterol levels. This includes high LDL cholesterol (called "bad" cholesterol) and low HDL cholesterol ("good" cholesterol).

Risk factors for atherosclerosis

- High blood pressure
- Smoking
- Insulin resistance
- Diabetes
- Overweight or obesity
- Lack of physical activity
- Unhealthy diet

Treatment plan

Non-pharmacological

- Lifestyle can cause increase in cholesterol- lack of exercise or high intake of saturated fatty acids
- Diet and exercise are first line of treatment.

Pharmacological

- Treatment goal is to ↓ LDL cholesterol and atheroma plaque formation

Drug names

- Lovastatin
- Pravastatin
- Atorvastatin
- Rosuvastatin
- Simvastatin

Mechanism of action

- Inhibit conversion of HMG-CoA to mevalonate, a cholesterol precursor, results in:
- ↓ liver cholesterol
- ↑ LDL-receptor expression
- ↓ plasma LDL
- ↓ VLDL synthesis results in: ↓ triglyceridemia

Side effects

- Myalgia, myopathy (check creatine kinase)
- Rhabdomyolysis
- Hepatotoxicity (check liver function tests)

Drug interactions and contraindications

- Pregnancy and teenagers
- Gemfibrozil (↑ rhabdomyolysis)
- Cytochrome P450 inhibitors enhance toxicity of statins

Bile acid resins

Examples

- Cholestyramine
- Colestipol
- Colesevelam

Mechanism of action

- Prevent intestinal reabsorption of bile acid → Complexation of bile acid in the guts, leads to:

1. ↑Enterohepatic recirculation of bile salts
2. ↑ Synthesis of new bile salts by the liver
3. ↓ Liver cholesterol
4. ↑LDL-receptor expression
5. ↓blood LDL

Clinical Uses

- Hyperlipidemia
- Bile acid malabsorption

Adverse effects

- ↑ VLDL and triglycerides
- GIT upset
- Malabsorption of lipid-soluble vitamins (A, D, E and K)
- Hyperglycemia
- Cholesterol gallstone

Fibrates

Examples:

- Gemfibrozil
- Bezafibrate
- Fenofibrate

Mechanism of action

- Bind to the PPARα (Peroxisome proliferator activated receptors) and increase expression of lipoprotein lipases, results in:
- ↓ Triglyceride
- ↓ LDL
- ↑ HDL in most patients

Clinical Uses

- Used in hypertriglyceridemia

Adverse effects

- Gallstones
- Myositis

Niacin (Vitamin D3-Nicotinic acid)

Mechanism of action

- Inhibit lipolysis
- Decrease hepatic VLDL, results in:
- ↓plasma VLDL
- ↓ plasma LDL
- ↑ plasma HDL

Side effects

- Flushing, pruritus, burning pain (use aspirin 30 minutes before) Due to vasodilation of blood vessels
- Hepatotoxicity
- Hyperglycemia (acanthosis nigricans)
- Hyperuricemia (predispose patient to gout)

Note:

- A severe deficiency in niacin causes the disease pellagra, which is characterized by dermatitis, diarrhea, and dementia

PCSK9 inhibitors

Examples:

- Alirocumab
- Evolocumab

Mechanism of action

- Monoclonal antibody
- PCSK9 is a serine protease produced by the liver which binds LDL receptors and creates a complex to be targeted for lysosomal degradation
- PCSK9-LDL complex inhibits LDL receptor recycling to the cell surface, resulting in decreased cellular reuptake of LDL-C and increased levels of free LDL-C in the plasma.

