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CARDIOVASCULAR SYSTEM

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Introduction

Embryology

Development Of The Heart

By the third week of development, the rapidly growing embryo can no longer rely on simple diffusion from the placenta for its metabolic and oxygen demands, so the heart starts to develop from splanchnic mesoderm in the latter half of week 3 within the cardiogenic area of the cranial end of the embryo during gastrulation. By week 4 of development, a primitive heart begins to beat.

Formation and Looping of Heart Tube

Neural crest cells move into the developing heart and play an essential role in cardiac growth. The cardiogenic cells consolidate to form a couple of primordial heart tubes, which will combine into a single heart tube during body folding.

The steps of looping are as follows:
1. Primitive heart chambers lined by endothelial cells develop along the cranial-caudal axis of the heart tube.
2. Rapid elongation of the heart tube occurs in an enclosed space (the pericardial cavity), requiring that it bend into a U-shaped loop that places the primitive atrium behind the more-notable primitive ventricle. (Note that in the early stages, the primitive ventricle is connected to the atrium via a common atrioventricular (AV) canal).

Formation of Septa

Heart septa divide the atrium, ventricle, atrioventricular canal, and aortopulmonary (the outflow of the ventricle) tract into separate chambers. Septa take shape between the 4th and 6th weeks of development from inward growth of the deepest (endocardial) cardiac surface.

EMBRYONIC STRUCTURE	ADULT STRUCTURE
Truncus arteriosus	Ascending aorta and pulmonary trunk
Bulbus cordis	Smooth parts (outflow tract) of left and right ventricles
Primitive ventricle	Trabeculated parts of left and right ventricles
Primitive atrium	Trabeculated parts of left and right atria (pectinate muscles)
Left horn of sinus venosus (SV)	Coronary sinus (largest venous drainage of heart)
Right horn of SV	Smooth part of right atrium (sinus venarum)
Primitive pulmonary vein	Smooth part of left atrium
Endocardial cushion	Atrial septum, membranous interventricular septum; AV and semilunar valves
Right common cardinal vein and right anterior cardinal vein	Superior vena cava
Vitelline veins	Portal system

CONGENITAL HEART DEFECT	DESCRIPTION
VENTRICULAR SEPTAL DEFECT (VSD)	A defect in the septum that divides the right and left ventricles (Most common congenital heart defect and it is associated with fetal alcohol syndrome).
ATRIAL SEPTAL DEFECT (ASD)	a defect in the septum that divides right and left atria; most common type is ostium secundum (constitute about 90% of cases).
PATENT DUCTUS ARTERIOSUS (PDA)	Failure in the closure of ductus arteriosus (associated with congenital rubella). Asymptomatic at birth with continuous -machine-like-murmur; may lead to Eisenmenger syndrome, resulting in lower extremity cyanosis.
TETRALOGY OF FALLOT	Characterized by:- 1- stenosis of the right ventricular outflow tract 2- right ventricular hypertrophy 3- VSD 4- an aorta that overrides the VSD
TRANSPOSITION OF THE GREAT VESSELS	pulmonary artery arising from the left ventricle and aorta arising from the right ventricle (Associated with maternal diabetes)

CONGENITAL HEART DEFECT	DESCRIPTION
TRUNCUS ARTERIOSUS	Characterized by a single large vessel arising from both ventricles (Truncus fails to divide).
TRICUSPID ATRESIA	Tricuspid valve orifice fails to develop; right ventricle is hypoplastic.
COARCTATION OF THE AORTA	Narrowing of the aorta classically divided into: 1- infantile (Associated with a PDA) 2- adult forms (Not associated with a PDA).

Anatomy

Borders of the Heart and its relations

1- **The right border** is formed by **the right atrium.**
2- **The left border** is formed by the left auricle and mainly by **the left ventricle.**
3- **The apex** is the tip of **the left ventricle**, and is found in **the left fifth intercostal space** which the point of maximal impulse (PMI) is normally palpated here.
4- **The superior border** is formed **by the right & left auricles** plus the conus **arteriosus of the right ventricle and the great vessels.**
5-**The inferior border** is formed **at the diaphragm**,mostly by the right Ventricle.
6-**The aortic arch** is located at the level of the sternal notch, corresponding to vertebral **level T2.**

Heart layers

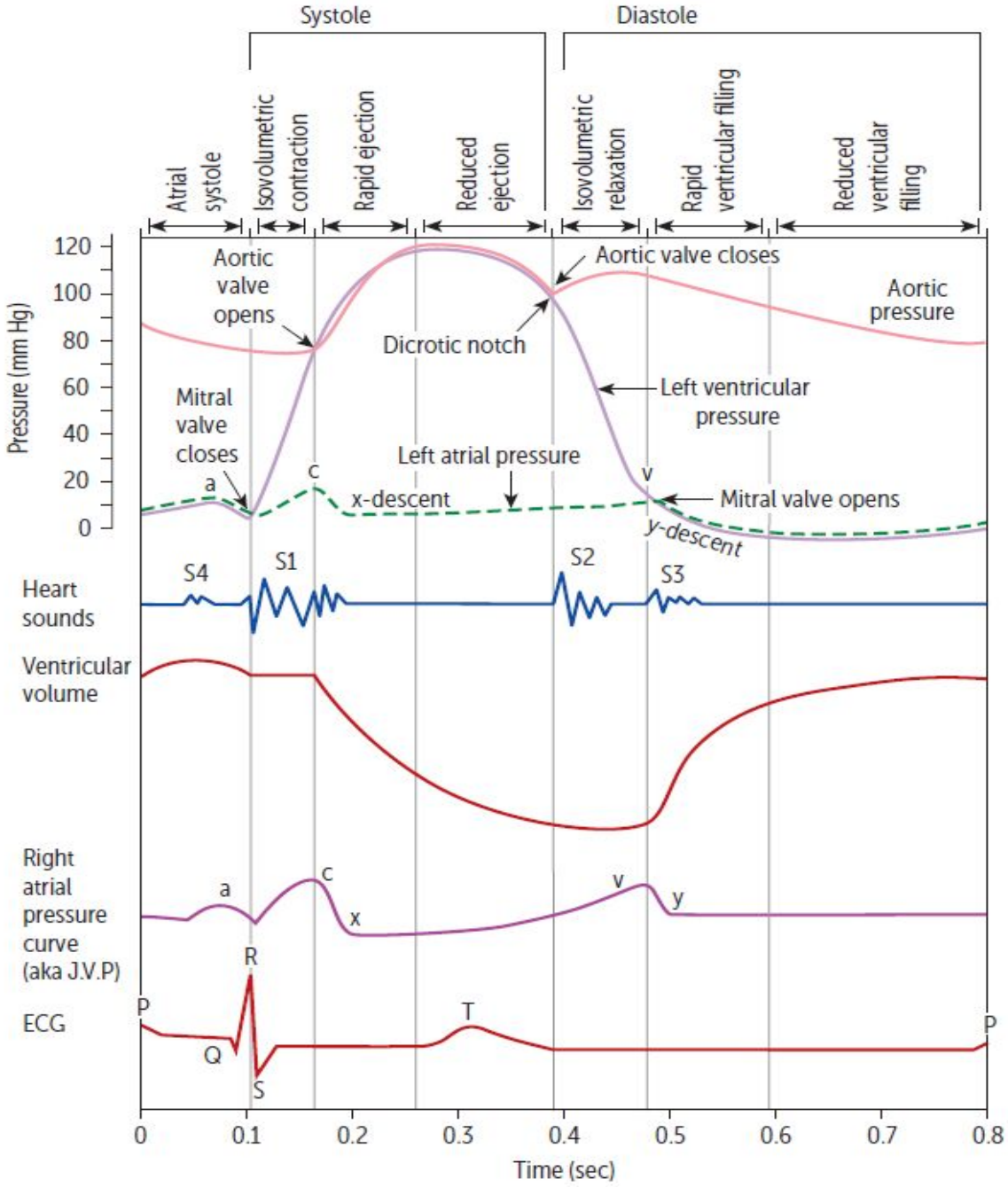
The heart consist of three layers :

1. **Endocardium:**
   The endocardium is the innermost layer. It is composed of simple squamous epithelium (endothelium) and underlying connective tissue.
2. **Myocardium:**
   The myocardium is the middle and **thickest layer** composed of myocytes, which is the responsible of pumping the blood throughout the heart.
3. **Pericardium:**
   The pericardium is composed of two layers: the outer fibrous pericardium and the inner serous pericardium. It covers the heart and proximal portion of the great vessels.
   Fibrous pericardium is a hard connective tissue that **binds** the heart in place via its connections to the **sternum anteriorly** and **the central tendon of the diaphragm** inferiorly.
   Serous pericardium comprises two layers:
   1- The parietal layer is continuous with the internal side of the fibrous pericardium.
   2- The visceral layer, also known as the **epicardium**, is the thin innermost layer of the pericardium. **This layer contains the major branches of the coronary arteries.2**

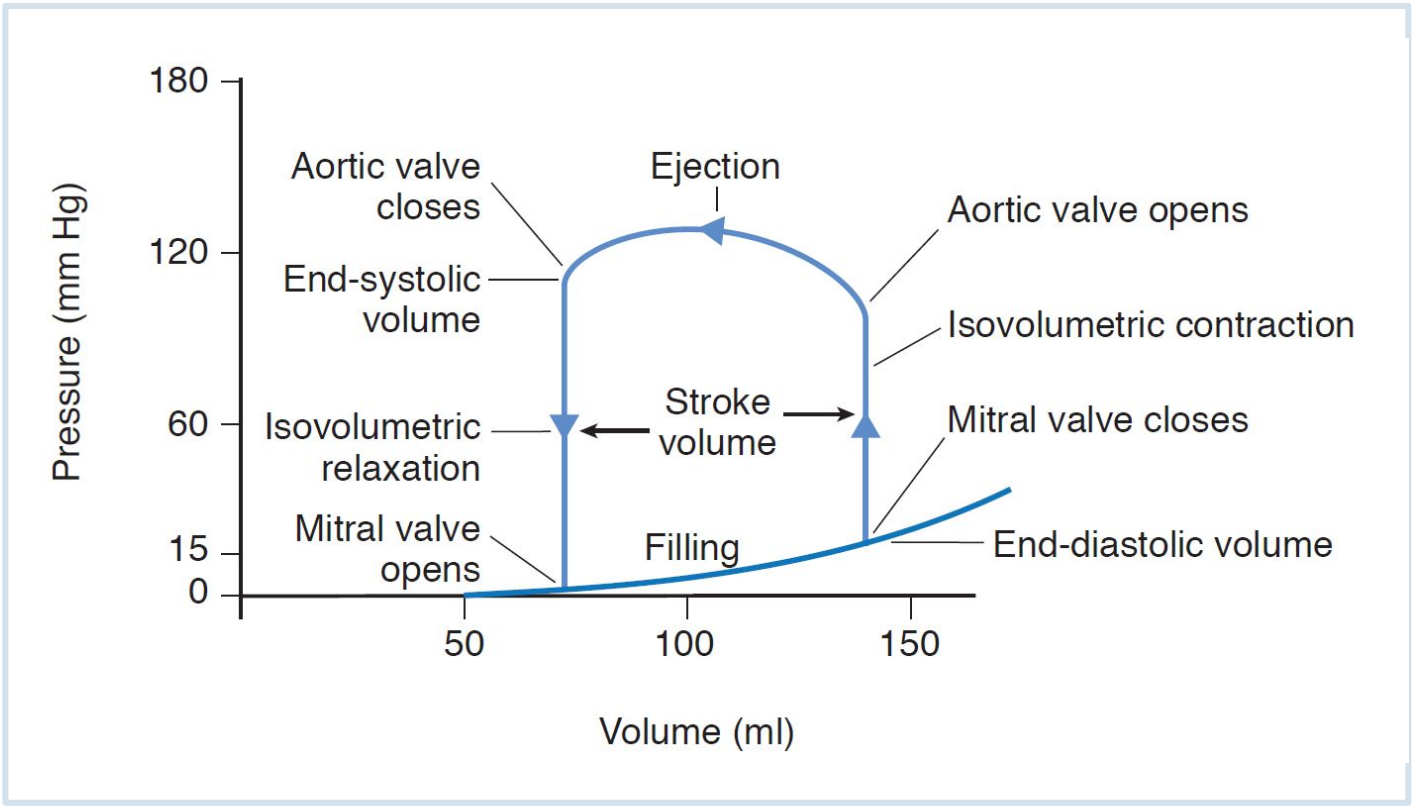
Physiology

Cardiac cycle

The cardiac cycle is the changes in hemodynamic and electrical activity that occur at each heart beat. The duration of the cycle depends on the heart rate. Normally, diastole is longer than systole, when the heart rate increases the duration of diastole decreases hence decreasing the duration of the cycle. Figure 1 shows the normal cardiac cycle, which demonstrate the simultaneous interaction between heart hemodynamic and electrical activity . Each cycle go through 7 phases (next page).



Phases	Significant
1- Atrial systole	Corresponding to P wave on ECG. Final filling of the ventricles (only 25%). Produce (a) wave on venous pulse.
2-Isovolumetric ventricular contraction	Corresponding to QRS complex on ECG. Increasing ventricular pressure causing AV valves closure (**S1**) but not enough to open the semilunar valves. Produce (c) wave.
3-Rapid ventricular ejection	Corresponding to ST on ECG. When the ventricular contraction produces enough pressure to open the semilunar valves, this phase start and blood ejects out to the pulmonary and systemic circulation. In the same time the atria relax due to the fact the the cusps of the AV valves are pulled away from the atria and it causes X descent.
4-Reduced ventricular ejection	Continuing blood ejection but slower. Atria are still filling which produce (v) wave.
5-Isovolumetric ventricular relaxation	Corresponding to T wave on ECG. Decreasing ventricular pressure causing the semilunar valves closure (**S2**) but not enough to open the AV valves.
6-Rapid ventricular filling	When the ventricular relaxation lower the pressure enough to open the AV valves, this phase starts and 60-70% of the blood enters the ventricles (**S3**). Produce (y) descent.
7-Reduced ventricular filling	The longest phase. <5% of the blood enters the ventricles.



Pressure-volume loop and cardiac cycle

When plotting the normal state pressure and volume in a graph, a loop is drawn to illustrate the cardiac cycle. In mechanically altered state (increased afterload or preload. etc) the loop changes in shape according to the condition.

Heart sounds

Usually only the first two heart sounds are present in normal adult.
S1: Low-pitched sound caused by Tricuspid and Mitral valves closure. Mitral valve closes first but not significant to produce a split.
S2: High-pitched sound caused by Aortic and Pulmonary valves closure. Aortic valve closes first, this produce a physiological split that is more pronounced in inspiration. Because of increased VR during inspiration due to more -ve intrapleural pressure, the pulmonary valve closes after the aortic valve.
S3: Soft low-pitched sound caused by rapid ventricular filling.
S4: Caused by ventricular filling when there is a stiff ventricle or high atrial pressure.

Heart murmurs

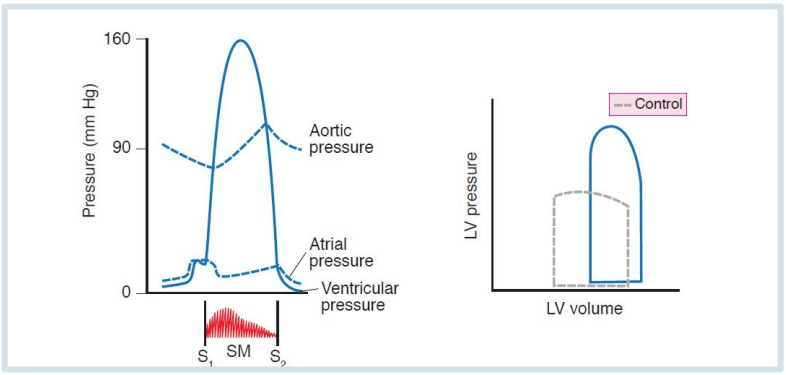
Murmur is the sound caused by turbulence of blood flow through a narrowed (stenosis), incompetant (regurgitation) valves, heart septal defect or in a normal physiological conditions (Pregnancy, children). Murmurs are divided into systolic or diastolic, and can be further subdivided according to the timing to help differentiate the cause .

	Timing and conditions
Systolic	**Pansystolic:** - Mitral Regurgitation ,Tricuspid regurgitation , Ventricular septal defect **Mid systolic:** - Aortic Stenosis , Pulmonary stenosis , Indirect murmur of the atrial septal defect , Hypertrophic cardiomyopathy **Late systolic:** - Mitral valve prolapse , Papillary muscle dysfunction
Diastolic	**Early diastolic:** - Aortic regurgitation ,Pulmonary regurgitation **Mid diastolic:** - Mitral stenosis , Tricuspid stenosis
Continuous	- Patent ductus arteriosus

Common causes of heart murmurs:

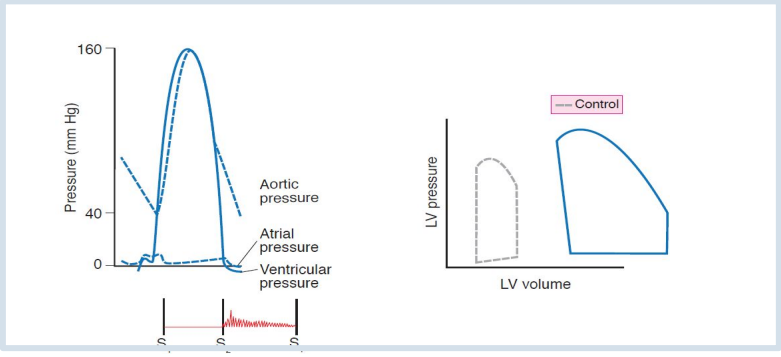
Aortic stenosis (AS):

Normally the aortic valve opening diameter is more than 2 cm^2, opening less than this produces a crescendo-decrescendo systolic ejection murmur. Sometime the narrowing is severe enough to cause the aortic valve to close after the pulmonary valve which results in paradoxical splitting.
Hemodynamic changes: Late peaking (tardus) and of small volume (parvus) pulse. Increased afterload, leads to a compensatory left ventricular concentric hypertrophy.
Causes: Degenerative calcific aortic stenosis (in elderly patients), congenital bicuspid valve and rheumatic heart disease.



Aortic regurgitation (AR):

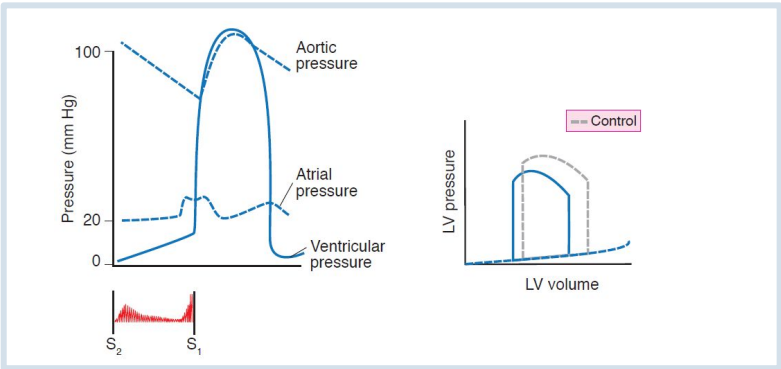
When the aortic valve does not close properly during diastole, an early decrescendo diastolic murmur occur. Occasionally an additional low-pitched rumbling mid-diastolic murmur is heard (Austin Flint murmur), it is produced by the regurgitated blood hitting the MV leaflet in diastole, preventing an opening snap (differentiating AR from MS).
Hemodynamic changes: Wide pulse pressures, increased preload, eccentric hypertrophy. All cardiac volumes are increased (EDV, ESV, SV).
Causes: rheumatic heart disease, infectious endocarditis, bicuspid valves, aortic dissection, hypertension, syphilis, or Marfan's syndrome.



Common causes of heart murmurs:

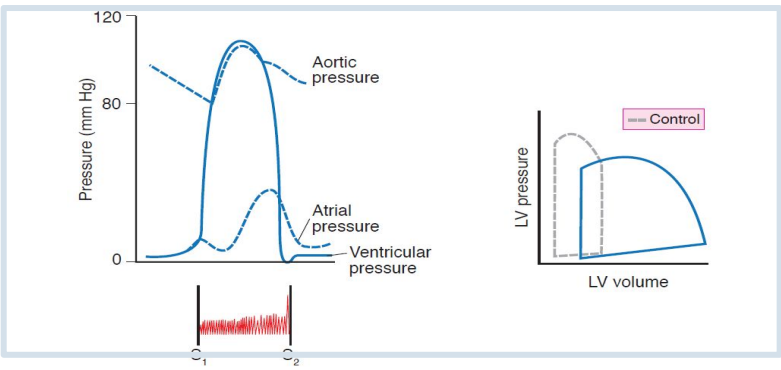
Mitral Stenosis (MS):

Narrowing of the mitral valve produces a high-pitched opening snap followed by a mid diastolic decrescendo murmur or rumble
Hemodynamic changes: Dilation of the left atrium due to elevation in the pressure and volume.
Causes: Almost always due to rheumatic heart disease.



Mitral Regurgitation (MR):

When the mitral valve does not close properly during systole, a pansystolic murmur is heard. May be acute or chronic.
Hemodynamic changes: Increased preload but with reduced afterload, left atrial dilatation due to increased volume only.
Causes: Any structural abnormalities in the valve itself, papillary muscles, chordae tendinae, or a structural change in the mitral annulus.



Clinical integration

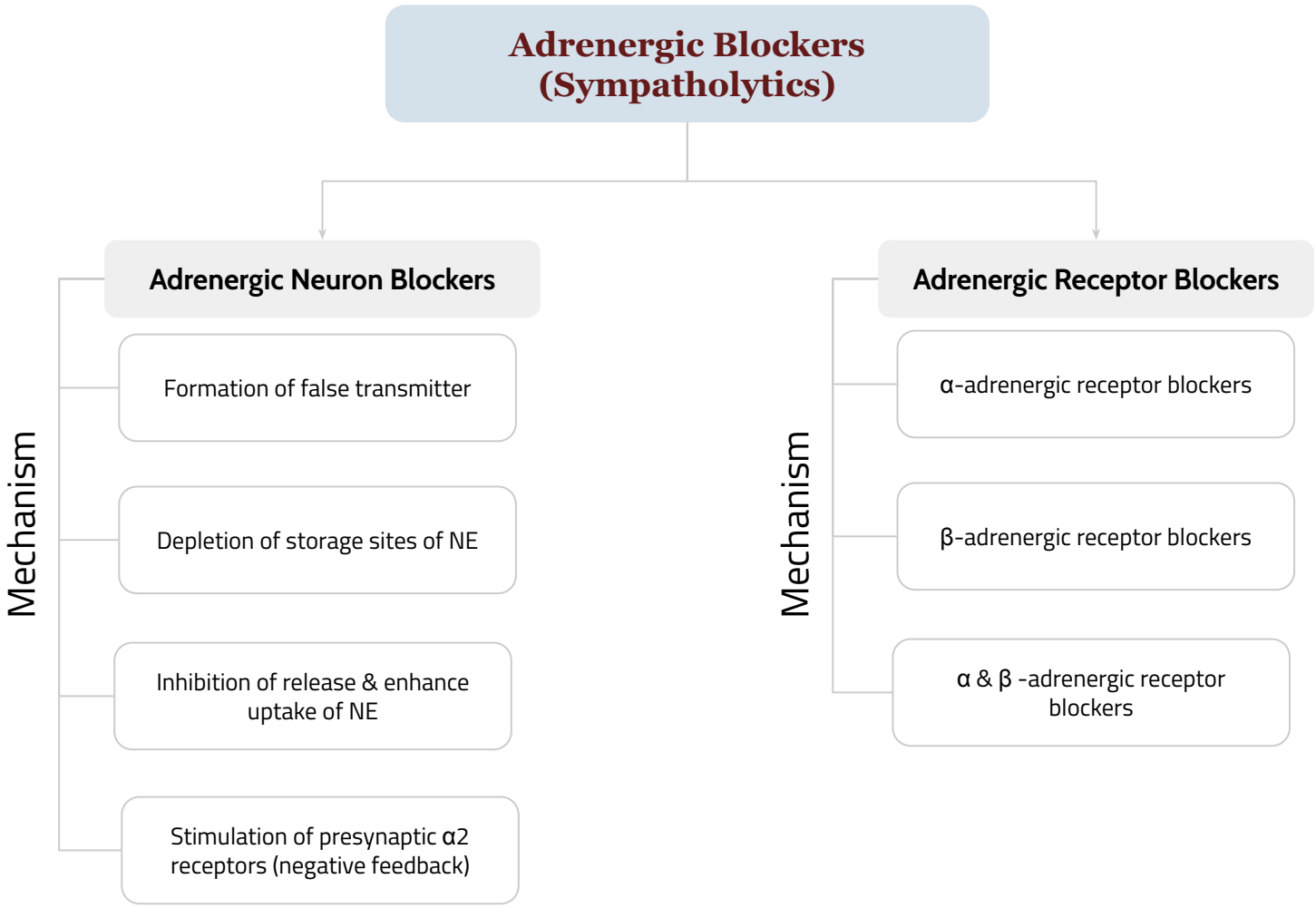
What are the normal and abnormal heart sounds?

S1	**Normal** It is due to mitral valve and tricuspid valve closure.
S2	**Normal** It is due to aortic valve and pulmonary valve closure.
S3	**Normal in children**, young adults, and pregnancy. It is due to turbulent blood flow. In which abnormalities o you hear S3? Heart failure-aortic regurgitation-mitral regurgitation
S4	**Abnormal** It occurs when the atrium contracts ("atrial kick") against a stiff ventricle. In which abnormalities do you hear S4? Hypertension-ischemic heart disease-aortic stenosis-advanced age.

Adrenergic Blockers

Overview : Adrenergic blockers are sympatholytics; drugs that inhibit the sympathetic nervous system by any mechanism. Adrenergic blockers can act by various mechanisms including blocking adrenergic receptors in target organs or by inhibiting the synthesis, storage, or release of endogenous catecholamines (mainly norepinephrine).

This class of medications is most commonly used for the treatment of cardiovascular problems like ischemic heart disease and hypertension. Antiadrenergic agents may also be used for urinary retention secondary to benign prostatic hyperplasia and for psychiatric conditions such as anxiety disorders and post-traumatic stress disorder.



Adrenergic Blockers

Sympathetic Effect on Cardiovascular System

In order to understand the mechanism of action of the antiadrenergic drugs, you must understand the physiological effects of the following adrenergic receptors when activated by sympathetic system.

Receptor	Effect on Cardiovascular System
α_1	• Vasoconstriction
α_2	• Central receptor: Decrease sympathetic outflow • Peripheral receptor: Arterial vasodilation
β_1	• Increase heart rate, increase cardiac contractility, increase Renin release
β_2	• Vasodilation

Adrenergic Neuron Blockers

Neuron blockers do not interfere with the adrenergic receptors found on target organs. They act by either inhibiting of endogenous catecholamines synthesis, storage, or release. They could also act by stimulation of presynaptic α2 receptors, inhibiting norepinephrine release by negative feedback.

Drug	Mechanism of Action
α-Methyldopa	• Forms false transmitter released instead of NE • Centrally acting α2 adrenergic agonist that inhibit NE release
Clonidine	• Centrally acting α2 adrenergic agonist that inhibit NE release
Guanethidine	• Inhibits release of catecholamines
Reserpine	• Inhibits storage by Inhibiting uptake of catecholamines into presynaptic vesicles of adrenergic neurons

Adrenergic Blockers

Centrally Acting Sympatholytics

A group of drugs that act by binding and stimulating α2 adrenergic receptors in the brainstem, resulting in reduced central sympathetic outflow. This reduces sympathetic outflow to the heart and vasculature. Thereby decreasing cardiac output and systemic vascular resistance resulting in decreased BP.

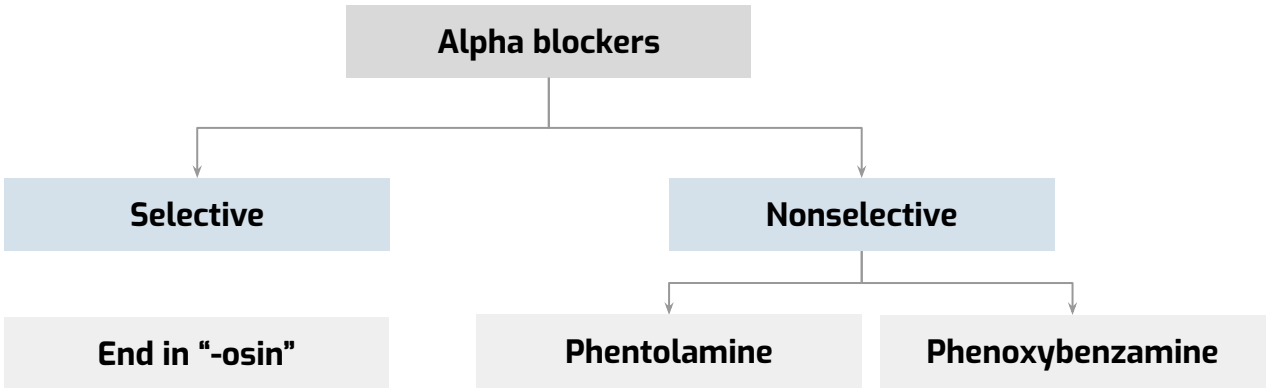
	α-Methyldopa	**Clonidine**
Mechanism	Selective α2 -agonists, induce negative feedback mechanism resulting in the inhibition of NE release. They reduce central sympathetic outflow resulting in decreased cardiac output and systemic vascular resistance.	
Site	Brain stem	
Indication	Due to their side effect profile, they are rarely used as first-line drugs to treat hypertension.	
	Hypertension in pregnancy	ADHD
Side effects	• Sedation • Autoimmune hemolytic anemia, positive Coombs test	• Sedation • Orthostatic hypotension • Severe rebound hypertension caused by abrupt discontinuation of medication • Dry mouth

Adrenergic Blockers

Adrenergic Receptor Blockers

A group of drugs that block the influence of norepinephrine on adrenergic receptors (α & β) on the effector organs.

α-Receptor Blockers



Nonselective α-Receptor Blockers

	Phentolamine	Phenoxybenzamine
Mechanism	Non-selective antagonists of both α1 and α2 receptors	
P.D.	• Decrease peripheral vascular resistance • Decreased mean blood pressure • Orthostatic hypotension • Reflex tachycardia	
P.K.	Reversible block (Competitive inhibitor)	Irreversible block (Noncompetitive inhibitor)
Indication	Pheochromocytoma	
Side effects	• Orthostatic hypotension • Vertigo & drowsiness • Male sexual dysfunction (Inhibits ejaculation)	

Adrenergic Blockers

Selective α-Receptor Blockers

	Prazosin	Doxazosin Terazosin	Tamsulosin
Mechanism	Selective α1 antagonists		Selective α1A antagonists
Site	Primarily on arterioles		Bladder sphincter and prostate
P.D.	• Blocked α1 causes arteriolar vasodilation, resulting in a decreased SVR therefore decreased blood pressure • May cause reflex tachycardia		
Indication	1. Mild to moderate hypertension 2. Urinary obstruction associated with Benign Prostatic Hyperplasia (by preventing bladder sphincter contraction)		1. Benign prostatic hyperplasia
Side effects	• Orthostatic hypotension		

Adrenergic Blockers

Effects of β-Receptor Blockade

Types of β receptors	Site of action	Effects of β-receptor blockade
β1	Heart	• ↓ HR, ↓ SV, ↓ CO • Anti-anginal effect: ↓ HR and ↓ cardiac contractility → ↓ BP and ↓ oxygen consumption by the heart → anti-ischemic effect • Anti-arrhythmic effect: ↓ AVN conduction velocity, ↑ AVN refractory time, and ↓ heart rate → anti-arrhythmic effect • Anti-remodeling effect
	Kidney	β1 blockade of the juxtaglomerular cells → ↓ renin release →↓ Blood Pressure
β2	Smooth muscles	• Vasculature: vasoconstriction • Bronchioles: bronchoconstriction
	Ciliary body of the eye	↓ Aqueous humor production → ↓ intraocular pressure
	Liver	↓ Glycogenolysis → hypoglycemia (esp. in diabetics)
β3	Adipose tissue	↓ Lipolysis → ↑ LDLs, TGs → weight gain

Adrenergic Blockers

β-Receptor Blockers - Pure Antagonists (No Intrinsic Sympathomimetic Activity)

	Mechanism	P.K.	Indication	Side effects
Propranolol	Non selective β1 &β2- antagonist	Lipophilic; cross BBB	Arrhythmia Hypertension Myocardial infarction Migraine Thyrotoxicosis , Performance anxiety Essential tremor	1. Bronchoconstriction and exacerbate asthma and COPD 2. Bradycardia 3. Hypo- or Hype - glycemia; dangerous for diabetics because it can mask hypoglycemia
Timolol		Lipophilic; can cross BBB	Glaucoma	
Sotalol	Non selective β1 and β2- antagonist & Cardiac K+ channel blockade	Hydrophilic; can't cross BBB	Arrhythmia	

Adrenergic Blockers

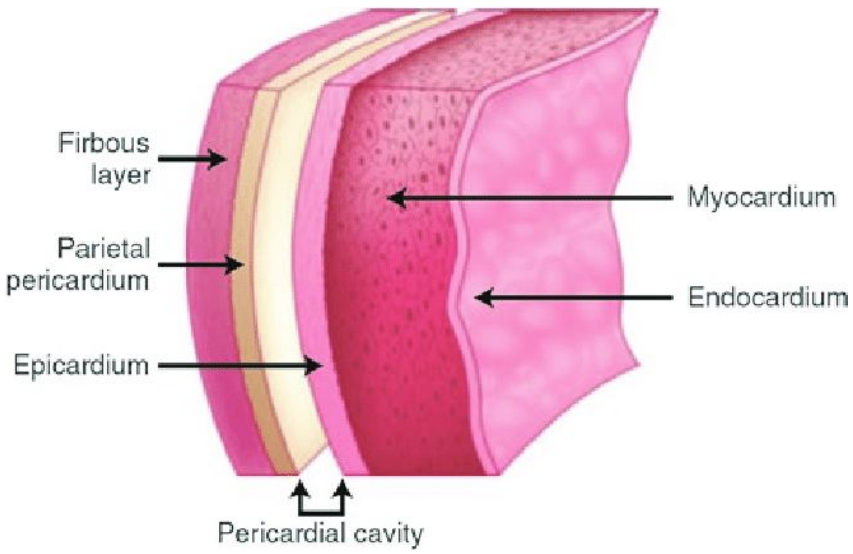
β-Receptor Blockers - Pure Antagonists (No Intrinsic Sympathomimetic Activity)

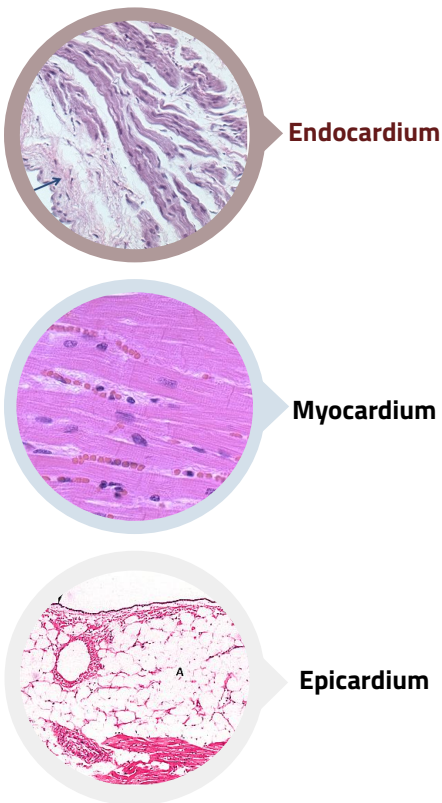
	Mechanism	P.K.	Indication	Side effects
Atenolol	Selective β1 antagonist	Hydrophilic; can't cross BBB	Hypertension Arrhythmia Myocardial infarction	1. Bradycardia 2. Generally safe in diabetics, do not interfere with glycogenolysis
Metoprolol		Lipophilic; can cross BBB	Hypertension CHF Myocardial infarction	
Esmolol		Hydrophilic; can't cross BBB	Arrhythmia	
Carvedilol	Mixed α- & β-receptor antagonist	Lipophilic; can cross BBB	CHF	1. Bronchoconstriction and exacerbate asthma and COPD 2. Bradycardia 3. Hypo- or Hype - glycemia; dangerous for diabetics 4. Orthostatic hypotension
Labetalol		Lipophilic; can cross BBB	Hypertension in pregnancy Hypertensive emergency	

Heart Failure

Cardiac Contractility

Layers of the heart	
Endocardium	It's the innermost layer,it lines the chambers of the heart **Histologically:** Composed of simple squamous epithelium, the endothelium and a thin layer of connective tissue
Myocardium	It is a thick muscular layer that lies in the middle, composed of contractile cardiac muscle cells (myocytes) responsible for pumping blood to the heart
Epicardium	It's the outermost layer also called visceral layer of serous pericardium **Histologically:** Simple squamous epithelium and its underlying connective tissue





Cardiac muscle :

Cardiac muscle is striated in appearance , rich in mitochondria muscles that is formed of actin and myosin forming sarcomere (functional unit of contractile cells). The cells are connected to each other by intercalated discs which appear as dark areas crossing the muscle fibers .Intercalated discs are cell membranes that separate cardiac muscle cells from one another . Intercalated disc kinds of membrane junctions include Gap junctions and Desmosomes.

Cardiac contractile filament contains:

1- Thick filament (myosin):contain 2 heads having ATPase activity

2- Thin filaments (actin,troponin,tropomyosin)

Cardiac muscle contraction is the force applied to the heart for a given fiber length that is responsible for pumping blood (from heart to blood vessels) to distribute oxygen and nutrients while removing wastes from tissues. The muscle contraction is regulated by Ca++, as it affects the power of contraction of the muscle (it causes Ca++ induced Ca++ release ;discussed more later on)

Types of cardiac cells	
Contractile cells	It represents 99% of cardiac muscle cells and responsible for mechanical work of pumping (rich in mitochondria). Its functional unit is sarcomere , fibers are connected to one another at intercalated Discs by 2 membrane junctions: gap junction and desmosomes (this allows the heart to work as a **functional syncytium**)
Conducting cells	Specialized conduction cells that send impulses (rhythmical electrical impulse) rapidly through the heart in a specific pathway(SA node, Internodal pathway ,AV node, Bundle of His ,,left and right bundle branches, purkinje fiber) they have 3 properties: • self-stimulating(automaticity) and rhythmicity • conductivity • excitability

Cardiac Action Potential

Types of action potential:

1- fast response (ventricular) AP

Occurs in the contractile cells (myocytes of the atria and ventricle) ,the bundle of his, and purkinje fibers,the duration of AP is 300-400ms .

Phase:

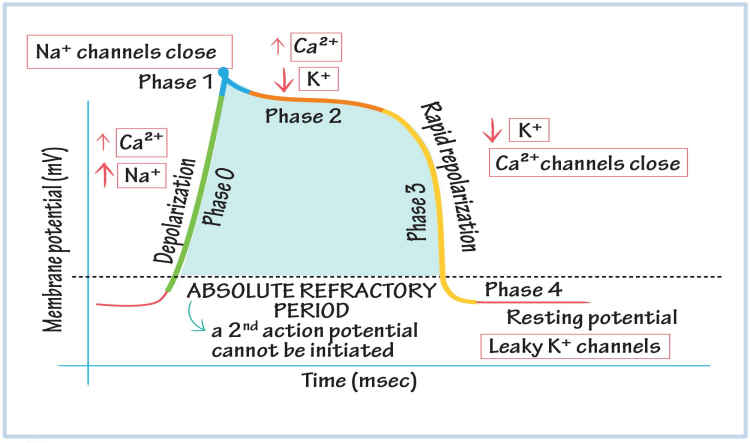
Phase 0: Rapid (upstroke) depolarization , caused by opening of voltage gated Na channels leading to rapid influx of Na into cells (magnitude=110 mv, from -90 to about 20)

Phase 1: Early rapid (initial) repolarization. Na channels close and voltage gated K channels begin to open. (5-10 mv)

Phase 2: Plateau, it is a flat portion of the curve. L-type Calcium channels opens and it causes slow Calcium influx that balances the K efflux (near 0 mv). In this phase calcium that enters triggers the release of intracellular calcium release from sarcoplasmic reticulum (calcium induced calcium) leading to myocardial contraction (explained more later on in excitation- contraction coupling)

Phase 3: Repolarization ,due to closure of Ca channels and opening of slow K channels with a sudden increase in K efflux .

Phase 4: Complete repolarization (resting potential) ,Na-K pump works to derive excessNa out of the cell and excess K into the cell .(membrane goes back into resting level -90mv)



2- Short response (pacemaker) AP

Occurs in conductive cells (in SA node and AV node)

Phases:

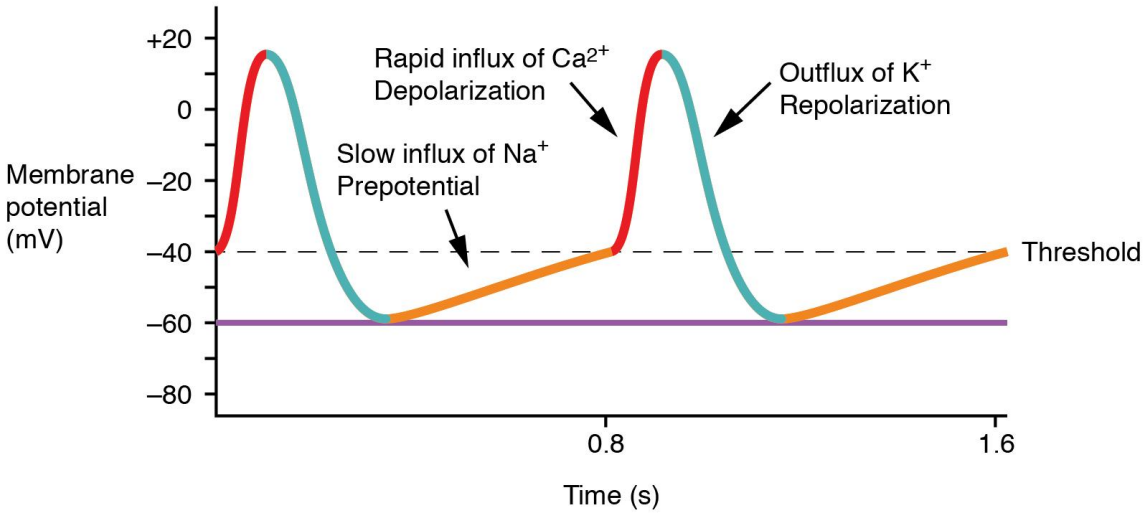
Phase 0: upstroke (slower and deeper than fast-response AP)and depolarization. Mostly due to voltage gated T-type Ca++ channels .Voltage-gated Na channels opens but it's less active in pacemaker due to it has negative resting membrane potential than in the ventricular cells (this decreases membrane potential from -60 to -40 mv)

Phase 1: not present

Phase 2: not present (no plateau)

Phase 3: repolarization. voltage -gated Ca++ channel closes and increase in K efflux .

Phase 4: slow diastolic depolarization. Increase Na influx through I(f)"funny" Na+ channels, this happens due to automaticity of SA node and AV node.



Role of Ca++ in regulation of cardiac muscle function

Calcium plays an important role in regulation of contraction.Sarcolemma has specialized voltage-gated (Ca++)channels that skeletal muscle does not have; This helps in forming phase 2 (plateau) of action potential in contractile cardiac muscle fiber. **Causes of plateau :**

1- opening of slow Ca++ channels

They are voltage activated Ca++-Na channels (L-type Ca++ channels), slow Ca influx the prolong opening of the chanel allow large quantities of Ca to go into the cardiac muscle, causing plateau.

2 - decrease K+ outflux during the action potential plateau

This is caused by decrease permeability of cardiac muscle membrane for K

This prolongs the ventricular contraction in the cardiac muscle to let blood pass to the blood vessels and allow more time for relaxation.

Refractory period

Significance: to ensure the heart has enough time to fill during diastole, enough time for contraction and relaxation and to prevent tetany

3 refractory periods:

1- Absolute refractory period: cardiac muscle cannot be excited while it is contracting (no AP can be generated) .All Na gates are inactive

Occur during: depolarization -from phase 0(upstroke) to the end of phase 2 (plateau) .

Mechanically, it occupies whole period of systole

2 - Effective refractory period: AP can't be generated because not enough Na gate have yet recovered

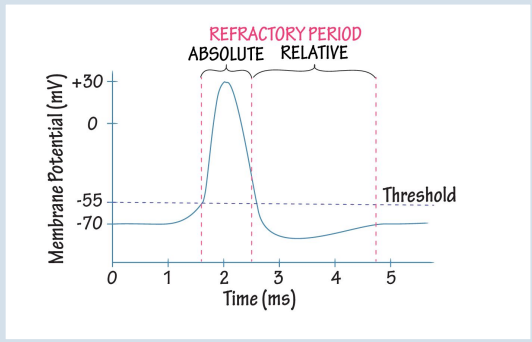
Occurs during: depolarization and the first 2/3 of repolarization (phase 0, 1, 2 and beginning of phase 3)

Mechanically, it occupies whole period of systole and beginning of diastole

3 - Relatively refractory period: As more Na channels are recovered, cardiac muscle can be excited by strong stimulus to produce a new systole called extrasystole. Starts at the end of absolute refractory period to the end of phase 3.

Occurs during: the last of repolarization (the rest of phase 3)

Mechanically, it occupies the middle of diastole.



Excitation-contraction coupling

It is the mechanism by which the action potential causes muscle contraction Contractile force is facilitated by generation of intracellular ca2+.In phase 2 of AP ,cardiac myocytes uses ca2+ influx through L-type ca++ channels which triggers more ca2+release from intracellular stores(ca induced ca release).