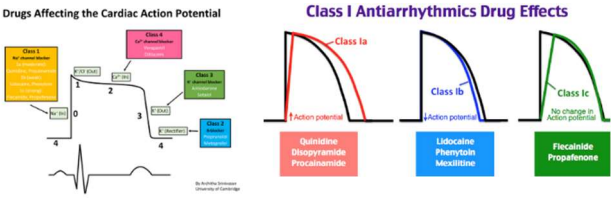
Clinical use

- Lower LDL
- Increase HDL
- Atherosclerosis Cardiovascular disease
- Familiar hypercholesterolemia (Heterozygous, Homozygous)

Adverse effects

- Myalgias and injection site reactions
- Delirium
- Dementia and neurocognitive effects

Anti-arrhythmic drugs class I



Class 1A

- Antiarrhythmic drugs mean eliminates irregular heartbeat while, proarrhythmic means promotes irregular heartbeat
- This type of action potential is found in non-nodal, cardiomyocytes (e.g., atrial and ventricular myocytes; purkinje tissue).
- Sinoatrial and atrioventricular nodes (nodal tissue action potential) do not depend on fast sodium channels for depolarization

Mechanism of action

- Class 1A are Na channel blockers (Especially fast Na+ channels) that are responsible for the rapid depolarization (phase 0) of fast-response cardiac action potentials
- Effective in "state-dependent" blockade
- Blocks K+ channel (prolongs repolarization), ↑ action potential duration and effective refractory period
- Quinidine causes muscarinic receptor blockade, which can ↑ HR and AV conduction.

Examples

- Quinidine
- Procainamide
- Disopyramide

Quinidine

Clinical uses

- Atrial fibrillation, flutter; supraventricular & ventricular tachyarrhythmias

Side effects

- Cinchonism due to anticholinergic effects (GI, tinnitus, ocular dysfunction, CNS excitation)
- Hypotension
- Thrombocytopenia
- Risk for torsades de pointes from prolonging QRS and ↑ QT interval
- Procainamide associated with lupus-like syndrome (rash/ arthralgia/fever)
- Disopyramide associated with heart failure

Procainamide

- The same mechanism of action of quinidine

Clinical uses

- Ventricular arrythmias (Ventricular fibrillation, ventricular tachycardia)
- Super ventricular arrythmia

Side effects

- Most of the side effects due to acetylation of acetylation of procainamide
- Systemic lupus erythematosus (SLE)–like syndrome that lead to polyarthralgia, myalgia and pleurisy
- Pericarditis, pleuritis
- Hematotoxicity (thrombocytopenia, agranulocytosis)
- prolongs QT interval of action potential and increases the risk of torsade de pointes

Disopyramide

- The same mechanism of action of quinidine

Side effects

- Stronger anticholinergic effects
- Dry mouth
- Constipation
- Urinary retention
- Blurred vision
- Torsade de pointes

Class 1B

- Block fast Na+ channels
- Block both activated and inactivated Na+ channels, but preferred for inactivated channels
- Decrease the slope of Phase zero and phase 4
- Slow conduction in hypoxic and ischemic tissues (Partially depolarized tissue)
- Decrease action potential

Examples

- Tocainaide
- Lidocaine
- Mexiletine

Lidocaine

Clinical uses

- Acute Ventricular arrythmia (Post myocardial infarction)
- Open-heart surgery
- Digoxin toxicity–ventricular arrhythmias

Side effects

- CNS drowsiness and nystagmus
- Slurred speech
- convulsions and seizures
- Note: Lidocaine is used IV use because of first-pass metabolism

Tocainide

- Ventricular arrhythmias, such as sustained ventricular tachycardia

Side effects

- Bradycardia
- AV node blockage
- Hypotension
- Ventricular tachycardia
- Pulmonary fibrosis
- Bone marrow aplasia

Mexiletine

- Same uses as lidocaine

Side effects

- Nystagmus
- Pancytopenia

Phenytoin

- Antiarrhythmic drug properties and is a potential treatment option for patients with refractory ventricular arrhythmia
- Phenytoin has a narrow therapeutic range

Side effects

- Nystagmus
- Ataxia
- Gingival hyperplasia

Class 1C

- Block Na channels in Purkinje tissue
- Block K channels in ventricular myocytes
- Has minimum effect in action potential