- AP (during plateau phase 2) travels though T tubule
- Extracellular Ca enters the cell through voltage gated Ca (L-type Ca) channel Ca binds to ryanodine receptors on the sarcoplasmic reticulum SR
- Due to conformational change this leads to Ca induced Ca release from SR
- Increase intracellular calcium will lead to binding of Ca++ to troponin C ; tropomyosin moves(to allow the interaction between myosin and actin)
- Myosin binds to actin causing cross bridge movement causing a reduction in sarcomere length
- Muscle contraction

Factors affecting cardiac contractility

Inotropic effect is the mechanism that affects the contractility of the heart and it can be either a positive or negative effect as illustrated below:

Positive inotropic effect (Factors increasing cardiac contractility)	Negative inotropic effect (Factors decreasing cardiac contractility)
• Sympathetic (increase catecholamines, caffeine, cocaine) • Increase calcium • Warming (ex:exercise) • Digoxin,Digitalis	• Parasympathetic (increase acetylcholine) • Hypoxia (decrease oxygen) • Decrease calcium • Cooling • Increase Adenosine • B-Blocker • Potassium ions

Cardiac Output and Regulation of Stroke Volume

Cardiac output (CO):

Is the volume of blood ejected by each ventricle in each minutes, ml/min.

Value	Around 5 liter in an average adult at rest.
Equation	CO = SV X HR, (CO is determined by SV & HR).
Measurement of CO	By Fick's principle: CO= Total O2 consumption/ Arterial O2 concentration - Venous O2 concentration

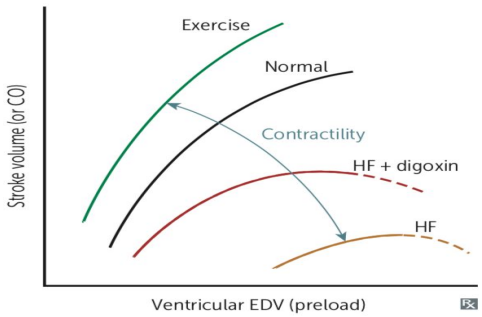
Stroke Volume (SV):

Is the volume of blood ejected by each ventricle per beat, ml/beat.

Value	Around 70 ml in an average adult at rest
Equation	SV= EDV - ESV

	End-Diastolic volume (EDV)	**End-Systolic volume (ESV)**
Definition	The volume of blood in the right/ left ventricle at the end of diastole	The volume of blood in the right/ left ventricle at the end of systole.
Value	=120 ml	= 50 ml
Affected by	EDV is affected by Preload (Venous return), which is affected by many factors. that will be discussed later	1. Cardiac contractility ↑ contractility → ↑SV → ↓ESV ↓ contractility → ↓SV → ↑ESV 2. The peripheral resistance (Afterload) ↑ in resistance (vasoconstriction) → ↓Flow ↓ SV → ↑ESV. ↓ in resistance (vasodilation) → ↑Flow ↑ SV → ↓ESV.

Cardiac Output and Regulation of Stroke Volume

Cardiac index	Is cardiac output per square meter of the body surface area CI=CO/m2 **Why is CI used?** Since CO vary with size, age and gender.
Cardiac reserve	It is the maximum percentage that the cardiac output can increase above normal. in the healthy young adult, the cardiac reserve is 300 to 400 percent. In athletically trained persons, it is 500 to 600 percent or more.
Preload	➔ It is the amount of blood that returns to the heart from veins. ➔ It **depends** on venous tone and circulating blood volume. ➔ ↑ in blood volume ↑ preload vice versa ➔ ↑ in venous tone ↑ preload vice versa.
Afterload	➔ It is the resistance against which the ventricles contract. ➔ If Aortic pressure ↑ Afterload in LV↑. ➔ If Pulmonary pressure ↑ Afterload in RV↑. ➔ Increases in: Aortic/pulmonary stenosis, Hypertension and Vasoconstriction.
Starling curve:	➔ Force of contraction is proportional to end- diastolic length of cardiac muscle fiber (preload). ➔ In other words, The greater the stretch of the cardiac muscle the greater would be the force of contraction. ➔ If VR↑ → EDV↑ → SV↑ vice versa ➔ If Afterload ↑ → ESV↑ → SV↓ vice versa 

Venous Return

Function of the veins :

Nearly 60% of the total volume of blood in the body is within the veins. "Reservoir" is what we call those veins, as it can be transferred to support cardiac output(1).

Measurement of central venous pressure (CVP) :

By inserting a catheter into either the subclavian or internal jugular veins The central venous pressure can be measured. The central venous pressure is monitored using a pressure transducer or amplifier(2). It indicates mean right atrial pressure and is used as an approximation of right ventricular preload. The CVP does not measure blood volume directly, although it is often used to estimate it(3).

Determinants of venous return :

The main factors to determine the venous return to the heart are:

- The degree of filling of the circulation.
- The ability of the heart to maintain a low right atrial pressure.
- The resistance to blood flow between the peripheral vessels and the right atrium(4).

Mean systemic filling pressure :

Mean systemic filling pressure (MSFP) is the pressure that would be measured at all points in the whole circulatory system if the heart were stopped suddenly and the blood were redistributed instantaneously in such a manner that all pressures were equal. it's about 7-8 mmHg (5)

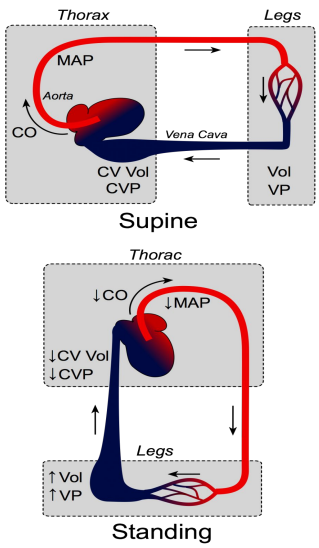
Mean systemic pressure increases if there is an increase in blood volume or if there is a decrease in venous compliance (where blood is shifted from the veins to the arteries). a shift of the vascular function curve to the right reflects An increase in mean systemic pressure(6).

The effect of gravity on venous pressure :

When a person stands up, baroreceptor reflexes are instantaneously activated to restore arterial pressure so that mean arterial pressure normally is not reduced by more than a few mmHg when a person is standing compared to lying down. However, in order to keep this normal mean arterial pressure, the person who is standing upright has higher systemic vascular resistance, lower venous compliance, lower stroke volume (due to decreased preload), and increased heart rate (baroreceptor-mediated tachycardia). Patients with autonomic nerve dysfunction or hypovolemia will not be able to utilize these compensatory mechanisms and therefore will be manifesting with orthostatic hypotension (7).

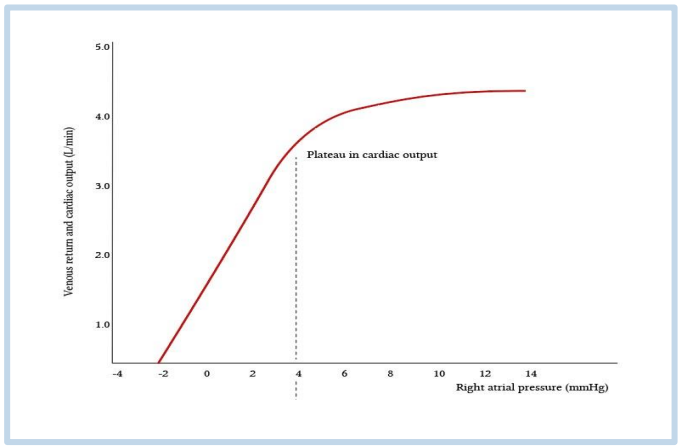
Pathophysiology of varicose veins :

The pathophysiology of varicose veins is related to congenital or acquired abnormalities of the deep venous system, venous valves, and/or fascial or vein wall weakness. Increased deep venous pressure may be both proximal and distal in etiology, arising from arteriovenous anastomoses, incompetent communicating veins, or venous obstruction. Primary valvular incompetence arises from venous obstruction (thrombosis), thrombophlebitis, or valvular agenesis. Secondary valvular incompetence occurs from deep venous obstruction or increased venous distensibility (usually secondary to circulating estrogens). Finally, fascial weakness of the vein wall or supporting fascia gives a genetic basis for the pathophysiology of varicose veins (8)

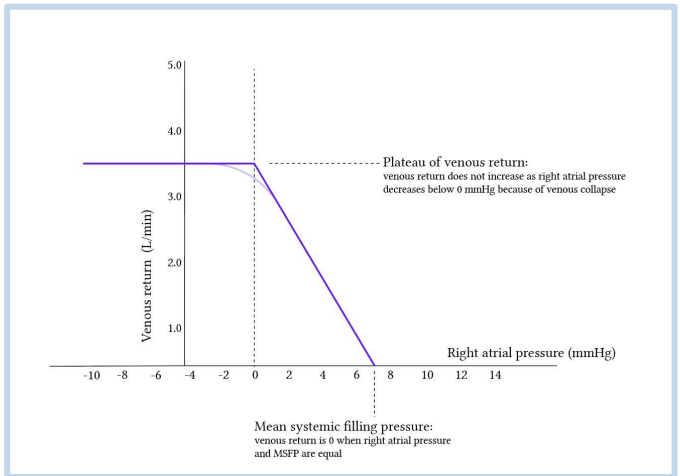


Vascular and cardiac function curves under physiological and pathophysiological conditions

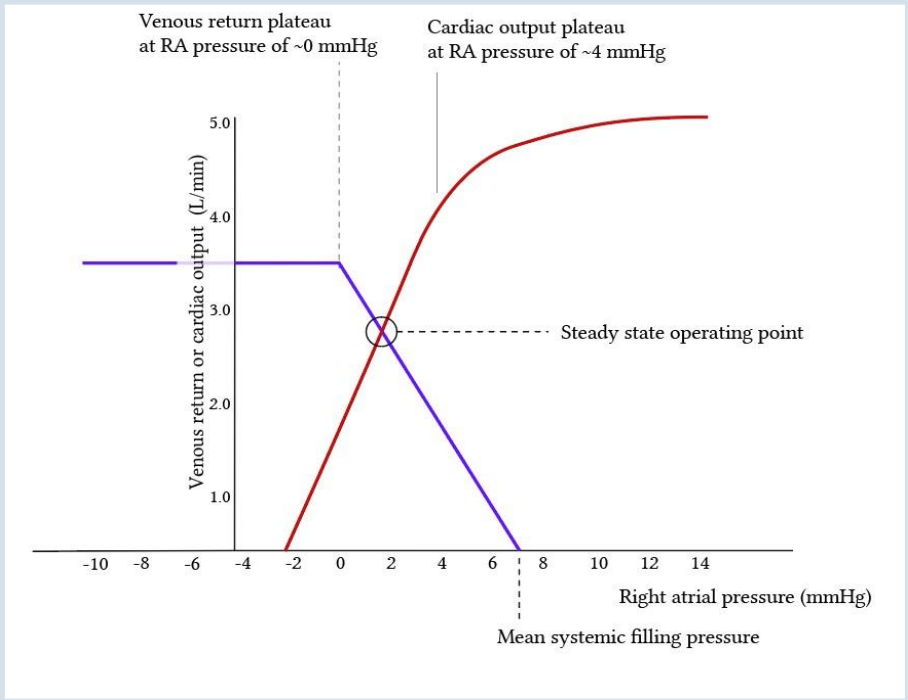
- The cardiac and vascular function curves describe the cardiac response to preload and the venous response to cardiac output as two interdependent functions.
- The cardiac function curve is cardiac output as a function of right atrial pressure.(9)
    - As contractility increases, the curve shifts up
    - A plateau is seen with higher Right Atrial pressures



- The vascular function curve is venous return as a function of right atrial pressure.
    - Crosses the x-axis at the mean systemic filling pressure
    - A plateau is seen with right atrial pressure below 0 mmHg.



- The curves intersect at the steady-state operating point where cardiac output and venous return are equal.
- Changes to the operating conditions of the cardiovascular system can change the position of this equilibrium point in a predictable manner:
    - An increase in preload (volume, MSFP) increases cardiac output, up to a maximum (plateau) permitted by contractility and heart rate, and is associated with an increase in the right atrial pressure.
    - An increase in contractility increases the cardiac output at any given volume/MSFP, and is associated with a decrease in right atrial pressure
    - An increase in peripheral vascular resistance sequesters blood in the arterial circulation, decreases the venous return and decreases cardiac output .



Jugular Venous Pressure

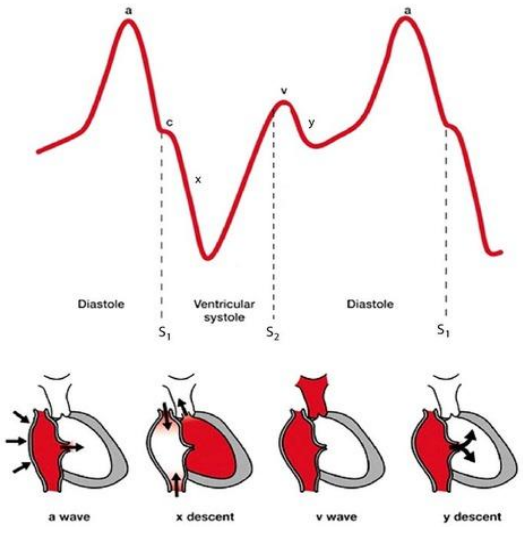
Identify the jugular venous pressure :

The jugular venous pressure (AKA: jugular venous pulse) is the indirectly visualized pressure over the venous system via observing the internal jugular vein (10). It is determined as the vertical distance above the midpoint of the right atrium, is 6 to 8 cm H2O (11)

The Normal pattern of the jugular venous pressure :

It has has a biphasic waveform:

- The a wave corresponds to right atrial contraction and ends synchronously with the carotid artery pulse. The peak of the 'a' wave demarcates the end of atrial systole.
- The x descent follows the 'a' wave and corresponds to atrial relaxation and rapid atrial filling due to low pressure.
- The c wave corresponds to right ventricular contraction causing the tricuspid valve to bulge towards the right atrium during RV isovolumetric contraction.
- The x' descent follows the 'c' wave and occurs as a result of the right ventricle pulling the tricuspid valve downward during ventricular systole (ventricular ejection/atrial relaxation). (As stroke volume is ejected, the ventricle takes up less space in the pericardium, allowing relaxed atrium to enlarge). The x' (x prime) descent can be used as a measure of right ventricle contractility(10)



- The v wave corresponds to venous filling when the tricuspid valve is closed and venous pressure increases from venous return – this occurs during and following the carotid pulse.
- The y descent corresponds to the rapid emptying of the atrium into the ventricle following the opening of the tricuspid valve .

The abnormalities of jugular venous pulse :

Many abnormalities of the cardiovascular system could be reflected and seen through the jugular pulse, here are some examples:

JVP

1-Raised JVP with a normal waveform indicates:

- Bradycardia - Fluid overload - Heart Failure

2-Raised JVP with a absent pulsations indicates:

- Superior Vena Cava Syndrome

a Wave

1-Large 'a' wave (increased atrial contraction pressure) seen with:

- Tricuspid stenosis
- Right heart failure
- Pulmonary hypertension

2-Cannon 'a' wave (atria contracting against closed tricuspid valve), seen with:

- Atrial flutter
- Premature atrial rhythm (or tachycardia)
- 3rd degree heart block
- Ventricular ectopics
- Ventricular tachycardia

Examination of the internal venous pressure :

1. Get the patient to relax, and raise the bed.
2. Take the pillow away.
3. If the room has a good light you don't have to shine a light against the neck.
4. Make your priority to just see a pulsation, and then decide if it is arterial or venous by applying the following criteria to identify venous waves:
    a. Venous wave is bifid, flicking like a snake's tongue.
    b. It rises when you lower the head of the bed and sinks when you raise the head of the bed.
    c. It changes with respiration, sinking into the chest with inspiration.
    d. It is not palpable.
        i. It is fine to use the external jugular vein, as long as you can see clear wave forms in it.
    e. Commonly, a prominent pulsation is mistaken for that of the carotid artery rather than of the JVP. To differentiate, press on the RUQ while watching the neck. The JVP should rise in all individuals with this maneuver; whereas a carotid pulsation should not change.
5. The JVP can be assessed on either the right or left. On occasion (musculoskeletal anatomy, venous clots) the pulsations can only be visualized on one side. If you cannot clearly define the JVP on the right internal jugular, examine the left.
6. If you cannot determine the JVP, report the exam as "JVP not visualized" rather than "no JVD" (which implies that the JVP was visualized and is not elevated).

Once you have determined that you are seeing the venous waves then measure the jugular venous pressure:

1. Identify JVP at the highest point of pulsation
2. Extend card or ruler horizontally from highest pulsation point , cross with ruler placed on the sternal angle (Angle of Louis), (let's say it was 8cm).
3. Add 5 cm (to get to the center of the atrium) and then report the JVP as "the jugular venous pressure was 13 cm of water" (not mercury)

Very helpful video!

Therapy Of Heart Failure

Drug class	Mechanism of action	Clinical uses	ADRs
ACEI (captopril, lisinopril) **ARBS** (losartan)	Block production of angiotensin II by inhibiting converging of angiotensin I to angiotensin II Resulting in ↓ aldosterone, vasodilation, ↓SVR ↓Na and water reabsorption.	• Mild-to-moderate hypertension • Protective of diabetic nephropathy • Renal disease. • CHF	• Dry cough (ACEIs) • Hyperkalemia • Proteinuria • Taste change • Angioedema • Hypotension • Rash • Contraindicated in pregnancy (because of fetal renal problems)
B-blockers (Metoprolol, carvedilol)	Reduces HR and cardiac contractility -> reduction in oxygen demand.	Used in angina of effort Used as first-line hypertension treatment for selected patients	• Bradycardia • AV block • Fatigue • Sexual dysfunction • ↑ LDLs and TGs **Take care when using in use:** • Asthma • Vasospastic disorders • Diabetics • Contraindicated in vasospastic angina

Therapy Of Heart Failure

Diuretics				
Drug class	**Mechanism of action**	**Clinical uses**	**ADRs**	**Drug interactions**
Loop Diuretics (furosemide, torsemide, and ethacrynic acid)	Inhibition of Na+/K+/2Cl– transporter in the ascending limb of Henle in ->↓ in renal vascular resistance, increase in blood and marked diuresis. As well as: – ↑ Ca2+ excretion. – ↓ intracellular K+ in TAL – ↓ back diffusion of K+ – ↓ positive potential – ↓ reabsorption of Ca2+ and Mg2+	• Diuretics • Pulmonary edema • Heart failure • Hypertension • Refractory edemas • Hypercalcemic states	• Hypersensitivity (furosemide) • Hypokalemia and alkalosis. • Hypercalciuria • Hypocalcemia • Dehydration • Ototoxicity	Aminoglycosides (enhanced ototoxicity) • Lithium (in chronic administration, it will result in decreased clearance) • Digoxin (↑ toxicity caused by electrolyte disturbances)
Thiazides (hydrochlorothiazide, chlorthalidone, and indapamide)	Mechanism: inhibits Na+/Cl– transporter, resulting in: – ↑ Na+ and Cl– excretion in DCT – ↑ diuresis As well as ↑ in Ca2 + reabsorption.	-Hypertension -CHF – Nephrolithiasis (calcium stones) – Nephrogenic diabetes insipidus -Idiopathic calciuria	– Sulfonamide hypersensitivity – Hypokalemia and alkalosis – Hypercalcemia – Hyperglycemia – Hyperlipidemia	– Digoxin (increased toxicity secondary to electrolyte disturbances)

Therapy Of Heart Failure

Diuretics				
Drug class	**Mechanism of action**	**Clinical uses**	**ADRs**	**Drug interactions**
K+-Sparing Agents (Spironolactone)	Indirect inhibition on Na+ reabsorption by competitive antagonist effect on aldosterone receptors.	• Hyperaldosterone state • Combined with loop diuretic • CHF	• Hyperkalemia and acidosis • Gynecomastia	Combining K+-sparing diuretics with ACEIs or ARBs may cause hyperkalemia.
K+-Sparing Agent (Amiloride and triamterene)	blockade of Na+ channels present in collecting tubules	• Combined with loop diuretic • Lithium-induced nephrogenic diabetes insipidus (amiloride)	Hyperkalemia and acidosis	-

Therapy Of Heart Failure

Drug class	Mechanism of action	Clinical uses	ADRs	Drug interactions
Sympathomimetics: (Dobutamine and Dopamine)	↑ cardiac contractility ->↑ cardiac output.	CHF only	-	-
Phosphodiesterase Inhibitors: (Inamrinone and Milrinone)	Increase cAMP in heart and smooth muscles -> in ↑ inotropy-> ↑ Cardiac output.	CHF only	-	-
Cardiac Glycosides (E.g. Digoxin)	<u>Direct effect:</u> -Inhibition of cardiac Na +-K+ ATPase, resulting in ↑ intracellular Na+. – Decreases activity of Na+/Ca 2+ exchanger , leading to increase Ca2+ intracellularly –The Increases in intracellular Ca2+ improves heart contractility, leading to increase in cardiac output. – Increases actin-myosin interaction – Increases contractile force <u>Indirect effect:</u> Inhibition of Na+-K+ ATPase in neurons (leading to increase in vagal activity)	- CHF supraventricular tachycardias - Atrial fibrillation	**Early signs:** anorexia, nausea, ECG changes **Later signs:** disorientation, visual effects (blurry yellow vision). **Toxic doses:** Arrhythmias, **Management of toxicity:** use of Fab antibodies and supportive therapy.	Diuretics: ↓ K+, ↓ Mg2+, ↑ Ca2+ Quinidine and verapamil

Heart Failure

A patient with heart failure may present with symptoms of left ventricular heart failure, right ventricular heart failure, or a mix of both.

	Left ventricular heart failure	Right ventricular heart failure
History/ Symptoms	The patient will come complaining of dyspnea, orthopnea, or Paroxysmal Nocturnal Dyspnea (PND).	The patient will come complaining of swelling (lower limb) and fatigue.
Clinical Examination	General examination: • Tachycardia • Pulsus alternans (alternating strong and weak beats) • Positive abdominojugular reflux • Pulmonary congestion (basal inspiratory crackles) • Pulmonary edema causing: crackles and wheezes throughout the lung + central cyanosis • Peripheral cyanosis	General examination: • High JVP (Kussmaul's sign) • Peripheral cyanosis • Hepatomegaly • Positive abdominojugular reflux • Pitting ankle and sacral edema • Ascites
	Palpation: Displaced apex beat.	Palpation: Parasternal heave.
	Auscultation: S3 gallop (apex)	Auscultation: S3 gallop (left lower sternal edge)
		

Heart Failure

New York Heart Association (NYHA) classification:

It's used to grade the severity of functional limitations in a patient with heart failure.

Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea.
II	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea. Comfortable at rest.
III	Marked limitation of physical activity. Less than ordinary activity causes fatigue, palpitation, or dyspnea. Comfortable at rest.
IIII	Unable to carry on any physical activity without discomfort. If any physical activity is undertaken, discomfort increases. Symptoms of heart failure at rest.