Clinical uses

- Supraventricular
- Ventricular arrythmia

Examples

- Flecainide
- Propafenone

Side effects

- Bronchospasm
- Bradycardia
- Proarrhythmic, especially post-MI

Anti-arrhythmic drugs class II III IV

Class II Beta blockers

Examples

- Sotalol
- Propranolol
- Esmolol

MOA

- revent β-receptor activation, which would normally ↑ cAMP
- ↓ SA and AV nodal activity
- Block K channel (Sotalol)
- Esmolol decrease automaticity (Decrease HR and AV conduction)
- ↓ Slope of phase 4 (diastolic currents) of AP in pacemakers

Clinical uses

- Esmolol (IV) is used in acute SVTs during surgery
- Ventricular arrythmia (Sotalol)
- Supraventricular arrythmia (atrial fibrillation, atrial flutter)

Class III (K+ channel blockers)

Examples

- Amiodarone
- Ibutilide
- Dofetilide
- Sotalol (can be considered as class III since it blocks K channels)

MOA

- ↓ IK (delayed rectifier current) slowing phase 3 (repolarization) of AP
- ↑ AD and ERP, especially in Purkinje and ventricular fibers

Clinical uses

- Atrial fibrillation
- Atrial flutter
- Ventricular tachycardia

Side effects

- Pulmonary fibrosis (Restrictive lung disease) FEV1/FVC ratio
- Blue pigmentation of the skin (“smurf skin”)
- Phototoxicity
- Corneal deposits
- Hepatic necrosis (ALT/AST mentoring)
- Thyroid dysfunction
- Blue decolorization
- Photosensitivity

Bretylium

MOA

Prolong ventricular action potential

Side effects

Hypotension

Clinical uses

- Refractory ventricular fibrillation
- Ventricular tachycardia

Class VI (Ca+ channel blockers)

Examples

- Verapamil (Cardiac tissue)
- Diltiazem (Periphery)
- Nifedipine (Periphery)

MOA

Block slow cardiac Ca2+ channels
↓ phase 0, ↓ phase 4
↓ SA, ↓ AV nodal activity

Clinical uses

- Supraventricular arrythmia (Atrial fibrillation/ Atrial flutter)
- Rate control in atrial fibrillation

Atrial fibrillation
The primary goals for treatment are:

1. Ventricular rate control with beta blockers, CCBs, or digoxin
2. Anticoagulation

Side effects

- Bradycardia
- Hypotension
- Dizziness
- Constipation

Magnesium Sulfate

MOA

- Unknown
- Stabilize the cardiac cell membrane

Clinical uses

- For torsade de pointes
- Digoxin induced arrythmia

Side Effects

- Paralysis
- Respiratory paralysis
- Flushing and Headache
- Bradycardia

The following drugs might precipitate torsade de pointes:

- Potassium-channel blockers (class 1A and class III)
- Antipsychotics (thioridazine)
- Tricyclic antidepressants

Adenosine

MOA

- Activate acetyl choline sensitive potassium channel in SA/AV node
- Activates adenosine receptors causes Gi-coupled decrease in cAMP
- ↓ SA and AV nodal activity

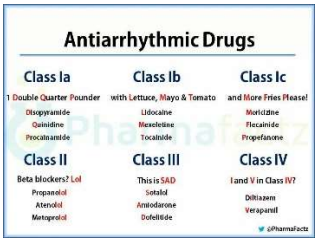
Clinical uses

- SVT Supraventricular tachycardia

Side effects

- Chest pain
- Dyspnea
- Flushing
- Headache
- Adenosine is antagonized by methylxanthines (theophylline and caffeine)

Summary for anti-arrhythmic drugs



Ivabradine

Mechanism of Action

Pacemaker action potential:

- Depolarization of pacemaker cells is mediated by voltage-gated calcium channels in phase 0
- There are no phase 1 or 2 in the AP of a pacemaker
- Phase 3 is repolarization which is mediated by opening potassium channels for potassium efflux
- Phase 4 is unique in pacemaker action potential:
    - Slow spontaneous diastolic depolarization
    - Due to I_f channels which allow for slow sodium and potassium influx
    - Responsible for the automaticity of SA and AV nodes

Mechanism of action:

- Ivabradine inhibits I_f channels → reduces cardiac pacemaker activity
- Prolongs the slow diastolic depolarization phase
- Reduces heart rate without reducing inotropy → reduces cardiac oxygen demand

Indications:

- Stable coronary arterial disease in patients who cannot take beta-blockers
- Chronic heart failure with systolic dysfunction

Side Effects:

- Luminous phenomena: enhanced brightness in a fully maintained visual field
  Possibly related to the inhibition of I_f channels in the retina
- Bradycardia
- AV block
- Headache

Introduction to hypertension management

Non-pharmacological treatment

- Lifestyle changes
- Decrease Na intake less than 4-gram day
- Weight loss
- Reduce alcohol
- Exercise(daily)
- Low saturated diet (Instead fruits and vegetables)
- Reduce stress

Pharmacological treatment

When to treat:

- Failed non-pharmacological treatment
- SBP 140-180 or DBP 90-110mmHg
- Start with a single drug at low dose
- 4-6 weeks period for apparent results in case of ineffective, consider increasing dose/ add another
- Use only one drug from one class then consider combination treatment
- For elderly patients start low and go slow

Treatment guidelines

- ↓ Total peripheral resistance (TPR) BP = CO x TPR
- ↓ CO
- ↓ body fluid volume
- ↓ BP may result in homeostatic regulation:
- Reflex tachycardia (↑ sympathetic activity)
- Edema (↑ renin activity)

Thiazides

- Decrease intravascular volume
- Increase urinary excretion of potassium

- Increase Cl^- and Na^+ excretion
- Examples: Hydrochlorothiazide

Side effects

- Decrease renal perfusion
- Hypokalemia
- Hyperglycemia
- Hyperlipidemia
- Hyper uremia
- Hypercalcemia

B-blockers

- Decrease heart rate and decrease CO
- Decrease renin release
- Vasodilation decrease preload decrease CO
- Block release renin

Examples:

- Propranolol
- Bisoprolol
- Metoprolol
- Atenolol

Side effects

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

Cautions in use:

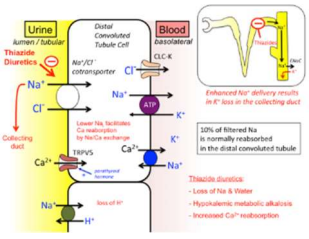
- Asthma
- Vasospastic disorders
- Diabetics (alteration of glycemia and masking of tachycardia due to hypoglycemic events)

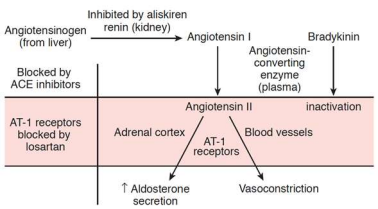
ACE inhibitors

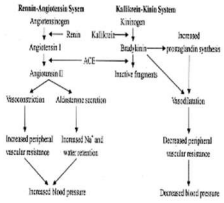
Drugs

- Captopril
- Enalapril
- Lisinopril
- Ramipril

Overview







Angiotensin II

vasoconstrictor

Aldosterone release from the adrenal gland

↑ blood pressure and ↑ sodium reclamation by the kidney.

Mechanism of action

- Block angiotensin-converting enzyme, preventing the conversion of angiotensin I to angiotensin II, therefore:
- Decrease (Glomerular filtration rate) GFR by preventing constriction of efferent arterioles
- Prevent AT1-receptor stimulation
- ↓ aldosterone, vasodilation
- prevent bradykinin degradation (Bradykinin is a potent vasodilator)

Clinical uses:

- Hypertension (Due to its potent vasodilatation effect)
- Heart failure (slow the progression of heart failure)
- Post-myocardial infarction patients

Adverse effects

- Persistent cough due to bradykinin release
- Angioedema (Tongue and swollen lips)
- Postural hypotension
- Protein urea
- Dizziness
- Low neutrophils

Drug interaction

- K-sparing diuretics can result in hyperkalemia
- NSAID

Contraindication

- Contraindication in bilateral renal artery stenosis
- Pregnancy (Teratogenic effects)

Angiotensin receptor blocker (ARBs)