Arrhythmia

Cardiac activity

To generate an electrical signal that can regularly contract the atria and ventricles, the heart contains two populations of cells: **conducting** and **contractile cells.** Conducting (nodal) myocytes form the specialized conduction pathway of the heart (SA node, AV node, bundle of His, bundle branches, Purkinje fibers) they have the ability to spontaneously generate action potentials (APs). APs travel along the normal conduction pathway to stimulate surrounding contractile myocytes via electrical gap junctions to contract and generate enough force to pump blood into the circulation.o generate an electrical signal that can regularly contract the atria and ventricles, the heart contains two populations of cells: conducting and contractile cells. Conducting (nodal) myocytes form the specialized conduction pathway of the heart (SA node, AV node, bundle of His, bundle branches, Purkinje fibers) they have the ability to spontaneously generate action potentials (APs). APs travel along the normal conduction pathway to stimulate surrounding contractile myocytes via electrical gap junctions to contract and generate enough force to pump blood into the circulation.

Resting Membrane Potential

By convention, the resting membrane potential of a cell is measured in mV relative to the extracellular space. Excitable cells, like cardiac myocytes have resting membrane potentials between –70 and –90 mV. At rest, the membrane conductance is higher for K+ than it is for the other major ions (Na+ or Ca2+). This explains why the resting membrane potential is close to the equilibrium potential for K+ (a function of the intracellular ([K+]i) and extracellular ([K+]e) potassium concentration gradient). conducting myocytes (eg, SA and AV node) have a less-negative resting potential because of a higher conductance to Ca2+ and Na+ at less-negative voltages due to spontaneous depolarization. In contrast to K+, since the [Na+] is higher in the extracellular space, Na+ tends to enter the cell and make the membrane potential more positive. The Na+-K+-ATPase pump maintains the ionic gradient across the cell membrane by pumping 3 Na+ out for every 2 K+ pumped in. This maintains the resting Na+ and K+ intracellular and extracellular concentration gradients.

Cardiac activity

Cardiac pacemaker:

Myocytes in the SA node, AV node, bundle of His, and Purkinje system all have the capacity to act as pacemakers of the heart, and each has different intrinsic firing rates (automaticity):
SA node: 60–100 bpm , AV node and proximal bundle of His: 50–60 bpm , Purkinje cells: 30–40 bpm The myocytes with the fastest intrinsic firing rates (ie, SA node) are the native pacemakers of the heart because they overdrive suppress the latent pacemakers (ie, AV node) bundle of His, Purkinje system) to maintain a regular rate and rhythm. If the SA node fails to fire, the next fastest pacemaker cells (ie, AV node) will take over and so on .

Refractory Period:

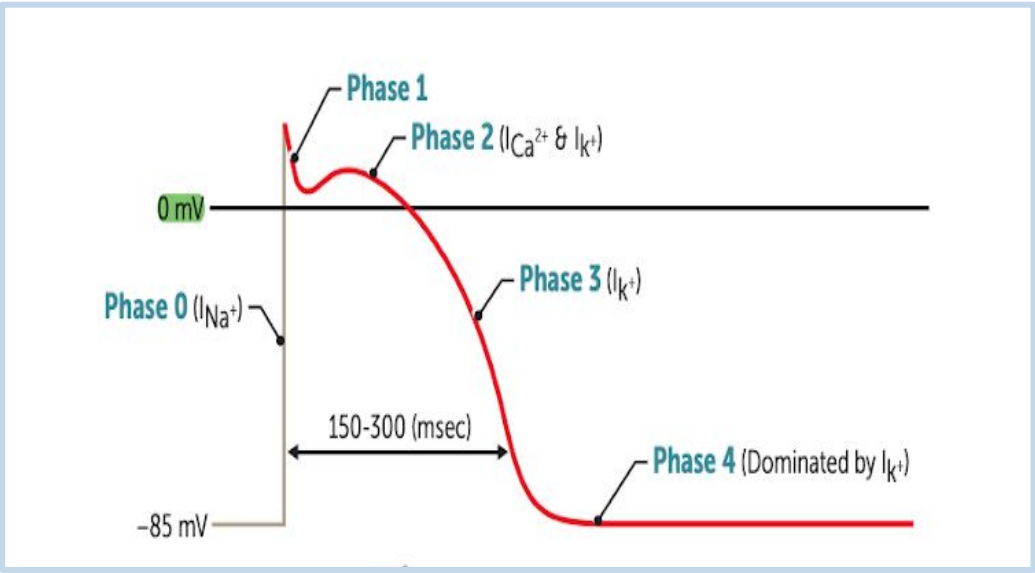
The duration of cardiac myocyte APs (150–300 msec) is longer than the duration of neuron and skeletal myocyte APs (1–2 msec). Since duration of an AP is directly proportional to duration of its refractory period, The underlying basis of the refractory period is closure of Na+ channel inactivation gates

Absolute: Begins at phase 0 (upstroke) to the end of phase 2 (plateau). "Absolutely" no AP can be generated, regardless of amount of inward current, because nearly all Na+ inactivation gates are closed. Effective: Begins at phase 0 (upstroke) to the beginning of phase 3 (start of repolarization). An "effective" AP (ie, an AP that can conduct to neighboring cells) cannot be generated because not enough Na+ inactivation gates have yet recovered. Relative: Begins at end of absolute refractory period to approximately end of phase 3 (repolarization). Because more Na+ inactivation channels recover during this period, a "relatively" larger-than-normal stimulus is able to generate a second AP.

Cardiac activity

Cardiac Action Potentials:

Fast-response APs occur in the atrial and ventricular myocytes, the bundle of His, and Purkinje fibers. Phase 0: Rapid upstroke and depolarization. Voltage-gated Na+ channels open. Phase 1: Initial repolarization. Inactivation of voltage-gated Na+ channels. Voltage gated K+ channels begin to open. Phase 2: Plateau. Ca2+ influx through voltage-gated L-type Ca2+ channels balances K+ efflux. Ca2+ influx triggers Ca2+ release of intracellular Ca2+ from sarcoplasmic reticulum and myocyte contraction. Phase 3: Repolarization. Massive K+ efflux due to opening of voltage-gated slow K+ channels and closure of voltage-gated Ca2+ channels (via calcium-dependent inactivation). Phase 4: Resting potential. High K+ permeability through K+ channels.



First Aid organ system (14 -19)

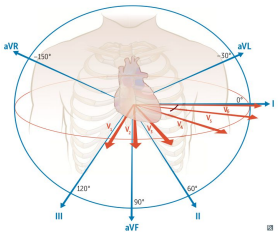
Electrocardiogram

Electrocardiogram Leads

In a standard 12-leads, 12 electrodes rested on chest wall and limbs:

(always positive pole of a lead correspond the view on ECG the the same lead)

6 limb leads: create electrical axes in the frontal plane



two categories:

- 3 bipolar limb leads: "bipolar" means connection between two electrode. They are : Lead I, II,III.
- 3 Augmented unipolar limb leads: Two limbs connected to negative terminal and the third limb is connected to the positive terminal. There are: aVR lead (positive terminal on Right arm), aVL lead (Left arm) and aVF lead(left leg "Foot").

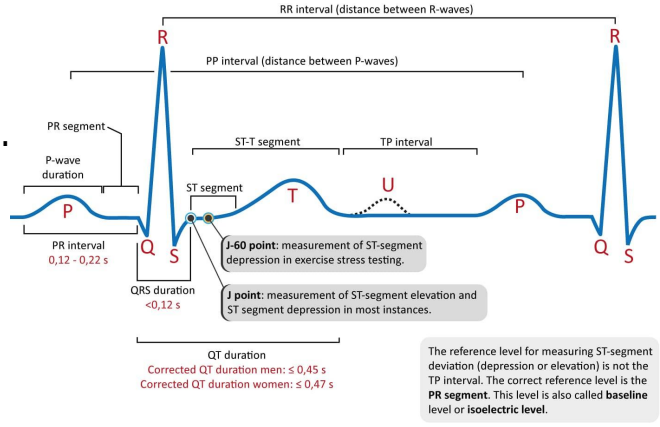
6 chest leads: create electrical axes in the horizontal(transverse) plane.

ECG represent each cardiac cycle by:

1- Three waves:

- P wave: Atrial depolarization
- QRS complex: ventricular depolarization + atrial repolarization.

  (reflect the net electrical vector).
- T wave: ventricular repolarization.



Electrocardiogram

2- Three intervals : (all have clinical significance)

- PR interval.
- QT interval: represents ventricular depolarization, contraction of the ventricles and ventricular repolarization.
- RR intervals

3- Segments: (include only ECG baseline):

- PR segment:correspond to conduction delay in the AV node.
- ST segment: when ventricles still-depolarized. (time between ventricular depolarization and repolarization)

Reading ECG

ECG graph:

X-axis is Time (one small box= 0.04 sec, one big box= 0.2 sec)

Y-axis is electrical potential (one small box= 0.1 mV, one big box= 0.5 mV).

Four rules of ECG

1. Action potential (depolarization) toward a positive pole of a lead represented as upward deflection on ECG.
2. Action potential (depolarization) toward a negative pole of a lead represented as upward deflection on ECG.
3. The extent of deflection is corresponding to how parallel the net electrical vector is to the electrode measuring it.
4. A net electrical vector represented as a baseline in any electrode perpendicular (vertical) to it.

A. Heart Rhythm:

Steady rhythm if the R waves occur regularly, in other word if the RR intervals is almost the same length; if not therefore it's unsteady rhythm.

Cardiac Arrhythmia

Pacemaker Action Potential

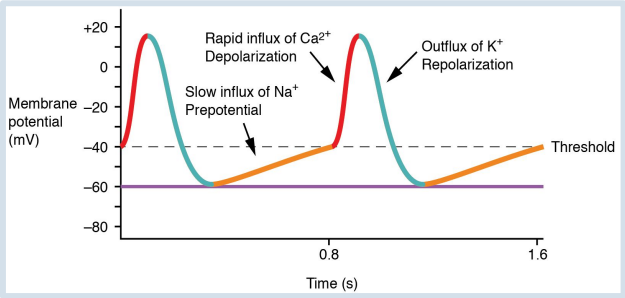
The heart has a spontaneous electrical activity. This spontaneous activity is achieved by having a special kind of cells termed "pacemaker cells".

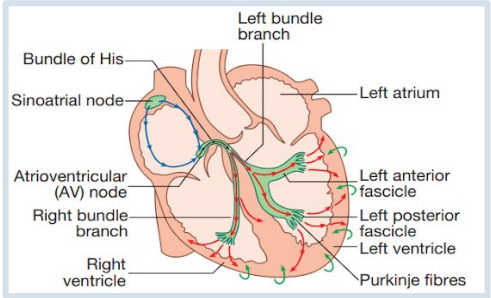
Pacemaker Action Potential: Pacemaker cells have a false resting membrane potential (RMP) which allow the slow entry of sodium ions, thereby gradually increasing the membrane potential.

- Slow depolarization **(Phase 4):** The slow entry of Na+ ions and decreased efflux of K+ serves to increase the RMP to the threshold required to open voltage-gated Ca++ channels.
- Depolarization **(Phase 0)**: is achieved when the RMP reaches a certain threshold that allows the opening of voltage-gated Ca++ channels, this leads to the generation of an action potential that propagates to other cells.
- Repolarization **(Phase 3):** Closure of voltage-gated Ca++ channels and opening of K+ channels.

Cardiac Conduction System

- **SA node:** Located in the junction of SVC and the right atrium. Made of specialized cardiac cells that depolarize spontaneously **(automaticity)**, however its rate of depolarization is influenced by the autonomic nervous system (60-100 beats per minute or BPM at rest).
- **AV node:** Impulses travel through atrial myocytes to the AV node, located in the interatrial septum (posteroinferior part), which normally delays conduction to allow atrial contraction and emptying of blood into the ventricles. Its activity is also influenced by the autonomic nervous system.
- **Bundle of His → Right and left branches** (left branch divides into anterior and posterior fasciculus) → **Purkinje fibers** in the walls of the ventricles, sweeping the ventricles to allow full contraction.



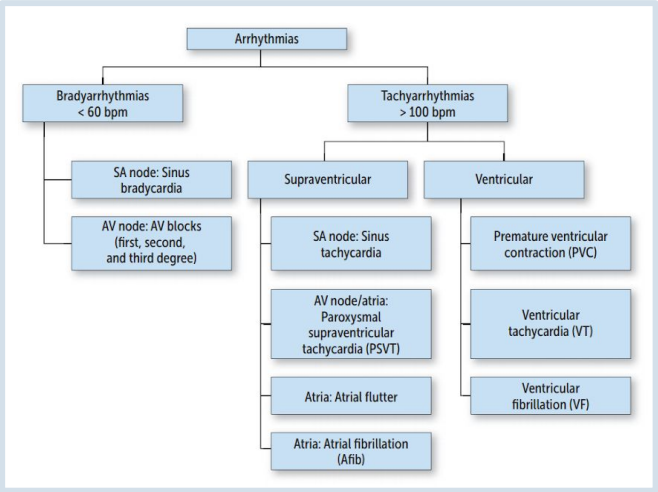


Cardiac Arrhythmia

Types of Cardiac Arrhythmia

Arrhythmias comprises conditions with cardiac conduction abnormalities.

- This can involve signal generation, conduction or both.
- They are often named based on the origin of the impulsis (e.g. supraventricular, ventricular arrhythmias).
- Based on the heart rate, arrhythmias are further divided into bradyarrhythmias (<60 bpm) and tachyarrhythmias (>100 bpm).



Bradyarrhythmias

HR <60, either SA node in origin (Sinus bradycardia) or AV node (AV node block).

Sinus Bradycardia

Clinical Findings & Symptoms: Common in healthy people especially athletes

ECG: Normal P wave and QRS complex with a HR of <60 bpm.

Treatment: Asymptomatic cases require no treatment. Symptomatic cases can be treated with atropine. Persistent cases require pacemaker implantation.

Pathophysiology: Decreased SA node automaticity, either physiologically (sleep), due to some medications (Beta blockers) or pathologically (hypothyroidism).

Cardiac Arrhythmia

Atrioventricular Block

Due to a disease affecting the AV node or the use of some medications.

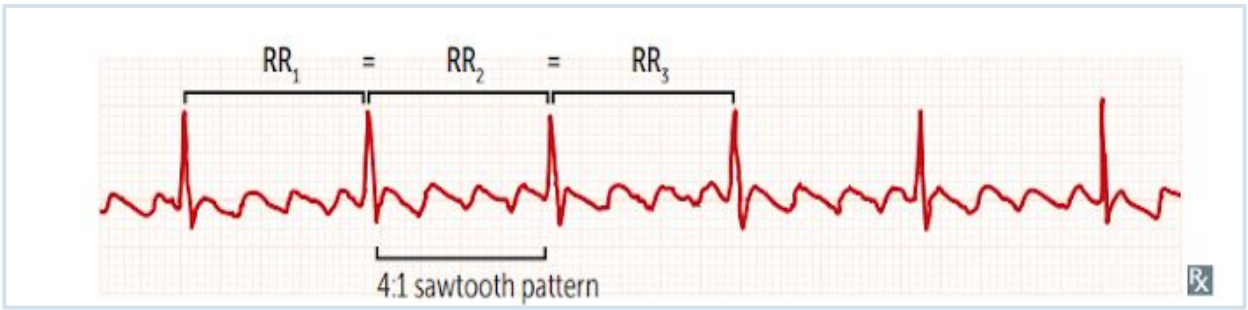
- **First-Degree AV Block**
  Clinical Findings & Symptoms: Generally asymptomatic.
  ECG: PR interval is prolonged (>0.20 seconds), no dropped heartbeats (each P wave is followed by a QRS complex).
  Treatment: No treatment required.
  Pathophysiology: Decreased conduction through the AV node due to degenerative changes of aging, medications (muscarinic drugs), or some diseases (amyloidosis)

- **Second-Degree AV Block**
  Clinical Findings & Symptoms: Often asymptomatic. Symptomatic episodes include bradycardia, syncope or near-syncope.
  ECG: (1) PR interval is variably prolonged (>0.20 seconds) in Mobitz Type I,
  (2) but is constant in Type II, wide QRS complexes due to ischemic tissues are more often encountered in Type II.
  Treatment:
  (1) Mobitz Type II should always be treated either with atropine, isoprenaline or a pacemaker because it can progress to Third-Degree AV Block.
  (2) Mobitz Type I is usually treated when symptomatic.
  Pathophysiology:
  1- Mobitz Type I (Wenckebach), results when PR interval increases to the point of allowing enough time for the SA node to discharge again, resulting in an occasional two successive P waves before a QRS wave (P wave not followed by QRS).
  Causes are usually physiological or ischemic conditions of AV node (supplied by AV nodal branch of the right coronary artery in 90% of cases, 10% from left circumflex artery). Rarely progresses to 3rd Degree AV Block.
  2- Mobitz Type II (Hay) in these cases, conduction through the AV node is normal with normal PR interval, but the abnormality results due to impaired conduction through bundle of His or its branches, resulting in some dropped beats.
  Usually results from ischemic conditions such as MI. Carries greater risk of 3rd Degree AV Block.

- **Third-Degree AV Block**
  Clinical Findings & Symptoms: Bradycardia can result in syncope and altered mental status.
  ECG: P wave and QRS occurring independently of one another. With more frequent P waves than QRS complexes.
  Treatment: Atropine, isoprenaline or a pacemaker. Avoid drugs that slow AV conduction such as digoxin, calcium channel blockers and adenosine.
  Pathophysiology: Failure of impulses to reach the ventricles (complete block), resulting in escape pacemaker activity generated in AV node or His-Purkinje system.
  1. Results in AV dissociation
  2. Most common causes in adults is MI and ageing. Rare causes include infections like Lyme disease.
  3. Hyperkalemia can also reduce myocyte excitability leading to AV block.

Stokes–Adams Attacks

- These are attacks that can complicate Type II Mobitz 2nd-Degree AV block or 3rd-Degree heart block.
- Characterized by syncope, seizure, pallor and a death-like appearance.
- Unlike epilepsy the recovery is rapid and there is a characteristic flushing following the attack.
- Caused by asystole (absence of ventricular contractions)



Cardiac Arrhythmia

Tachyarrhythmias

HR >100, either supraventricular or ventricular in origin.

- **Supraventricular Arrhythmias**
  They originate above the ventricles thereby cause all parts of the ventricle to contract simultaneously.
  - Simultaneous ventricular contraction usually results in a narrow-width QRS complex (supraventricular arrhythmia with a bundle branch block is an exception, can have a wide QRS complex).
  - They are subdivided into SA and AV nodal arrhythmias.

- **Sinus Tachycardia**
  Clinical Findings & Symptoms: Palpitations
  ECG: Normal looking P and QRS complexes but with rates >100 bpm.
  Treatment: Treat underlying cause (hyperthyroidism, shock, fever).
  Pathophysiology: Increased SA node automaticity due to physiological states (pregnancy, exercise, emotional states), pathological states (hyperthyroidism) or drugs (sympathomimetics)

- **Atrioventricular Nodal Reentrant Tachycardia (AVNRT)**
  Clinical Findings & Symptoms: Palpitation, dyspnea and maybe polyuria.
  ECG: Retrograde P waves (via a reentry circuit) may be inverted or hidden.
  Treatment: IV adenosine and AV nodal blockers, vagal stimulation (valsalva maneuver and carotid massage).
  Pathophysiology: Individuals affected usually have a fast and slow pathway in the AV node, the signal first travels through the fast pathway to the ventricles, but after a while signals can travel in a retrograde manner from the slow pathway upwards through fast pathway towards the atrium, this phenomenon is called “re-entry”.

Cardiac Arrhythmia

- **Atrial Flutter**

  Clinical Findings & Symptoms: Palpitation
  ECG: Characteristic sawtooth appearance marking successive P waves.
  Treatment: Vagal stimulation, restoration of sinus rhythm through cardioversion, AV nodal blockers (class IA, class Ic antiarrhythmics)
  Pathophysiology: Re-entry circuit within the atrial tissue that travel in and a cycle and depolarize recently repolarized atrial tissue resulting in successive depolarization.

- **Atrial Fibrillation**

  Clinical Findings & Symptoms: Rapid atrial rhythm (350–600 bpm) which is "irregularly irregular," palpitations, and breathlessness. Might be asymptomatic.

  Can be classified as paroxysmal , persistent or permanent.
  ECG: Absence of P waves. The QRS complex is irregular. (In chronic atrial fibrillation the ventricular rate may be slower due to nodal fatigue)
  Treatment: Heart rate control, treatment of the underlying cause, anticoagulant therapy.
  Pathophysiology: Result from ectopic beats from pulmonary veins or diseased atrial tissues. Associated with atrial enlargement. Might be associated with thyrotoxicosis and alcoholism and most importantly hypertension.

Ventricular Arrhythmias

They originate in the ventricles (cardiac myocytes or the conduction system below the AV node).
Usually more life-threatening than supraventricular arrhythmias.

- **Ventricular Tachycardia**

  Sustained VT: Rhythm persists > 30 seconds, causes symptoms mentioned below and requires pharmacologic therapy.
  Nonsustained VT: Rhythm self-limited.
  Clinical Findings & Symptoms: Generally palpitations, dyspnea and dizziness.
  ECG: Broad QRS complexes (if only a single ectopic focus), HR 100-200 bpm. (Distinguished from supraventricular tachycardia by broad QRS complexes).

Cardiac Arrhythmia

- **Torsades de Pointes:** Polymorphic, rapid and irregular QRS complexes, complication of prolonged QT interval, the irregularity is caused by a QRS complex compounded on a T wave. Can be caused by congenital mutations in sodium and potassium channels.

  Treatment: It can progress to ventricular fibrillation, requires immediate treatment.
  - Hemodynamically unstable patients: Electrical cardioversion is the first-line.
  - Hemodynamically stable patients: IV amiodarone and lidocaine are antiarrhythmic options. IV magnesium is often given for torsade de pointes if hypomagnesemia is a suspected cause.

  ICD placement for patients with underlying cardiac disease.
  Pathophysiology: Usually occurs as complication of acute MI, coronary heart disease or myocardiopathy. caused by increased automaticity or activity in ischemic tissue.

- **Premature Ventricular Contraction**
  Clinical Findings & Symptoms: Palpitations or "skipped beat"
  ECG: They present as a premature widened QRS complexes with no association to any prior P wave.
  Treatment: Avoidance of PVC triggers such as caffeine and electrolyte repletion.
  Pathophysiology: PVCs usually arise from ectopic foci in the ventricle. In patients with cardiovascular diseases, re-entry and digoxin toxicity can also play role.

Cardiac Arrhythmia

- **Ventricular Fibrillation**

  Clinical Findings & Symptoms: Syncope, chest pain and shortness of breath. Patients may also be unconscious if episode is prolonged or severe.

  ECG: Rapid, irregular QRS complex with indiscernible waveforms.