- Used for treatment of hypertension

Drugs

- Losartan
- Valsartan

MOA

- Block angiotensin receptor II directly to prevent persistent cough associated with bradykinin

Adverse effects

- Hyperkalemia
- Fetal renal toxicity

Vasodilators

- ↓ TPR via arteriolar dilation

Examples:

- Hydralazine

Side effects:

- Edema
- Reflex tachycardia

Hypertension treatment for special cases

- Primary essential hypertension: Thiazides, ACE inhibitors, ARBs, dihydropyridine Ca^{+2} channel blockers
- Hypertension with heart failure: Diuretics, ACE inhibitors/ARBs
- Hypertension with diabetes mellitus: ACE inhibitors/ARBs
- Hypertension in asthma: ARBs, Ca^{+2} channel blockers, thiazide
- Hypertension in pregnancy: Methyldopa, Hydralazine, Labetalol, Nifedipine

Antianginal drugs

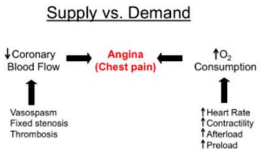
Overview

Cardiac ischemia:

- Secondary to coronary artery disease
- Due to imbalance of myocardial oxygen supply and demand,
- Most common in middle age men and postmenopausal

Angina pectoris

- Squeezing or pressure-like sensation in the chest that patients have during myocardial ischemia.
- Angina is caused by an imbalance of O2 supply vs. demand, resulting in myocardial ischemia



Types of Angina:

1-Stable angina

- Most common type is caused by coronary artery atherosclerosis with luminal narrowing >75%.
- Chest pain developed due to increased cardiac demand (exertional or emotional) and is relieved by rest or nitro-glycerine (vasodilation).

2-Unstable angina

- Typically occur at rest
- Due to nonocclusive coronary arterial thrombi, characterized by increased frequency or intensity
- This form of angina has a high risk for myocardial infarction
- +/− ST depression with T-wave inversion on ECG

3-Prinzmental angina

- Chest pain occur at rest due to coronary artery vasospasm
- Electrocardiogram shows transient ST segment elevation (transmural ischemia).
- Triggered by smoking, cocaine, alcohols and triptans
- Respond to Nitro-glycerine and Ca2+ channel blockers

Note: Drugs that decrease mortality in patients with stable angina include aspirin, nitroglycerin, and beta blockers.

Angina pectoris treatment guidelines

- ↓ oxygen requirement by ↓ TPR, CO, or both (nitrates, CCBs, and beta blockers)
- ↑ oxygen delivery by ↓ vasospasm (nitrates and CCBs).

Nitrates

Examples: Nitro-glycerine, Isosorbide Dinitrate, Isosorbide Mononitrate

- Nitroglycerin: sublingual, transdermal, and IV formulations

- Isosorbide: oral, extended release for chronic use
- Nitroglycerin is the preferred drug for acute management of both stable and vasospastic angina.

MOA:

Nitrates release nitric oxide (NO)

↓

Activates guanylate cyclase in vascular smooth muscle cells

↓

Causes elevated cyclic guanosine monophosphate (cGMP) levels

↓

Causing smooth muscle relaxation (vasodilation)

↓

Vendodilation

↓

↓ preload → ↓ cardiac work → ↓ oxygen requirement

Clinical uses:

- Angina
- Acute coronary syndrome
- Pulmonary edema

Side effects

- Orthostatic hypotension
- Flushing
- Headache
- Reflex tachycardia
- Fluid retention

B-blockers

1. Decrease cardiac oxygen demand by:

- ↓ Heart rate
- ↓Contractility
- ↓Lowering blood pressure

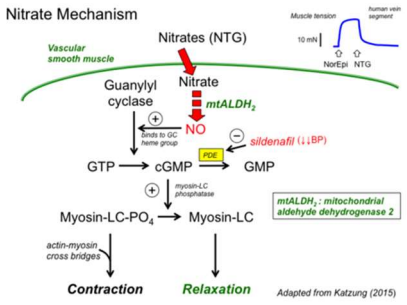
2. Increase myocardial perfusion by

- Increase diastolic perfusion time
- Used in angina of effort and acute treatment of unstable angina
- β-blockers are <u>contraindicated in vasospastic angina</u>
- Examples: propranolol, metoprolol, atenolol

Ca^{+2} channel blockers

- Dilate peripheral arterioles which reduce afterload
- Diltiazem or Verapamil used for Prinzmetal angina through dilation the main coronary arteries
- Potent inhibitor of coronary artery spasm

Ranolazine



- Anti-ischemic with anti-anginal effect through inhibition of the inward Na^{+} current in cardiac myocytes, thereby decreasing calcium accumulation

↓

↓decreased end diastolic pressure and improvement of diastolic coronary flow

- Ranolazine does not affect heart rate or contractility.

Side effects:

- Constipation
- Dizziness
- Headache
- Nausea
- QT prolongation

Diuretics

Types of hypertension

Essential **Represent 95%**	**Secondary** Represent 5%
High blood pressure that is not related to another medical condition.	medical condition that causes high blood pressure, usually occurring in the kidneys, arteries, heart, or endocrine system.
Risk factor for hypertension ○ **Obesity** ○ **Family history** ○ **Race African American** ○ **Lack of exercise** ○ **Smoking**	○ Renal artery stenosis ○ Fibromuscular dysplasia more in white or younger people ○ Cushing syndrome ○ Primary aldosteronism ○ Hyperthyroidism ○ Coarctation of aorta

Malignant hypertension

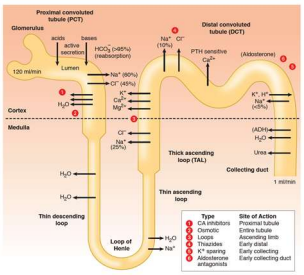
- CNS: Seizures, strokes, encephalopathy
- Eyes: Hemorrhage
- Lung: Pulmonary edema
- Heart: MI, aortic dissection
- Kidneys: Nephropathy, increased BUN/ Creatinine

Antihypertensives drugs

- Diuretics
- ACE inhibitors
- B-blockers

Vasodilator

Diuretics



Thiazides

Examples: Hydrochlorothiazide, Chlorthalidone

MOA

- Work in the distal convoluted tubule of the nephron (Na+/Cl− transporter inhibition) lead to:
- ↑ luminal Na+ and Cl− in DCT
- ↑ diuresis
- ↑ Na^+ and K loss
- Blockage of sodium uptake here by thiazide diuretics leads to increased calcium reabsorption.

Clinical uses

- Hypertension
- CHF
- Idiopathic hypercalciuria (Thiazides contraindicated in case of hypercalcemia)
- Nephrogenic diabetes insipidus

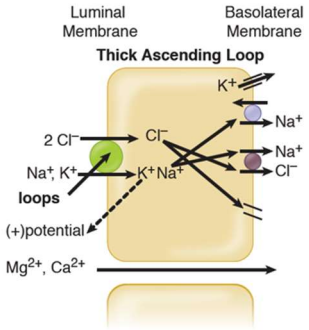
Side effects

- Hypokalemia and alkalosis
- Hypercalcemia
- Hyperuricemia
- Hyponatremia
- Hyperglycemia
- Hyperlipidemia

Drug interactions

- Thiazides are sulfa drugs, therefore avoid in sulfa allergy

Loop diuretics



Examples: Furosemide (Lasix)= last six hours

MOA:

- Inhibit cotransport system (Na+/K+/2Cl−) of thick ascending limb of loop of Henle.

Clinical uses:

- Used for rapid high-volume diuresis in cases such as
  - Pulmonary edema
  - Congestive heart failure
  - Liver cirrhosis
- Hypertension
- Hypercalcemia

Side effects

- Hypokalaemia and metabolic alkalosis
- Hypocalcaemia
- Hypomagnesemia
- Hyperuricemia
- Ototoxicity
- Nephritis
- Gout

Drug interactions

- Thiazides are sulfa drugs, therefore avoid in sulfa allergy