  Treatment: Quick cardiac defibrillation then ICD to prevent future incidents

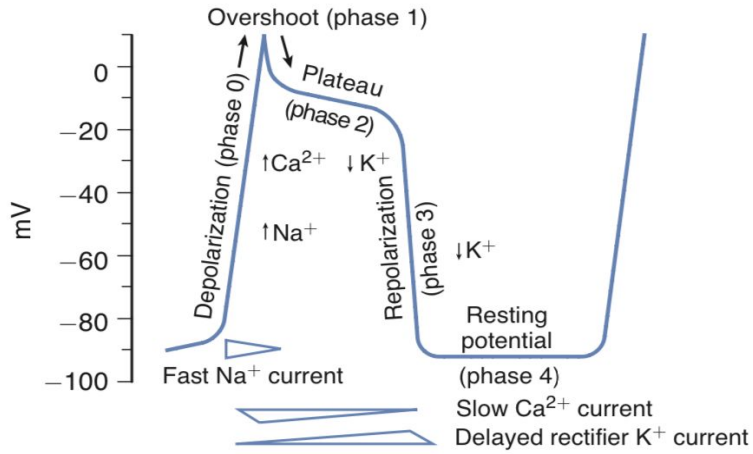
  Pathophysiology: VF mostly develops from sustained untreated ventricular tachycardia. However, it's rarely idiopathic.

  Bundle Branch Block

  - Occurs when a branch of the bundle of His is blocked due to damage.
  - Characterized by a wide QRS complex due to delayed and more prolonged depolarization.
  - Right BBB can occur in normal people, but left is usually associated with underlying heart disease.
  - Damage at this point (hemiblock) does not broaden the QRS complex but alters the mean direction of ventricular depolarisation (mean QRS axis), causing left axis deviation in left anterior hemiblock and right axis deviation in left posterior hemiblock

Antiarrhythmic Drugs

CARDIAC ACTION POTENTIAL



- **Phase 0** Na+ channels open: sodium enters the cell down its concentration gradient (fast INa), causing membrane depolarization. Rate of depolarization depends on number of Na + channels open, which in turn depends on resting membrane potential of the cell. Class I antiarrhythmic drugs can slow or block phase 0 in fast-response fibers
- **Phase 1** Na + channels are inactivated. In some His-Purkinje cells, transient outward K + currents and inward Cl– currents contribute to the "notch" and overshoot. Antiarrhythmic drugs have no significant effects on these transient currents.
- **Phase 2** Plateau phase in which a slow influx of Ca 2+ (ICa-L) is "balanced" by a late-appearing outward K + current (the delayed rectifier current IK). Antiarrhythmic drugs have no significant effects on these currents during this phase of the action potential (AP).
- **Phase 3** Repolarization phase in which the delayed rectifier K + current rapidly increases as the Ca 2+ current dies out because of time-dependent channel inactivation. Class III antiarrhythmic drugs slow this repolarization phase. Note that during phases 0 through 3 a slow Na + current ("window current") occurs, which can help prolong the duration of the action potential.
- **Phase 4** Return of membrane to resting potential—maintained by activity of the Na + /K + -ATPase.

Antiarrhythmic Drugs

Class 1: Na Channel blockers

Class 1A

Antiarrhythmic that block fast Na channels,prolongs repolarization by blocking K channel, increase the duration of action potential.

- **Quinidine**

Mechanism of action :muscarinic receptor blocker cause an increase heart rate and increase conduction through AV node , vasodilation and reflex tachycardia because of the alpha blocking effect.

Clinical use: atrial fibrillation

Administration: effective orally

Adverse effect : hypotension, syncope,prolongation of QRS and QT intervals which can lead to torsades de pointes.

Drug interaction: hypokalemia and hyperkalemia inducing drugs and digoxin.

- **Procainamide**

A less muscarinic receptor blocking

Adverse effect (ADRs): systemic lupus erythematosus like syndrome, hypotension , torsades de pointes.

Antiarrhythmic Drugs

Class 1B

Antiarrhythmic that block fast Na channels,blocking the Na current lead to a decrease the duration action potential.

- **Lidocaine**

Clinical uses : ventricular arrhythmia, surgeries eg. open heart surgery, following myocardial infarction.

Administration : IV because of the first pass metabolism

Adverse effect : CNS effect (suziurs-convulsion)

- **Mexiletine**

Clinical uses: ventricular arrhythmia

Administration: orally

Adverse effect(ADRs): CNS effect

Class 1C

Block fast Na channels,no effect in the duration of action potential.

- **Flecainide**

Clinical use: limited use because of high risk to develop proarrhythmia.

Adverse effect : proarrhythmia, heart failure.

Antiarrhythmic Drugs

Class 2: Beta blockers

Prevent activation of beta-receptor which lead to activation of cAMP, decrease SA and AV node activity.

Propranolol (nonselective) , **Esmolol** (cardioselective) given IV

Clinical use: prophylaxis post-MI,and supraventricular tachyarrhythmia.

Class 3: K channel blockers

slowing phase 3 (repolarization) of AP Increase the duration of action potential, and refractory period, especially in Purkinje and ventricular fibers.

Amideron

Mechanism of action: Mimics classes I, II, III, and IV Increase APD and ERP in all cardiac tissues.

Clinical uses: any arrhythmia

Pharmacokinetics: t1/2 >80 days Binds extensively to tissues (large Vd and multiple effects).

Averes effects : pulmonary fibrosis, blue pigmentation of the skin ("smurf skin"), phototoxicity, corneal deposits, hepatic necrosis, thyroid dysfunction.

Class 4:Ca channel Blockers

Slow cardiac Ca 2+ channels Decrease phase 0, decrease phase 4 decrease SA, decrease AV nodal activity blocker.

Verapamil and Diltiazem

Clinical use: supraventricular tachycardias eg. Atrial fibrillation

Adverse effect : constipation (verapamil), dizziness, flushing, hypotension, AV block.

Antiarrhythmic Drugs

Decreases SA and AV nodal activity

Clinical uses: paroxysmal supraventricular tachycardias and AV nodal arrhythmias

Administered IV: t1/2 <10 seconds

Adverse effects(ADRs): flushing, sedation, dyspnea Adenosine is antagonized by methylxanthines (theophylline and caffeine)

Clinical Coloration

Long QT Syndrome A familial condition associated with increased risk of ventricular arrhythmias may result from a mutation in the gene encoding cardiac potassium channels. In such patients, class IA and class III antiarrhythmic drugs may increase the risk of torsades.

Drugs which cause torsades include:

- Potassium-channel blockers (class 1A and class 3
- Antipsychotics (thioridazine)
- Tricyclic antidepressants.

To treat the torsades, correct the hypokalemia, correct the hypomagnesemia, and discontinue drugs that prolong the QT interval.

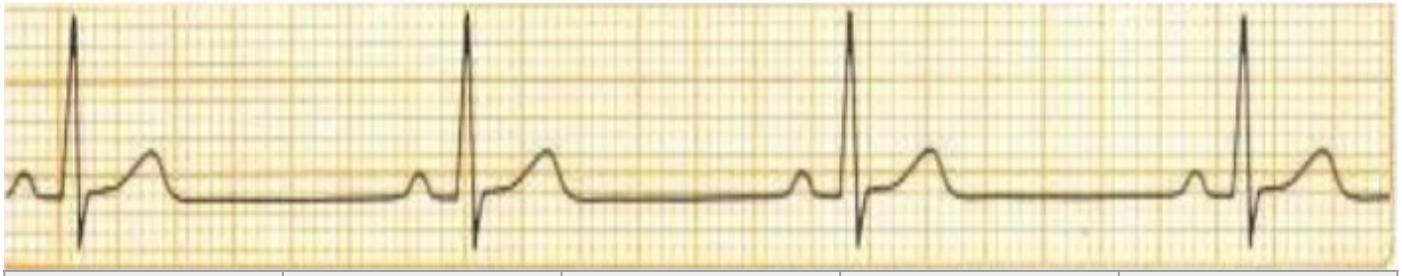
Unclassified Antiarrhythmic drugs

Adenosine

Activates adenosine receptors: causes Gi -coupled decrease in cAMP.

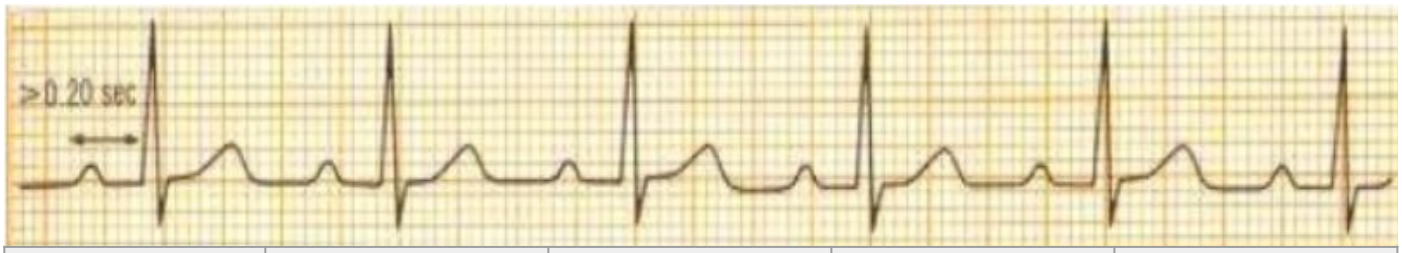
Clinical Integration

Sinus Bradycardia



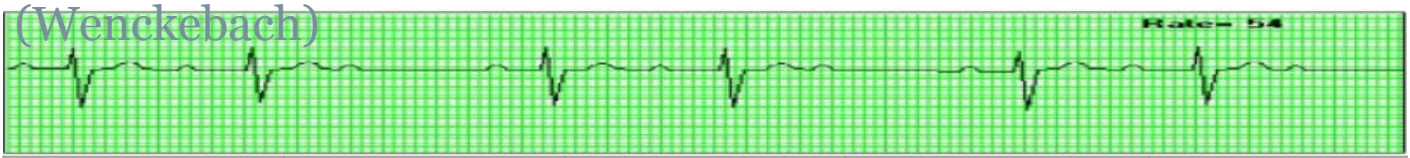
Heart Rate	Rhythm	P wave	P-R interval (sec)	QRS (sec)
<60	Regular	Identical	.12 - .20	<.12

First Degree Heart Block



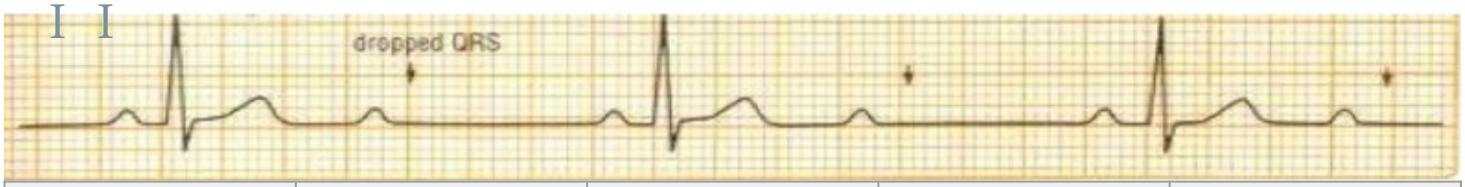
Heart Rate	Rhythm	P wave	P-R interval (sec)	QRS (sec)
Normal	Regular	Identical	>.20	<.12

Second Degree Heart Block Mobitz Type I (Wenckebach)



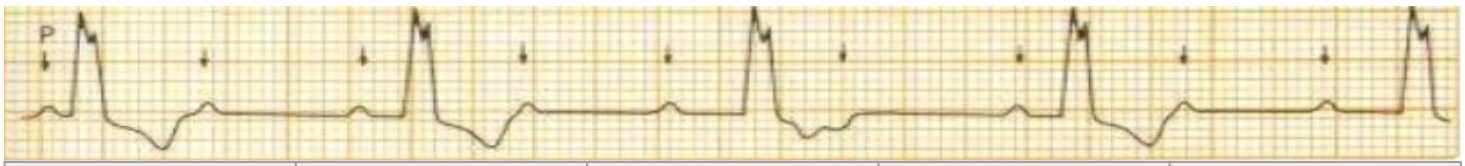
Heart Rate	Rhythm	P wave	P-R interval (sec)	QRS (sec)
Normal, can be slow	Irregular	Present but some not followed by QRS	Progressively longer	<.12

Second Degree Heart Block Mobitz Type I I



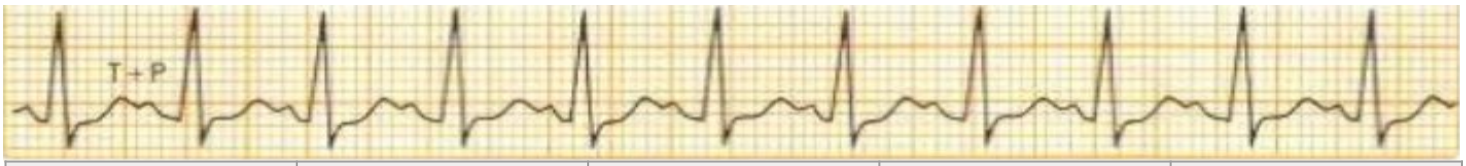
Heart Rate	Rhythm	P wave	P-R interval (sec)	QRS (sec)
slow	Regular or irregular	2, 3 or 4 before each QRS	.12 - .20	<.12

Third Degree Heart Block (Complete)



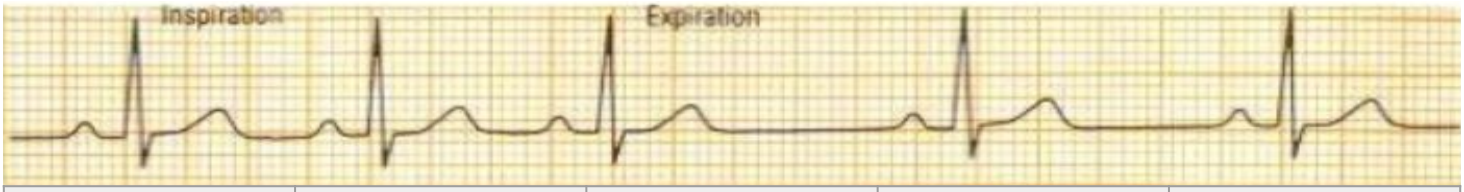
Heart Rate	Rhythm	P wave	P-R interval (sec)	QRS (sec)
30 - 60	Regular	Present but no correlation to QRS	Varies	<.12

Sinus Tachycardia



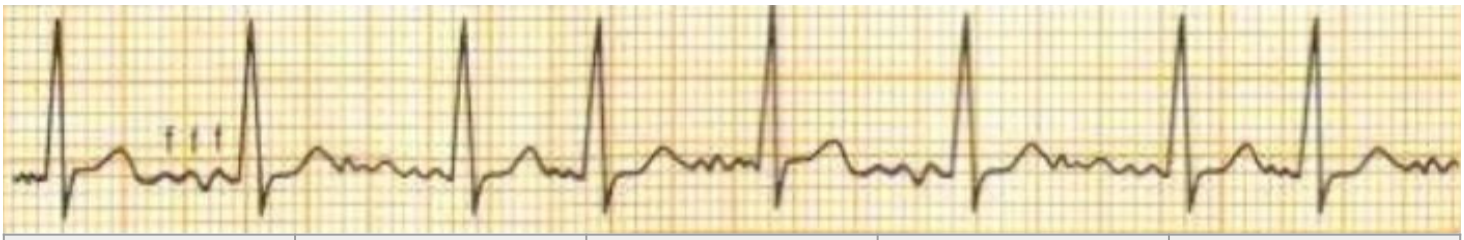
Heart Rate	Rhythm	P wave	P-R interval (sec)	QRS (sec)
>100	Regular	Identical	.12 - .20	<.12

Sinus Arrhythmia



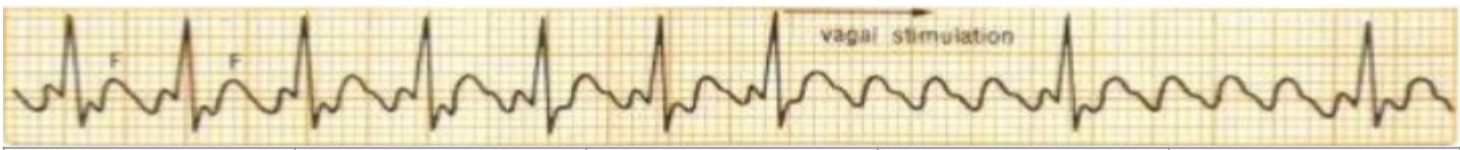
Heart Rate	Rhythm	P wave	P-R interval (sec)	QRS (sec)
Varies	irregular	Identical	.12 - .20	<.12

Atrial Fibrillation



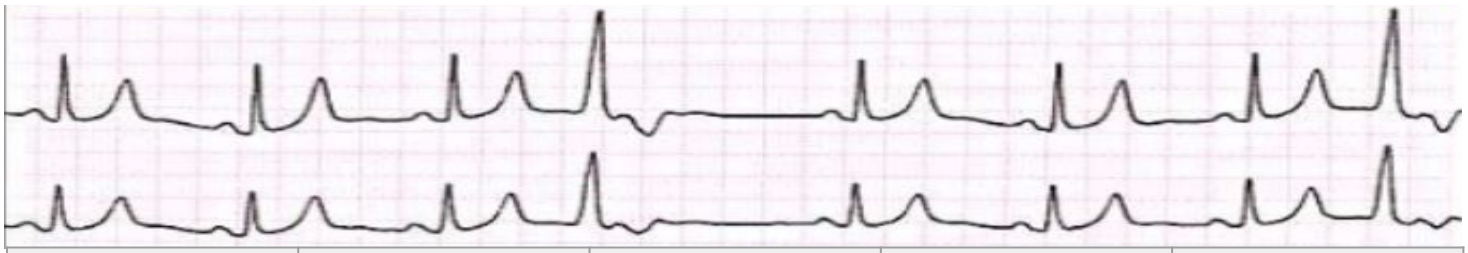
Heart Rate	Rhythm	P wave	P-R interval (sec)	QRS (sec)
Varies	irregular	Absent	NA	<.12

Atrial Flutter



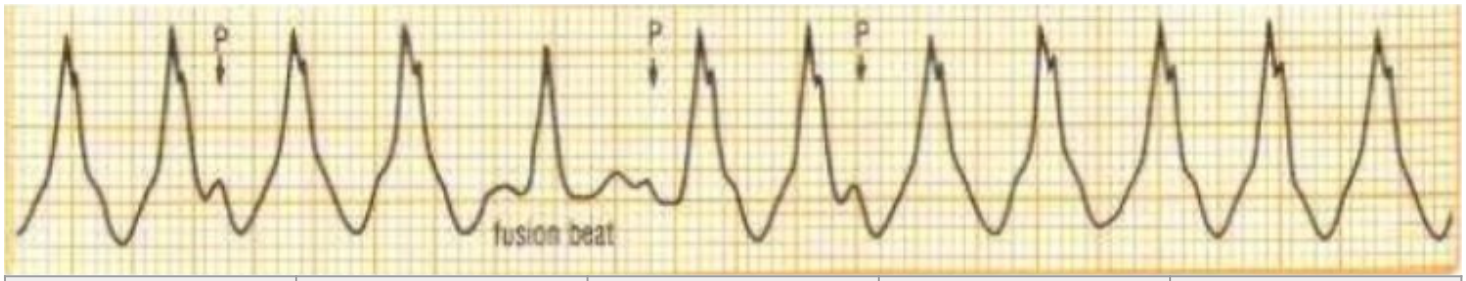
Heart Rate	Rhythm	P wave	P-R interval (sec)	QRS (sec)
Atrial: 250-400 Ventricular: Varies	irregular	Sawtooth	NA	<.12

Premature Ventricula Contraction (PVC)



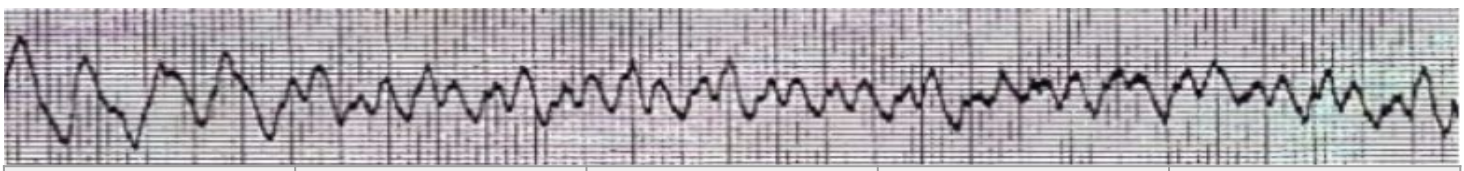
Heart Rate	Rhythm	P wave	P-R interval (sec)	QRS (sec)
Varies	irregular	Absent	NA	>.12

Ventricular Tachycardia



Heart Rate	Rhythm	P wave	P-R interval (sec)	QRS (sec)
100 - 250	Regular	Absent	NA	>.12

Ventricular Fibrillation



Heart Rate	Rhythm	P wave	P-R interval (sec)	QRS (sec)
0	Chaotic	Absent	NA	None

Myocarditis, Pericarditis and Endocarditis

Myocarditis

Myocarditis : an inflammatory disease of the heart muscle.

Epidemiology

no accurate estimate of incidence as many cases are mild & brief and diagnosis is not made.

Etiology

- Myocarditis can be due to a variety of infectious and non infectious causes eg. toxins, drugs and hypersensitivity immune response.
- Viral infection is the most common cause

Infectious		
Viruses	• Coxsackie virus B: the most common cause of myocarditis. • Coxsackie virus A • Echoviruses • Adenoviruses • Influenza	• Epstein Barr Virus • Rubella • Varicella • Mumps • Rabies • Hepatitis viruses • HIV
Bacteria	• Corynebacterium diphtheriae • Syphilis	• Lyme disease • Complication of bacterial endocarditis
Protozoan	• Trypanosoma cruzi (Chagas disease) • Trichinella spiralis	• Taxoplasma gondii • Echinococcus
Others	• Rickettsiae • Fungi • Chlamydia	• Enteric pathogens • Legionella • Mycobacterium tuberculosis

Noninfectious		
Systemic Diseases	• SLE • Sarcoidosis • Thymoma	• Vasculities (Wegener's disease) • Celiac disease • Thyrotoxicosis
Neoplastic infiltration		
Drugs & Toxins	• Ethanol • Cocaine	• Radiation • Chemotherapeutic agents - Doxorubicin

Clinical presentation

- Highly variable :may occur days to weeks after onset of acute febrile illness or with heart failure without any known antecedent symptoms .
- Fever, headache, muscle aches, diarrhea, sore throat and rashes similar to most viral infections
- Chest pain, arrhythmias ,sweating , fatigue and may present with congestive heart failure.

Diagnosis

- WBCs, ESR, Troponin and CK-MB: elevated
- ECG: nonspecific ST-T changes and conduction delays are common)
- Blood culture
- Viral serology and other specific tests for Lyme disease, diphtheria and Chagas disease may be indicated on a case by case basis.
- Chest X-rays : show cardiomegaly
- Radiology : MRI and Echocardiogram
- Heart muscle biopsy (for some cases)

Management

- Often supportive: Most cases of viral myocarditis are self limited.
- Restricted physical activity in heart failure.
- Specific antimicrobial therapy is indicated when an infecting agent is identified.
- Treatment of heart failure arrhythmia
- Other drugs indicated in special situations like anticoagulant, NSAID (non-steroidal anti-inflammatory drugs) , steroid or immunosuppressive immunomodulatory agents.
- Heart transplant in patient with intractable heart failure and cardiomyopathy.
- Patient should be followed regularly every 1-3 months.

Complication

- Mild conduction defects
- Severe heart failure.
- Sudden death may be the presentation of myocarditis in about 10% of cases

Pericarditis

Pericarditis is an inflammation of the pericardium usually of infectious etiology

Etiology

Infectious causes

Viral	• Coxsackie virus A and B: the most common causes. • Herpes viruses • Hepatitis B	• Mumps • Influenza • Adenovirus • Varicella • HIV
Bacterial	• S. pneumoniae • M. tuberculosis • S. aureus • H. influenzae	• K. pneumoniae • Legionella pneumophila • Mycoplasma pneumoniae • Chlamydia pneumoniae
fungal	• Histoplasma	• Coccidioides

Non-infectious pericarditis:

- Immune mediated : rheumatic fever & SLE
- Miscellaneous : due to myocardial infarction , malignancy and uremia.

Spread of Pericarditis

- Contiguous spread: lungs, pleura, mediastinal lymph nodes, myocardium, aorta, esophagus, liver.
- Hematogenous spread: septicemia, toxins, neoplasm, metabolic
- Lymphatic spread
- Traumatic or irradiation

Types

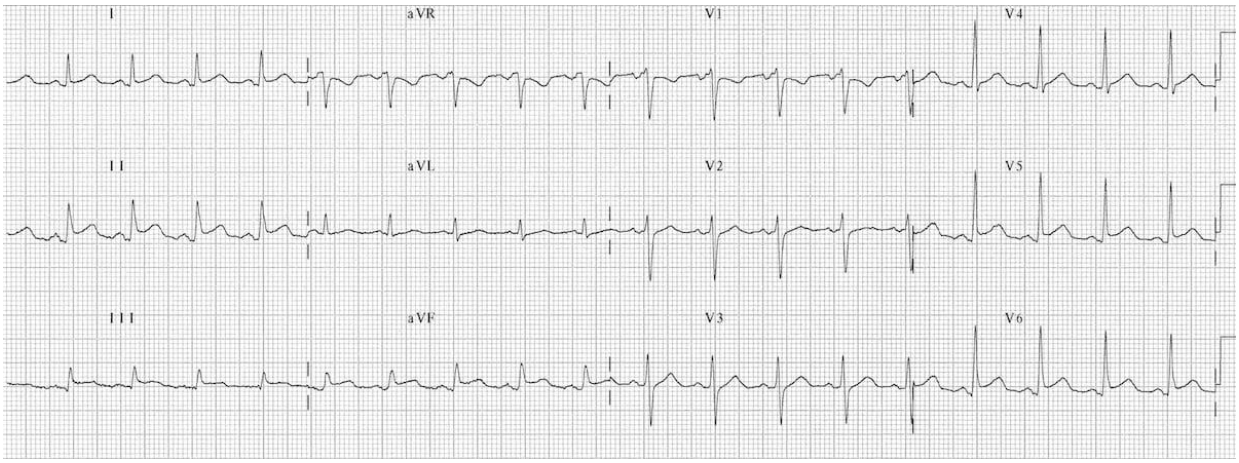
1. Caseous Pericarditis commonly tuberculous in origin.
2. Serous Pericarditis due to autoimmune diseases (rheumatoid arthritis, SLE), viral infections. Cause Transudative serous fluid
3. Fibrinous Pericarditis due to acute MI, uremia, radiation. Cause Fibrinous exudative fluid
4. Purulent/Suppurative pericarditis due to bacteria, fungi or parasites. Cause Purulent exudative fluid
5. Hemorrhagic pericarditis usually caused by infection (e.g. TB) or malignancy. Cause blood mixed with a fibrinous or suppurative effusion
6. Constrictive Pericarditis caused by Radiotherapy, Cardiac surgery, Connective tissue disorders, Dialysis, Bacterial infection (viral, TB, fungal) or could be Idiopathic

Clinical Presentation

- Sudden pleuritic chest pain which is positional retrosternal l(relieved by setting forward)
- Dyspnea
- Fever
- On examination : Pericardial rub, exaggerated pulses , paradoxus JVP (jugular venous pressure) and tachycardia.
- As the pericardial pressure increases, palpitations , presyncope or syncope may occur.

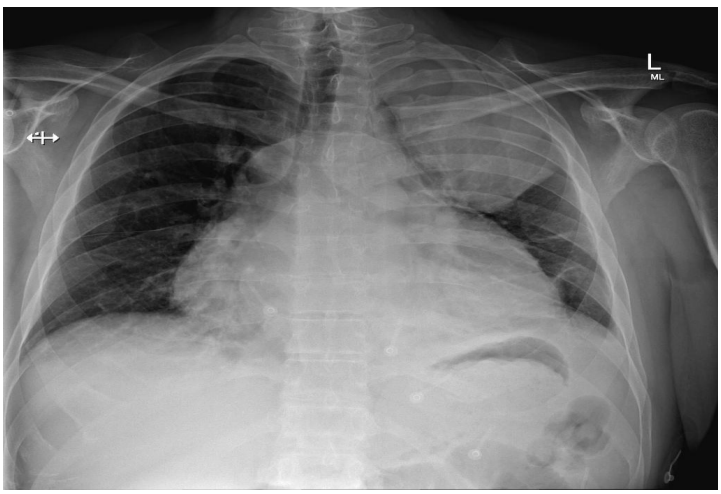
Investigations & Diagnosis

- ECG: ST elevation, PR depression and T-wave inversion may occur later.



Source

- Blood culture
- CBC: Leukocytosis and an elevated ESR
- Other routine testing : urea and creatinine.
- Tuberculin skin test is usually positive in tuberculous pericarditis cases but Fluid smear for acid fast bacilli (AFB) often negative
- Chest x-ray: may show enlarged cardiac shadow or calcified pericardium

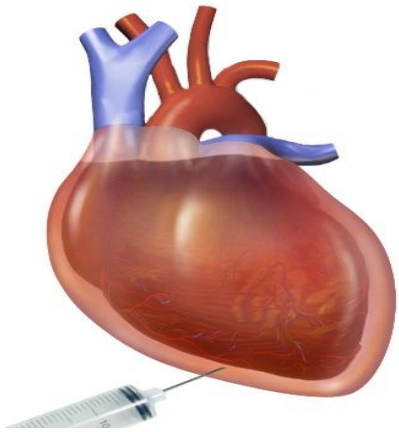


Source

- CT scan: pericardial thickening >5mm.
- Pericardial fluid or pericardial biopsy specimens for fungi.
- Immunology /Serology : Antinuclear antibody tests and Histoplasmosis complement fixation indicated in endemic area.

Management

- Management is largely supportive for cases of idiopathic and viral pericarditis including bed rest , NSAIDS and Colchicine.
- Corticosteroid use is controversial and anticoagulants usually contraindicated.
- Specific antibiotics must include activity against S. aureus and respiratory bacteria.
- Antiviral: Acyclovir for Herpes simplex or Varicella . Ganciclovir for CMV .
- Pericardiocentesis : a therapeutic procedure to remove fluid from the pericardium (to relief Tamponade) in severe cases with pericardial effusion.



adapted from an original image by Wikimedia Commons user BruceBlaus (Blausen Medical)

- Patients who recovered should be observed for recurrence.
- Symptoms due to viral pericarditis usually subsided within one month.

Endocarditis

Infectious Endocarditis (IE): an infection of the heart's endocardial surface

Epidemiology

- Incidence: 1.7— 6.2 / 100 000 person years. M:F 1.7
- Becoming a disease of the elderly Due to two factors: The decline of rheumatic heart disease, The increasing proportion of elderly

Classification

1. Acute
    - Affects normal heart valves
    - Rapidly destructive
    - If not treated, usually fatal within 6 weeks

2. Subacute
    - Often affects damaged heart valves
    - Indolent nature
    - If not treated, usually fatal by one year

Etiology

Native Valve	• Staphylococcus aureus • Strep, mostly S. viridans • Enterococci • Viridans group streptococci (VGS)=HACEK (Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species) • Fungi

Prosthetic Valve	• Early (<12 months)
	  ○ Staph aureus
	  ○ Staph epidermidis
	• Late (>12 months)
	  ○ Staph aureus
	  ○ Staph epidermidis
	  ○ Viridans strep
	  ○ Enterococcus

IV drug abusers	• Staph. aureus

Risk Factors

- Injection drug use
- Structural cardiac abnormality. E.g. Prosthetic valve, Coarctation, Complex cyanotic congenital, Hypertrophic Obstructive Cardiomyopathy (HOCM)
- Previous infective endocarditis
- Poor dental hygiene
- Hemodialysis
- DM
- HIV

Clinical Presentation

Acute Endocarditis

- High grade fever and chills
- Shortness of breath
- Arthralgias and myalgias
- Abdominal pain
- Pleuritic chest pain
- Back pain

Subacute

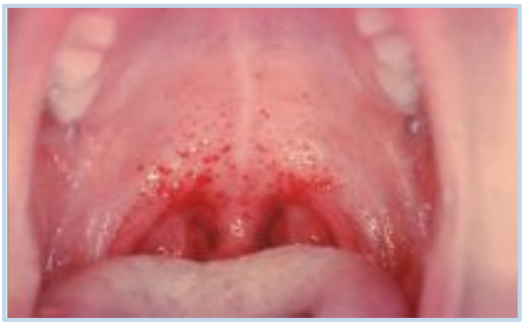
- Low grade fever
- Anorexia
- Weight loss
- Fatigue
- Arthralgias and myalgias
- Abdominal pain
- Nausea and vomiting

Physical Exam

- Cardiac examination may reveal signs of new regurgitation murmurs and signs of CHF
- Neurologic evaluation may detect evidence of focal neurologic impairment
- Nonspecific signs – petechiae, subungual or "splinter" hemorrhages, clubbing, splenomegaly, neurologic changes
- More specific signs - Osler's Nodes, Janeway lesions, and Roth Spots

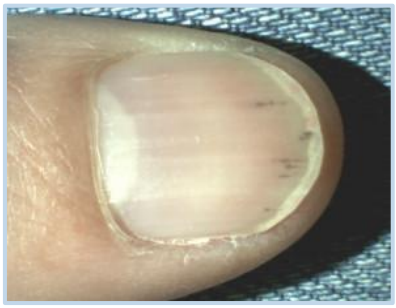
Petechiae

Photo credit, Josh Fierer, M.D.



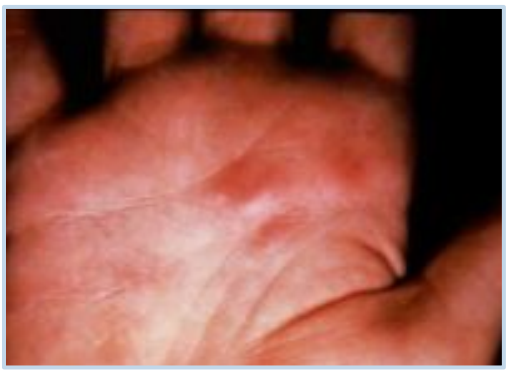
Source: Harden Library for the Health Sciences

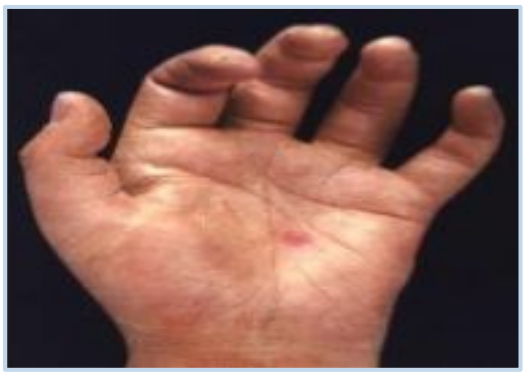
Splinter hemorrhages: Linear reddish-brown lesions found under the nail bed Usually do NOT extend the entire length of the nail



Source

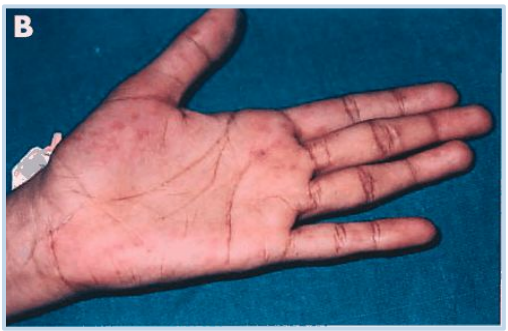
Osler's Nodes: Painful and erythematous nodules, Located on pulp of fingers and toes





Source: American College of Rheumatology

Janeway Lesions: Nonpainful, Located on palms and soles



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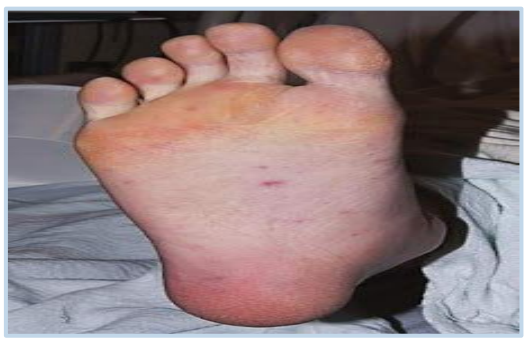

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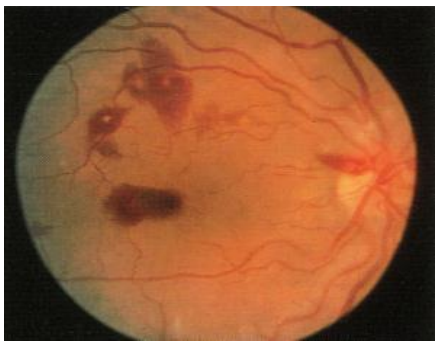
Roth spots



Source

Diagnosis

1. Positive blood culture results
    - A minimum of three blood cultures should be obtained over a time period based upon the severity of the illness
2. Additional laboratory Nonspecific test
    - An elevated ESR and/or an elevated level of CRP is usually present
    - Most patients quickly develop a normochromic normocytic anemia
    - The WBC count may be normal or elevated
3. Abnormal urinalysis
    - The combination of RBC casts on urinalysis and a low serum complement level may be an indicator of immune-mediated glomerular disease
4. ECG
    - New AV, fascicular, or bundle branch block
5. Echocardiographic findings
    - Oscillating intracardiac mass
        - On valve or supporting structure,
        - In the path of regurgitation jets,
        - On implanted material, in the absence of an alternate anatomic explanation
    - Abscess
        - New partial dehiscence of prosthetic valve
        - New valvular regurgitation (increase or change in pre-existing murmur not sufficient)

Duke Criteria

Major criteria	Minor criteria
1. Microbiology ○ Typical organism from 2 separate cultures OR ○ Microorganism from persistently positive BC OR ○ Single BC + for Coxiella burnetii, or titer >1:800 2. Endocardial Involvement ○ New (not changed) murmur of regurgitation 3. Positive ECHO ○ TEE if prosthetic valve, complicated, or pretest probability possible infective endocarditis	1. Predisposition (heart condition or IV drug use) 2. Fever >= 38ºC 3. Vascular phenomenon (excludes petechiae, splinter hemorrhage) 4. major arterial emboli ○ Mycotic aneurysm, intracranial or conjunctival hemorrhages. Janeway lesions 5. Immunologic phenomena ○ RF,.Roth's spots glomerulonephritis, Osler's nodes 6. Microbiologic evidence ○ Not meeting major criteria single BC not CNS, serology

Definite infective endocarditis:

- 2 major
- 1 major and 3 minor
- 5 minor

Possible infective endocarditis:

- 1 major and 1 minor
- 3 minor

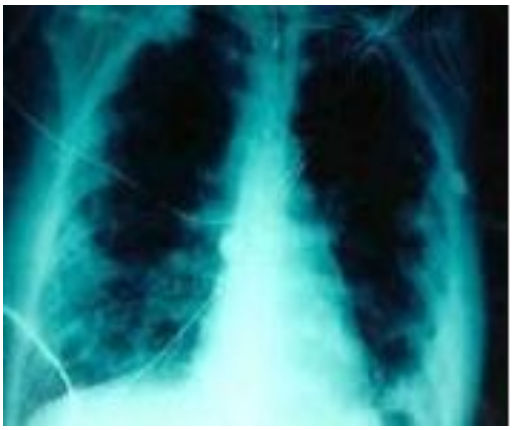
Rejected infective endocarditis:

- Firm alternate diagnosis
- Resolution of infection with antibiotic therapy for ≤ 4 days
- No pathologic evidence of IE at surgery or autopsy with antibiotic therapy for ≤ 4 days
- Does not meet criteria of possible IE

Complications

Embolic Complications

- Stroke
- Myocardial Infarction
- Fragments of valvular vegetation or vegetation-induced stenosis of coronary ostia
- Ischemic limbs
- Hypoxia from pulmonary emboli
- Abdominal pain (splenic or renal infarction)



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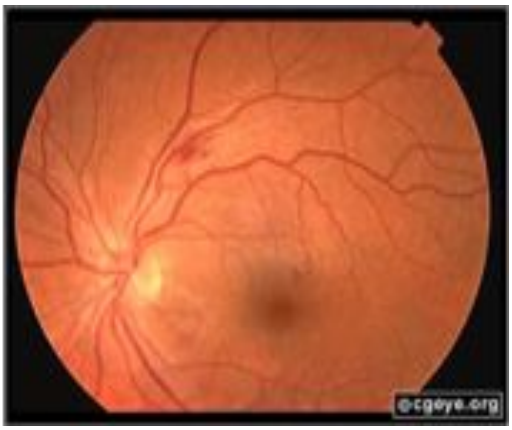


Local Spread of Infection

- Heart failure
  - Extensive valvular damage
- Paravalvular abscess
  - Most common in aortic valve, IVDU, and S. aureus
  - May extend into adjacent conduction tissue causing arrhythmias
  - Higher rates of embolization and mortality
- Pericarditis
- Fistulous intracardiac connections

Metastatic Spread of Infection

- Metastatic abscess in the Kidneys, spleen, brain, soft tissues
- Meningitis and/or encephalitis
- Vertebral osteomyelitis
- Septic arthritis

Culture Negative infective endocarditis

- Tend to happen in subacute with valve destruction and congestive heart failure
- 50% culture negative are due to previous antibiotics
- It could be due to Fastidious bacteria (needs special media to grow)

Lab Diagnosis

PCR of vegetation/emboli: Tropheryma whipplei, Bartonella

Histology/stain /culture of vegetation/emboli: Fungus

Prolonged, cultures: Brucella

Lysis centrifugation system (Isolator): Bartonella, Legionella (BCYE), fungal

Serology: Endemic fungi, Bartonella, Q fever, Brucella, Legionella, Chlamydia

Thioglycolate or cysteine supplemented media: S.aureus

Satellitism: Abiotrophia (NVS)

Management

Acute

- Give IV antibiotics empirically. Nafcillin and Gentamicin are consider good choices

Subacute

- Don't give antibiotics until you have positive culture
- For native valve: ampicillin + gentamicin
- For prosthetic valve: Vancomycin, Gentamicin, Rifampin

Prosthetic valve endocarditis that one may attempt medical treatment alone:

- > 12 months post surgical
- VGS or HACEK or Enterococci
- No perivalvular extension

Indications for surgery

- Refractory congestive heart failure
- Perivalvular invasive disease
- Uncontrolled infection on maximal medical therapy
- Recurrent systemic emboli, particularly in the presence of large vegetations
- Some pathogens: Pseudomonas, Brucella, Coxiella, Fungi, Enterococci

Prophylaxis

- For High or Mod. cardiac risk conditions (previous list)
- For Dental, rigid bronchoscopy, esophageal procedures, G I mucosal procedures, cystoscopy, prostate surgery

Timing: One hour prior to procedure

Antibiotics

- Amoxicillin orally or
- Clindamycin orally or
- Cephalexin orally or
- Clarithromycin orally or
- Ampicillin intramuscularly

Pathology

Endocarditis

Introduction:

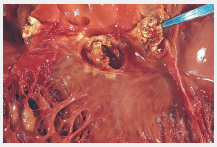
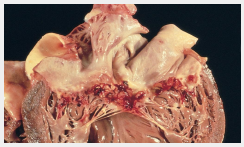
inflammation of Endocardium

- results in fibrin deposition on valve leaflets forming tiny thrombi along lines of closure called **rheumatic vegetations.**
- Vegetations may be single or multiple, involve one or more valve(s), differ in appearance according to the causative agent.
- Main involved valves are **Mitral and aortic**
- Either resolve completely or or progress to scarring with chronic fibrotic deformities of the heart valves and chordae tendineae.

Definition:

infection of the cardiac valves or mural/ inner surface of the endocardium, resulting in the formation of an adherent mass of thrombotic debris mixed with microorganisms.

Main Types & Other:

	Acute IE 	**Subacute IE** 
Microorganism	highly virulent	low virulence
Valves involved	normal/healthy valves,	previously abnormal/ damaged valves
Prognosis	rapidly	slowly
host reaction	little and local	local inflammatory reaction
Prognosis	▪Depends to some extent on the offending organism and the stage at which the infection is treated. ▪1/3rd of cases of Staph. aureus endocarditis are still fatal.	
Libman Sacks endocarditis	Less common, non infective, verrucous endocarditis associated with elevated levels of circulating immune complexes. Seen in patients with systemic lupus erythematosus.	
Endocarditis of carcinoid syndrome 	Secretory products of carcinoid syndrome,especially 5 hydroxytryptamine can cause endocarditis. The endocardial plaques are seen in the right side of heart.	
Nonbacterial thrombotic endocarditis (marantic endocarditis)	▪Characterized by sterile (no infection) vegetations. ▪There is no infective organism. It is aseptic. ▪Pathogenesis/ association: - Subtle endothelial abnormalities. - Hypercoagulability. - Malignancy ▪Aortic valve most common site.	

Risk Factors:

1-Children: commonly congenital heart disease

2-Adults: Mitral valve prolapse and congenital heart disease are the most frequent cause

3-Rheumatic Heart Disease

4-I.V drug abusers: The tricuspid valve is infected , caused by S. aureus.

5-Prosthetic valves: by coagulase negative staphylococci (e.g. S. epidermidis).

6-Transient bacteremia: from any procedure (e.g. dental procedures)

Compilation:

1-Septicemia or septic systemic **embolization** of infected vegetations

2-Pulmonary emboli: seen in tricuspid valve/ right sided endocarditis

3-Rheumatic Heart Disease

4-Arrhythmias, valvular regurgitation and congestive heart failure

5-Valve ulceration & perforation, rupture of chordae tendineae.

6-Aneurysms & renal failure

Clinical Correlate

- *S. bovis* endocarditis or septicemia is associated with a higher incidence of occult colorectal tumors.
- Colonoscopy should be performed in all patients with *S. bovis* bacteremia or endocarditis.

Valvular Heart Diseases (VHD)

Classification:

1-Stenosis (Failure to open)

2-Regurgitation (Insufficiency or failure to close leading to backflow of blood)

Causes:

1-Acquired

- post inflammatory scarring e.g. as a late complication of rheumatic fever (most common).
- prosthetic cardiac valves.
- secondary to thrombus formation or infectious endocarditis.

2-Congenital

Mitral valve

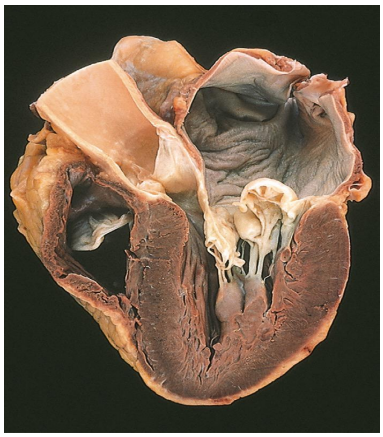
Prolapse (MVP) (Pic A)	**Stenosis** (Pic B)	**Regurgitation**
Epidemiology ● most frequent in developed countries. ● Seen in young women. associated with Marfan syndrome	Epidemiology ▪caused by Rheumatic heart disease ▪more common than mitral regurgitation.	Epidemiology ▪Caused by Rheumatic heart disease, mitral valve prolapse, infective endocarditis, papillary muscle injury in myocardial infarction.
Pathogenesis ▪unknown ▪myxoid/mucoid degeneration of the valve → ballooning of mitral valves (floppy cusp) → parachute deformity during systole. ▪systolic murmur with a click.	Pathogenesis ▪increased pressure in the left atrium leading to hypertrophy and dilatation → pulmonary hypertension and chronic passive congestion → right ventricular hypertrophy. ▪fish mouth/buttonhole deformity ▪secondary deposition of Ca++	Complication left vent. hypertrophy and dilatation.
Clinical features asymptomatic		
Complications Subacute infective endocarditis		

Aortic valve

Stenosis	Regurgitation
Epidemiology Usually seen in old people over 60 years old.	Caused by: 1- Non-dissecting aortic aneurysm. 2- Rheumatic heart disease. 3- Infective endocarditis. 4- Syphilitic (luetic) aortitis(rare).
Caused by: calcification and is called as calcific aortic stenosis.	
Calcific aortic stenosis affects (Pic C) **a)** as part of the aging degenerative process in > 60 yrs old. (C1) **b)** Congenital bicuspid aortic valve(C2) **c)** Valves scarred by rheumatic heart disease	

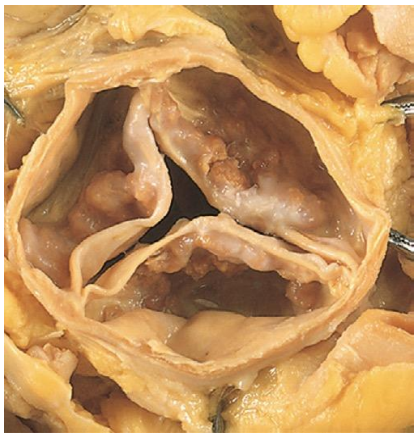
Useful Pictures:

(Pic A)

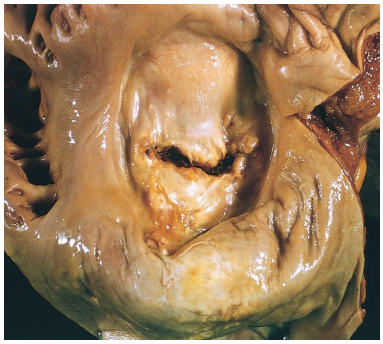


(C1)

(Pic C)



(Pic B)



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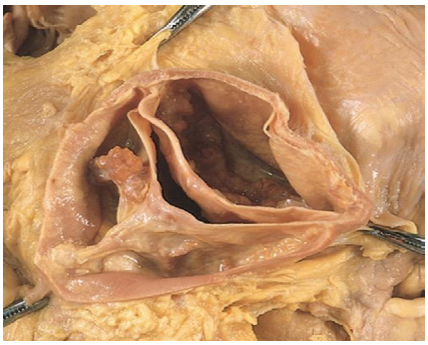


Table 11.4 Etiology of Acquired Heart Valve Disease

Mitral Valve Disease	Aortic Valve Disease
Mitral Stenosis	**Aortic Stenosis**
Postinflammatory scarring (rheumatic heart disease)	Postinflammatory scarring (rheumatic heart disease) Senile calcific aortic stenosis Calcification of congenitally deformed valve
Mitral Regurgitation	**Aortic Regurgitation**
Abnormalities of leaflets and commissures Postinflammatory scarring Infective endocarditis Mitral valve prolapse "Fen-phen"–induced valvular fibrosis Abnormalities of tensor apparatus Rupture of papillary muscle Papillary muscle dysfunction (fibrosis) Rupture of chordae tendineae Abnormalities of left ventricular cavity and/or annulus Left ventricular enlargement (myocarditis, dilated cardiomyopathy) Calcification of mitral ring	Intrinsic valvular disease Postinflammatory scarring (rheumatic heart disease) Infective endocarditis Aortic disease Degenerative aortic dilation Syphilitic aortitis Ankylosing spondylitis Rheumatoid arthritis Marfan syndrome

Fen-phen, Fenfluramine-phentermine.
Data from Schoen FJ: Surgical pathology of removed natural and prosthetic valves, *Hum Pathol* 18:558, 1987.

Rheumatic fever

Rheumatic Fever

Rheumatic fever is a systemic autoimmune disease usually affects children aged 5-10 years, that typically follows infection with Group A Streptococcus (aka; Streptococcus pyogenes). Classically, patients complain of a pharyngeal infection 1-4 weeks prior to the disease.

Rheumatic Heart Disease

A disease caused by autoimmune destruction of cardiomyocytes which develops after a Group A Streptococcus (GAS) infection.

- Antibodies against streptococcal antigens cross-react with cardiac muscle cell proteins.
- The aforementioned process results in an immune complex deposition (Type II Hypersensitivity reaction), creating new antigens that entice new immune responses.

From Rheumatic fever to Rheumatic heart disease

GAS present in, for example, pharyngitis; expresess amounts of *M protein* which then the body responds to by producing *IgG* against the protein on GAS. These antibodies, however, bind to myocardium & joints -because they're similar to *protein M*-, leading to an antibody induced injury (type II hypersensitivity).

Interplay Between Streptococcal Antigens and the Immune System

- **Streptococcal pyrogenic exotoxins** (SPE-A, B, C, D) act as superantigens, activating T-cell responses in a manner not dependent on antigen presenting cells.
- **Hyaluronic acid:** produced by the body as well, a renowned glycosaminoglycan, not immunogenic.
- **Streptolysin O:** immunogenic, its antibodies are used as marker for diagnosis given that cultures turn out to be negative, hemolytic and a cytolytic.
- **Streptolysin S:** Not immunogenic, nonetheless it's hemolytic and cytolytic.
- **Streptokinase**: Dissolves fibrin clots by activating plasminogen into plasmin, potentially immunogenic.
- **Streptococcal DNAse:** Aggravates pathogenic lesions and purulent processes.
- **Hyaluronidase:** Hydrolysis of extracellular matrix components.

Rheumatic fever

Acute rheumatic fever is mainly due to *Group A beta-hemolytic streptococci* which is a result of streptococcal pharyngitis on children between 5-15 years old. This infection will produce antibodies that will cross react with cardiac antigene.
Diagnosis of rheumatic fever will be based on **Jones criteria** (which will be mentioned in the coming pages).

Rheumatic heart disease

Acute rheumatic heart disease

The most serious complication of rheumatic fever, affecting all three layers of the heart. The most characteristic features of myocarditis is Aschoff bodies (caterpillar chromatin pattern). Endocarditis can affect mitral and aortic valve, when it involve tricuspid is highly suggestive of IV drug abuser.

Chronic rheumatic heart disease

Is identify by aortic and mitral valvular fibrosis, valve thickening and calcification and short thick chordae tendineae. It may complicated to mitral stenosis, mitral regurgitation, aortic stenosis, aortic regurgitation, congestive heart failure, infective endocarditis and atrial fibrillation which is irregular rapid impulses.

Aschoff bodies:

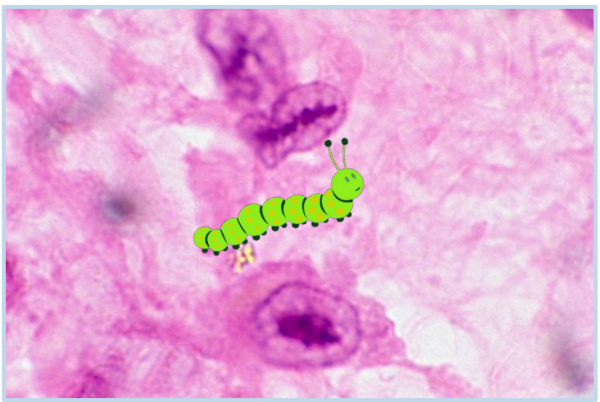


Image credit to: Ed Uthman.

Notice the narrowing of the mitral valve, being fused, and hypertrophied.

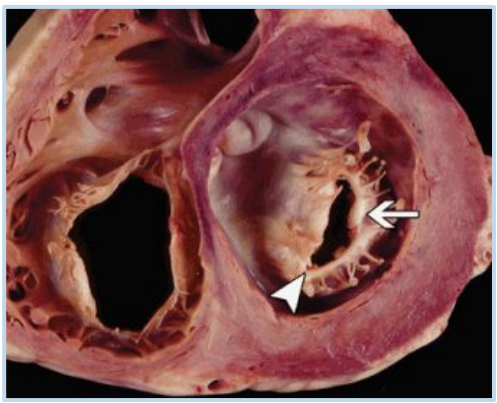


Image credit to:MEDsphere

Clinical Integration

Acute rheumatic fever (ARF) is a multisystem disorder that usually presents with fever, anorexia, lethargy and joint pain.

The major clinical features are as follows:

Carditis

A 'pancarditis' involves the endocardium, myocardium and pericardium. It may manifest as breathlessness (due to heart failure or pericardial effusion), palpitations or chest pain (usually due to pericarditis or pancarditis).

A soft systolic murmur due to mitral regurgitation is very common. Leaving a permanent damage.

Plyarthritis

Acute painful **asym**metric and migratory inflammation of the large joints.

Skin manifestations

Erythema marginatum (transient pink coalescent rings develop on the trunk) and small non-tender subcutaneous nodules which occur over tendons, joints and bony prominences.

Sydenham's chorea

('St Vitus' dance') indicates involvement of the central nervous system and presents with 'fidgety' and spasmodic, unintentional movements.

Chronic valvular heart disease

develops in at least half of those affected by rheumatic fever with carditis. The mitral valve is affected in more than 90% of cases.

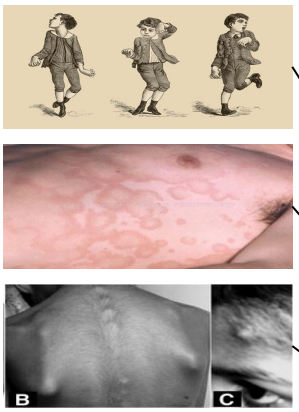
	Treatment
streptococcal pharyngitis	penicillin to prevent rheumatic fever. *Highly sensitive to penicillin
Acute rheumatic fever	Bed rest, NSAIDs, and steroids.
Chronic rheumatic heart disease	Treat the valvular pathology.
Secondary prevention	long-term prophylaxis with penicillin.

Clinical Integration

2015 Revision of Jones Criteria:

According to AHA, the diagnosis of acute rheumatic fever depends on degree of prevalence of ARF/RHD in a population.

For low risk populations
(where; **ARF** incidence <2:100000 school-age children
OR all-age prevalence of **RHD** is <1:1000 per year)



Major criteria	Minor criteria
Carditis	Fever (>=38.5)
Polyarthritis	Polyarthralgia (joint pain)
Chorea	↑ ESR (>=60 mm)
Erythema marginatum	Prolonged PR interval
Subcutaneous nodules	-

For moderate-high risk populations:
(children not from low-risk populations have been considered to be at moderate to high risk)

Major criteria	Minor criteria
Carditis	Fever (>=38.0)
Polyarthritis, Polyarthralgia, monoarthritis	-
Chorea	↑ ESR (>=30 mm)
Erythema marginatum	Prolonged PR interval
Subcutaneous nodules	-

A firm diagnosis requires:

1) 2 major + 1 minor **OR** 1 major + 2 minor

AND

2) Evidence of recent group A Streptococcus infection

Ischemic heart disease

Coronary Artery of the heart

	Left coronary artery (LCA)	Right coronary artery (RCA)
Course	The left coronary artery travels a short course between the left auricle and ventricle	The right coronary artery courses in the posterior coronary sulcus and supplies major parts of the right atrium and the right ventricle.
Braches	**1- The anterior interventricular artery or left anterior descending (LAD)** descends in the anterior interventricular sulcus **2- The circumflex artery (LCX)** courses around the left border of the heart in the coronary sulcus	**1- Sinoatrial (SA) nodal artery:** One of the first branches of the right coronary, it encircles the base of the superior vena cava **2-Atrioventricular (AV) nodal artery:** It arises from the distal end of the right coronary artery as it forms the posterior interventricular artery and penetrates the interatrial septum **3- Right marginal artery:** It originates from the right coronary artery at the inferior (acute) margin of the heart, as one of its largest branches. **4- Posterior interventricular artery or posterior descending artery:** It is the terminal distribution of the right coronary artery and courses in the posterior interventricular sulcus
Supply	**1- LAD provides branches to the** - Anterior left ventricle wall (including *anterolateral* papillary muscle), - Anterior two-thirds of the interventricular septum, - Bundle of His - Apex. **2- LCX supplies** - The left border of the heart via the marginal branch - Ends on the posterior aspect of the left ventricle and supplies the posterior-inferior left ventricular wall.	1- supplies the SA node. 2- supplies the AV node. 3- supplies most of the myocardium of the right ventricle of the heart. It courses along the inferior margin towards the apex of the heart and terminates by anastomosing with the branches of the anterior interventricular artery. 4- parts of the right and left ventricles (including *posteromedial* papillary muscle) and, most importantly, the posterior third of the interventricular septum.

Clinical pictures of coronary arteries occlusion

In myocardial infarction, the coronary artery **most commonly occluded** (40-50%) is the left anterior descending (LAD) resulting in infarction of the anterior portion of the ventricles, the cardiac apex, and/or the interventricular septum.

- The right coronary artery is the second most commonly occluded, followed by the left circumflex.

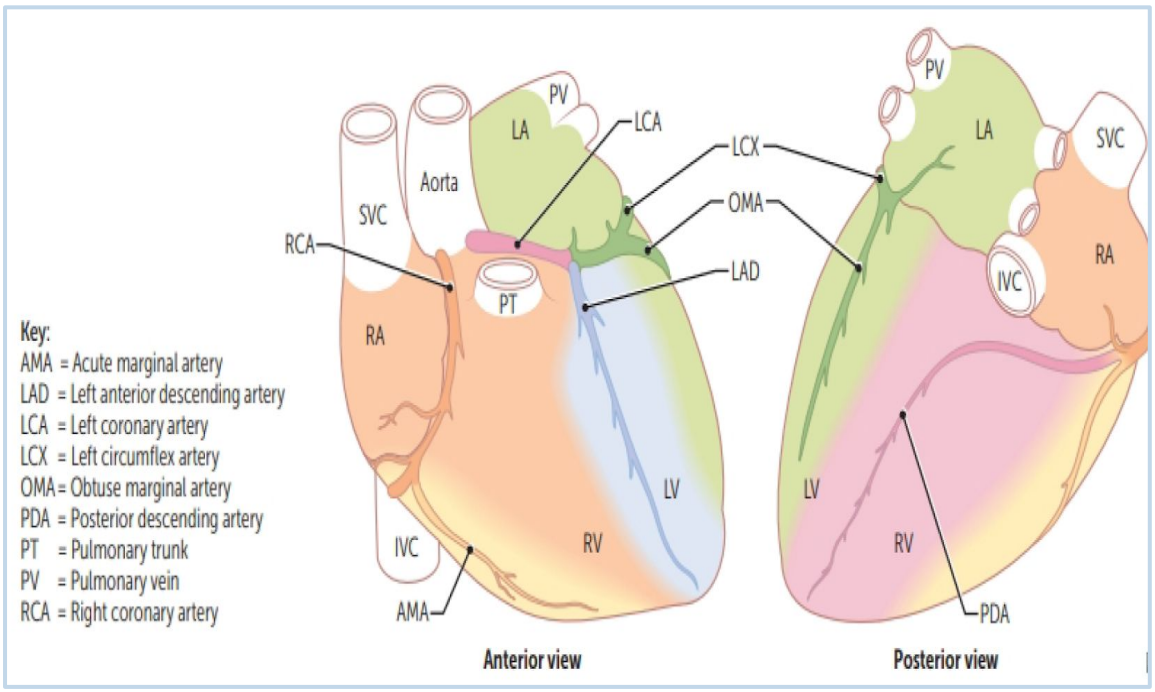
LAD infarctions are associated with high mortality rates by **infarction of the anterior ventricle,**

The RCA usually supplies the heart's conduction system (sinus and AV node) so that stenosis or occlusion of this vessel often **leads to cardiac arrhythmias, bradycardia or heart block.**

Following an inferior wall MI (occlusion of RCA), a fatal complication could occur due to papillary muscle rupture, commonly in the *posteromedial muscles* (of the mitral valve); as it's only blood supply is the PDA (or LCX depending on dominance). Why not the *anterolateral*? I am glad you asked, because the *anterolateral* muscle has dual supply by both LAD and the marginal branch of LCX.

So, What is this 'Dominance'?

- Right-dominant circulation = PDA arises from RCA. (majority or people)
- Left-dominant circulation = PDA a rises from LCX.
- Codominant circulation = PDA arises from both LCX and RCA.



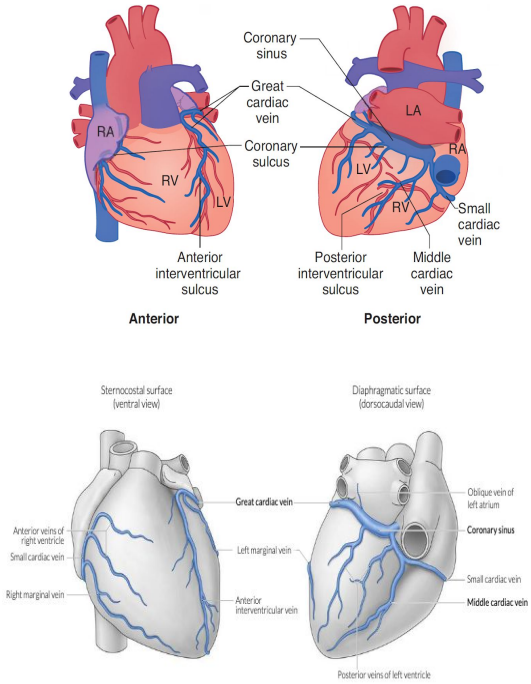
Venous Drainage of the Heart

The major cardiac veins draining the heart course in the sulci and accompany the arteries but *do not carry the same names*. The major veins are the following:

Coronary sinus:

It is the main vein of the coronary circulation; it lies in the posterior coronary sulcus and drains to an opening in the right atrium. It develops from the left sinus venosus.

Veins draining in the coronary sinus:



- **Great cardiac vein (from the left side):**

It lies in the anterior interventricular sulcus with the LAD artery; it is the main tributary of the coronary sinus.

- **Middle cardiac vein (from the right side):**

It lies in the posterior interventricular sulcus with the posterior interventricular artery; it joins the coronary sinus.

- **Venae cordis minimae (thebesian veins) and anterior cardiac veins:**

They are open directly to the chambers of the heart.

LAD	Left Circumflex	RCA
Apex	Lateral wall of LV	Lateral wall of RV
Anterior wall of LV	Posterior wall of LV (20%)	Posterior wall of LV (80%)
Anterior two thirds of IVS	Posterior one third of IVS (20%)	Posterior one third of IVS (80%)
		SA node
		AV node

AV = atrioventricular; IVS = interventricular septum; LAD = left anterior descending; LV = left ventricle; RCA = right coronary artery; RV = right ventricle; SA = sinoatrial.

Coronary Circulation

Coronary Artery Anatomy With A Hint Of Physiology:

The blood vessels of the heart lie just deep to the epicardium on the surface. Blood flow during diastole and systole differ mainly in the **left ventricle** because of the drastic difference in the pressure gradient.
Unlike the **right ventricle** where the pressure gradient is almost the same. Furthermore, the contraction of the myocardium during systole causes an external pressure on the vessels causing diminished blood flow. The area that is most vulnerable when blood flow is compromised is the subendocardial tissue because it is the farthest zone from the blood supply.

Autoregulation

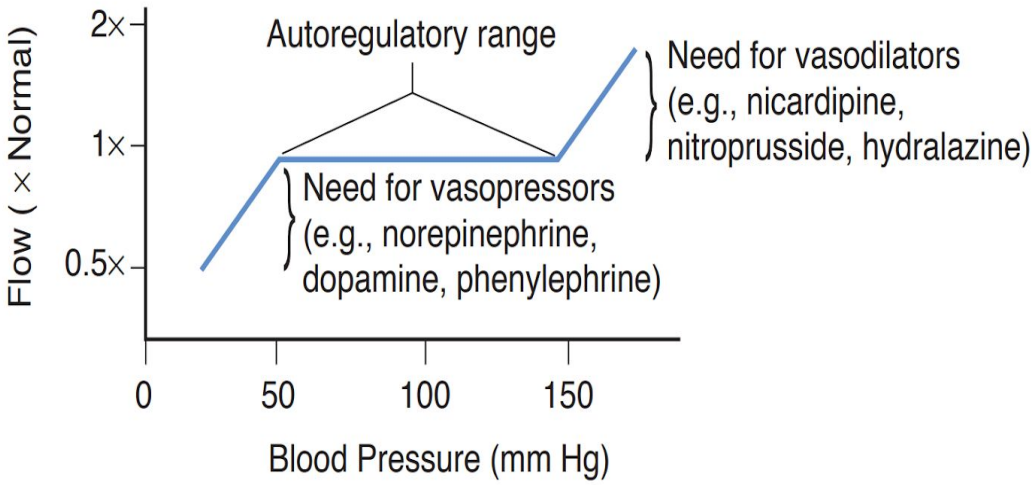
Micro-Circulations are tightly regulated by mechanisms, an important one is the autoregulation, which means ability of the tissues to regulate their own blood flow according to their metabolic needs **by constricting and dilating the smooth muscle surrounding the arterioles.** This mechanism works well in the heart, kidney and others. There are substances that either works **systemically** or **locally** to control blood flow or blood pressure.

- The **local** ones include, **histamine**, nitric oxide, prostaglandins, endothelin and others.
- while the **circulating agents** include: angiotensin II, vasopressin, adrenaline and others.

Coronary circulation is one of special circulations as it supplies the heart and it is well controlled by specific factors:
1) Pressure gradient during the cardiac cycle and aortic pressure,
2) Autoregulation
3) chemical factors
4) neural factors.

When flow through the coronaries is reduced to a point that the myocardium becomes hypoxic, substance 'P' accumulates and angina develops.

How does blood flow to an organ remains constant over a wide range of perfusion pressures?



One of the major characteristics of an autoregulating tissue is that blood flow is independent of blood pressure. The figure shows the range of pressure over which flow remains nearly constant is the autoregulatory range.

Autoregulation involves either a myogenic or metabolic mechanism

• Myogenic :

Increased perfusion pressure causing an stretch of the arteriolar wall causing the contraction of the smooth muscle as a natural reaction.

•Metabolic (Chemical Control):

The tissue itself can produce vasodilator metabolites that regulate blood flow including an increase in: NO, Prostaglandins, Adenosine, lactate , K+ and H+ . These will all cause vasodilation. Also lack of O2 will cause in vasodilation because of the high concentration of CO2.
Furthermore the coronary circulation is regulated by endothelial control.
As a result of endothelial injury the metabolites nitric oxide and prostacyclin will decrease causing vasoconstriction.

Neural control :

During coronary circulation sympathetic stimulation is termed as functional sympatholysis that is when the *alpha* receptors in the heart are constricted, increased metabolic activity will increase metabolic demand of the heart resulting in the secretion of vasodilator metabolites causing in coronary vasodilation. Parasympathetic control (vasodilation through *beta* adrenoceptors) is minimal in coronary blood flow.
Autoregulating tissues which least affected by nervous reflexes include : Cerebral circulation, Coronary circulation and Skeletal muscle vasculature during exercise.

Organ Specific Modes Of Autoregulation:

- **Heart :** Local metabolites (vasodilatory): adenosine, NO, C02, O2
- **Brain:** Local metabolites (vasodilatory): C02 (pH)
- **Kidney:** Myogenic and tubuloglomerular feedback
- **Lung:** Hypoxia causes vasoconstriction; The pulmonary vasculature is unique in that alveolar hypoxia causes vasoconstriction so that only well-ventilated areas are perfused. In other organs, hypoxia causes vasodilation.
- **Skin:** Sympathetic stimulation most important mechanism for temperature control
- **Skeletal Muscle:** Local metabolites
  during exercise:
  C0 2, **H**+, **A**denosine, **L**actate, **K**+ summarized in **CHALK**..
  At rest: sympathetic tone

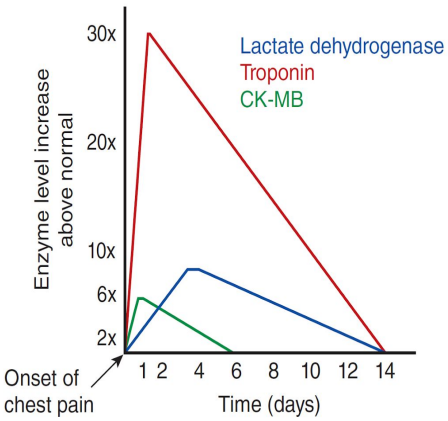
Diagnosis of myocardial infarction

Features Of An Ideal Cardiac Marker:

- High specificity
- Good prognostic value
- Easily measured
- High concentration in the myocardium
- Rapid release into plasma following myocardial injury
- High sensitivity

Cardiac enzymes which widely used for diagnosing MI are summarized bellow:

Serum markers	Elevated after pain starts by	Peak	Returns to Normal by
Troponin I & T	4-6 h	24 h	7-10 days
CK-MB	6-12 h	16- 24 h	2 days
LDH	24 h	3-6 days	8-14 days



- Troponin:

It is currently the most definitive marker and are replacing CK-MB and highly specific to heart muscle damage (MI). It remains elevated in plasma longer than CK-MB. It is the most sensitive and specific marker (gold standard) for MI.

- CK-MB:

It is an enzyme predominantly found in the myocardium, but may also be released from skeletal muscle. Its main advantage is detecting reinfarction that occurs days after an initial MI because levels return to normal after 48 hours.

- LDH :

It may be helpful if a patient reports chest pain that occurred several days previously.

- Other heart markers :

B-type natriuretic peptide (BNP), is a Heart failure marker while Heart fatty acid binding protein (h-FABP) is an early marker for detecting acute ischemia prior to necrosis of heart tissue.

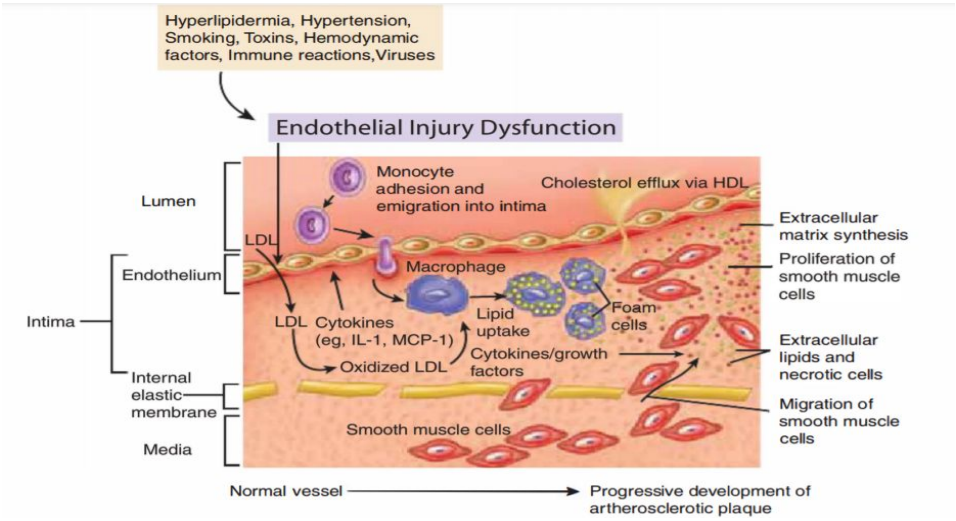
Atherosclerosis

Usually affects medium and large arteries such as the aorta and the coronary, carotid, cerebral, and popliteal arteries. Lipid deposition, fatty streaks, and fibrous plaques form in the intima of medium to large arteries. Risk factors are divided into major and minor categories.

- **Major** : Hyperlipidemia, hypertension, smoking, diabetes, and obesity.
- **Minor** : Male gender, oral contraceptives, increased age, sedentary lifestyle, stress, elevated homocysteine level, family history, and infections.

Pathogenesis

Endothelial cell injury ⟶ macrophages/platelets adhere to damaged endothelium and release cytokines ⟶ smooth muscle hyperplasia/migration of cells to the tunica intima ⟶ macrophages form foam cells within smooth muscle ⟶ fibrous cap develops ⟶ fibrous cap (plaque) calcifies dystrophically and ulcerates ⟶ platelets adhere to the ulcer, causing vessel thrombosis.



Complications :

- Plaque rupture
- myocardial infarction (MI)
- unstable angina
- transient ischemic attacks
- renal artery ischemia
- impotence
- claudication
- hypertension
- stroke
- death

Ischemic heart disease

Epidemiology

is usually secondary to coronary artery disease (CAD); It is most often seen in middle-age men and postmenopausal women.

Risk factors

A healthy lifestyle involves a range of healthy behaviors. One way to think about heart disease risks and corresponding lifestyle changes is the acronym ABCDES:
Alcohol
Blood pressure
Cholesterol
Diabetes
Exercise
Smoking
Other important risk factors include, Age and family history.

Clinical presentations

1. Angina pectoris is due to transient cardiac ischemia without cell death resulting in substernal chest pain.

- stable angina (most common type) is caused by coronary artery atherosclerosis with luminal narrowing. Chest pain is brought on by increased cardiac demand and is relieved by rest or nitroglycerin. Electrocardiogram shows ST segment depression.

- Prinzmetal variant angina is caused by coronary artery vasospasm and produces episodic chest pain often at rest; it is relieved by nitroglycerin. Electrocardiogram shows transient ST segment elevation.

- Unstable or crescendo angina is caused by formation of nonocclusive thrombus in an area of coronary atherosclerosis, and is characterized by increasing frequency, intensity, and duration of episodes; episodes typically occur at rest. This type of angina has a higher risk for myocardial infarction

Morphologic changes of MI :

Time Post-Infarction	Gross Appearance
0-12h	No visible gross change
12-24h	Vague pallor and softening
1-7 days	Yellow pallor
7-10 days	Central pallor with a red border
6-8wks	White, firm scar

Time Post-Infarction	Microscopic Appearance
0-4h	None or wavy myocyte fibers at border or contraction band necrosis
3h-4 days	Coagulation necrosis
1-3 days	Neutrophilich infiltrate
3-7 days	Macrophages
7-10 days	Granulation tissue
3-8wks	Remodeled type III collagen becoming dense , collagenous scar

2. Sudden cardiac death
is defined to be death within 1 hour of the onset of symptoms. The mechanism is typically a fatal cardiac arrhythmia (usually ventricular fibrillation).

- Coronary artery disease is the most common underlying cause (80%);
- other causes include hypertrophic cardiomyopathy, mitral valve prolapse, aortic valve stenosis, congenital heart abnormalities, and myocarditis.

3.Chronic ischemic heart disease
is the insidious onset of progressive congestive heart failure. It is characterized by left ventricular dilation due to accumulated ischemic myocardial damage and functional loss of hypertrophied non-infarcted cardiac myocytes.

Angina

Definition:

Angina is a chest pain due to MI. when ischemia occurs the heart demand exceeds the supply of the coronary artery. Therefore, most of the agents work on reducing the oxygen demand of the heart by affecting the preload, afterload, heart rate and cardiac contractility which are the main factors that contribute the oxygen demand.

Types of angina:

Stable angina	Unstable angina	Variant angina
occurs with activity, relieved by rest	not associated with activity, not relieved by rest	due to coronary artery vasospasm which lead to decrease blood flow.

Different type of drugs can be used in case of Angina:

1- Agents that improve symptoms and ischemia which are the traditional Approaches including : Nitrates , Beta-blockers and Calcium channel blockers.

2- Agents that improve prognosis which Halt progression, prevent acute insult, and improve survival. These drugs including: ACE inhibitors, Beta-blockers and Aspirin.

Main mechanism of antianginal drugs:

1- By Increase the Oxygen Supply: Flow to ischemic subendocardial tissue improved by nitrates, CCBs, B-blockers which they act as vasodilatation

2- By Decrease the Oxygen Demand: Both Heart rate and Cardiac contractility can be decreased by B-blockers and some CCBs. In addition both Preload and afterload can be decreased by nitrates and CCBs respectively.

Anti-Anginal Therapy

Nitrates

- Example:

Short-acting: nitroglycerin (sublingual)
Long-acting: Isosorbide Dinitrate (oral).

- MOA: preload reduction by vasodilation of vein via releasing nitic oxide.
- Uses: all types of angina
- Preferred using in acute management of angina, due to the evidence of decrease mortality.
- Side effects: tachycardia, orthostatic hypotension, headache.

B-blockers

- Example: Metoprolol, Atenolol, Propranolol.
- MOA: decrease heart rate and cardiac contractility.
- Uses: stable angina. Contraindicated in variant angina.
- Side effects: bradycardia, AV block.

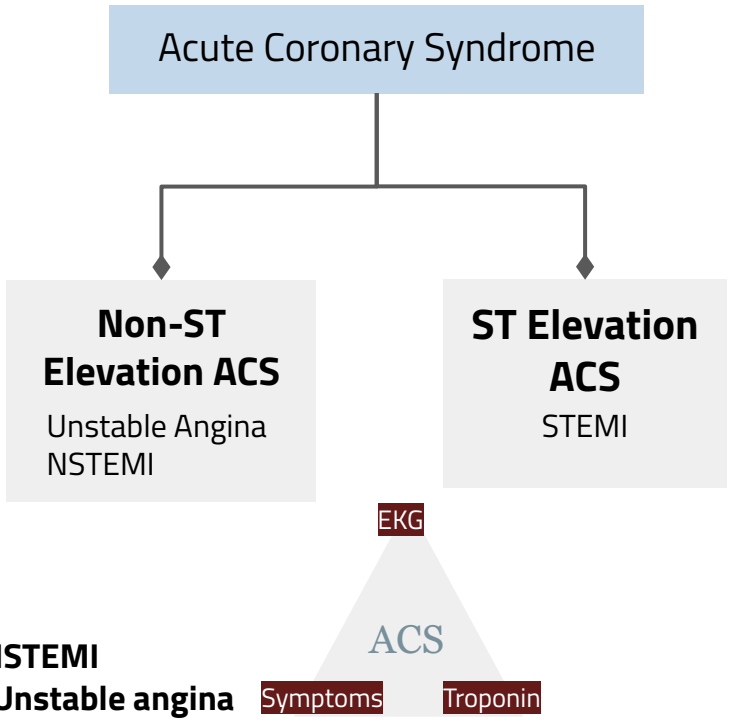
Calcium channel blocker

- Example: Verapamil, Diltiazem, Nifedipine.
- MOA: decrease oxygen demand by decreasing the contractility and increase the vasodilation
- Uses: stable and drug of choice for variant angina.
- Side effects:
  - Diltiazem and Verapamil: constipation, bradycardia and AV block.
  - Nifedipine: reflex tachycardia.

Clinical integration

DDx of Chest pain:

- Acute Coronary Syndrome
- Aortic dissection
- Acute pulmonary embolism
- Tension pneumothorax
- Esophageal rupture
- Acute pericarditis
- Others :
  (GI and respiratory causes)



1. Symptoms + EKG (STE) **-> STEMI**
2. Symptoms + troponin / Normal EKG **-> NSTEMI**
3. Symptoms / Normal troponin & EKG **-> Unstable angina**

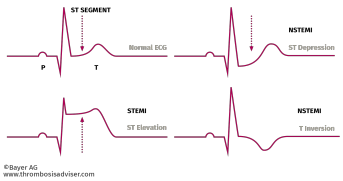
How to Approach chest pain?

1. Clinical Presentation

- Site & onset: Substernal, severe & persistent pain.
- Character: dull, heavy and pressure-like pain.
- Radiation: shoulders, arms and jaws.
- Associated Symptoms:
  - Sympathetic effect: Diaphoresis, cool & clammy skin, palpitation and syncope.
  - Parasympathetic effect: Nausea, Vomiting and weakness
  - Inflammatory response: Mild fever

2. ECG

- ST segment elevation is seen with STEMI due to *transmural* ischaemia.
- Normal ECG does not exclude the possibility of ACS.



3. Cardiac Markers

ACS	STEMI	NSTEMI	Unstable Angina
Troponin I + CK-MB *(good marker for reinfarction)	Elevated	Elevated	Normal

Thromboembolism

Major veins of the body

The superior vena cava

Formed by the union of right and left brachiocephalic veins.

terminates at the lower edge of the right third costal cartilage, where it joins the right atrium, receives the azygos vein before entering the pericardial sac and may also receive pericardial and mediastinal veins.

Drains venous blood from: Head, neck, thoracic wall & upper limbs.

The right brachiocephalic vein begins posterior to the medial end of the right clavicle.

Tributaries include:

the vertebral first posterior intercostal, and internal thoracic veins. The

inferior thyroid and thymic veins may also drain into it.

The left brachiocephalic vein begins posterior to the medial end of the left clavicle.

Tributaries include:

the vertebral first posterior intercostal, left superior intercostal, inferior thyroid, and internal thoracic veins. It may also receive thymic and pericardial veins.

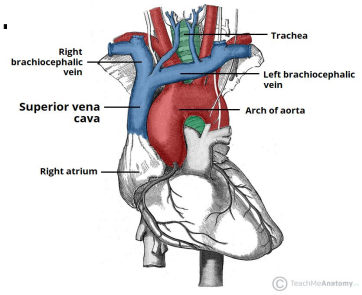
The Inferior vena cava

formed by the union of two common iliac veins.

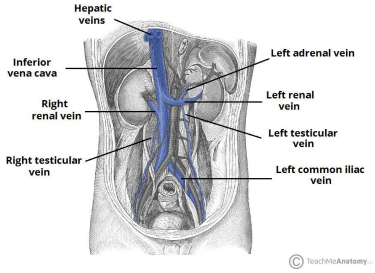
The inferior vena cava returns blood from all structures below the diaphragm to the right atrium of the heart.

It leaves the abdomen by piercing the central tendon of the diaphragm at the level of vertebra T8 .

Tributaries to the inferior vena cava: common iliac veins & lumbar veins, right testicular or ovarian vein, renal veins, right suprarenal vein, inferior phrenic veins, and hepatic veins.



Superior Vena Cava



Inferior Vena Cava

Pulmonary embolism

Any mass that obstruct the pulmonary arteries will cause a pulmonary embolism (PE).
Most common cause is an embolism from a deep vein thrombosis usually the femoral, iliac, or popliteal veins.

Pathophysiology:

The pathophysiology of this starts with Virchow's triad of the leg veins. Virchow's triad of hypercoagulability, endothelial damage, and stasis of blood flow leads to recruitment of activated platelets, which precipitate thrombosis. Venous thrombi form and flourish in an environment of stasis, low oxygen tension, and upregulation of proinflammatory genes. The thrombus can dislodge, becomes an embolus and lodges in the pulmonary arteries.
This will cause a decrease in perfusion to the affected area of the lungs with normal ventilation (V/Q mismatch). This should lead to hypercapnia and respiratory acidosis, but patients often hyperventilate and may be surprisingly hypocapnic and with respiratory alkalosis.

Symptoms:

When an embolus obstructs a large or medium pulmonary artery, the patient may presents with:

- Shortness of breath
- Hemoptysis
- Pleuritic chest pain
- Pleural effusion

Otherwise most patients are asymptomatic due to dual arterial supply to the lungs (Bronchial and pulmonary arteries)

Risk factors:

- Immobility
- Pregnancy
- Recent surgery
- Multiple fractures
- Inherited hypercoagulability
- Cancer
- Oral contraceptive

Metabolic Disorders

Metabolic disorders are changes that occur to Bicarbonate concentration in the blood(HCO3).

Metabolic acidosis is characterized by low ph and HCO3. The decrease in ph will stimulate the peripheral chemoreceptors so the respiratory response would be the first to respond.

Metabolic alkalosis on the other hand is due to an increase in ph and and an increase in HCO3, so the respiratory response would be hypoventilation to retain the CO2 concentration.

The causes of metabolic disorders (especially metabolic acidosis); because an increase in the anion gap usually indicates a disturbance in the organic acid levels in the body, are differentiated based on a quick simple mathematical tool that is called the anion gap.
The anion gap is the measurement of the major anions and cations in the blood. (Na+ , Cl- and HCO3-)

Here is quick mnemonic that helps you to memorize the elevated and non elevated gap metabolic acidosis.

MUDPILES (elevated gap)	HARDUP (non-elevated gap)
M: Methanol	**H:** Hyperchloremia (parenteral nutrition)
U: Uremia (kidney failure)	**A:** Acetazolamide
D: Diabetic ketoacidosis	**R:** Renal tubular acidosis
P: Paraldehyde	**D:** Diarrhea
I: Iron; Isoniazid	**U:** Ureteral diversion
L: Lactic acidosis	**P:** Pancreatic fistula
E: Ethylene glycol; ethanol ketoacidosis	
S: Salicylates; starvation ketoacidosis; sepsis	

As you can see that lactic acidosis is a high anion gap acidosis the reason is that lactic acid will lose its hydrogen ion through the cori cycle and as a result there is a free hydrogen ion that will react with HCO3 and concurring into the unmeasured anion and cause the disturbance (increase) of the anion gap.

Lactic acidosis

Lactate is a normal product in the body in anaerobic conditions its the result of the cori cycle, but in cases of increase in plasma lactate its called lactic acidosis.

The reason for this increase may be of two main reasons: a failure in the circulatory system(hemorrhage , MI, and pulmonary embolism) or a disruption in the hepatic metabolism (cori cycle). Furthermore the deficiency of pyruvate dehydrogenase enzyme is a congenital malformation that would cause lactic acidosis because of the accumulation of lactate.

When hypoxia occurs the cell is not able to produce ATP, as a result glycolysis will occur normally and the cell will undergo anaerobic glycolysis. However this is not enough to compensate the lost amount of oxygen, in highly anaerobic tissues like cardiac muscles. The result is that cell will swell and release enzymes as an effect of diminished oxygen supply and coagulation necrosis will occur if the problem persists, as in the case of myocardial infarction. The lost oxygen that was lost during this period must be recovered (hyperventilation) and the amount that is lost is called oxygen debt.

THROMBOSIS

- It's a pathologic formation of an intravascular blood clot (thrombus), can occur in an artery or vein.
- The most common location is the deep veins of the leg below the knee.
- It characterized by (1) lines of Zahn (alternating layers of platelets/ fibrin and RBCs, and (2) attachment to vessel wall, both features distinguish thrombus from postmortem clot.
- Three major risk factors for thrombosis, which are disruption in blood flow, endothelial cell damage and hypercoagulable state which known as Virchow triad.

EMBOLISM

- It's an intravascular mass that travels and occludes downstream vessels; symptoms depend on the vessel involved .
- Thromboembolus is due to a thrombus that dislodges; most common type of embolus (>95 %)
- Atherosclerotic embolus is due to an atherosclerotic plaque that dislodges, characterized by the presence of cholesterol clefts in the embolus.
- Fat embolus is associated with bone fractures, particularly long bones, and soft tissue trauma, it develops while fracture is still present or shortly after repair and characterized by dyspnea and petechiae on the skin overlying the chest.
- Gas embolus is classically seen in decompression sickness when a nitrogen gas precipitates out of blood due to rapid ascent by a diver. Usually presents with joint and muscle pain ('bends') and respiratory symptoms. It may also occur during laparoscopic surgery (air is pumped into the abdomen).
- Amniotic fluid embolus enters maternal circulation during labor or delivery, they Presents with shortness of breath, neurologic symptoms, and DIC (due to the thrombogenic nature of amniotic fluid). It characterized by squamous cells and keratin debris, from fetal skin, in embolus.

PULMONARY EMBOLISM (PE)

- Usually due to thromboembolus; the most common source is deep venous thrombus (DVT) of the lower extremity, usually involving the femoral, iliac, or popliteal veins.
- Most often clinically silent because (1) the lung has a dual blood supply (via pulmonary and bronchial arteries) and (2) the embolus is usually small (self- resolves).
- Pulmonary infarction occurs if a large or medium sized artery is obstructed in patients with preexisting cardiopulmonary compromise; only 10% of PEs cause infarction.

Symptoms:

Presents with shortness of breath, hemoptysis, pleuritic chest pain, and pleural effusion.

Investigation:

  - V/Q lung scan shows mismatch; perfusion is abnormal
  - Spiral CT shows a vascular filling defect in the lung
  - Doppler ultrasound to detect DVT
  - D-dimer is elevated
  - Gross examination reveals a hemorrhagic, wedge-shaped infarct.

- Sudden death occurs with a large saddle embolus that blocks both left and right pulmonary arteries or with significant occlusion of a large pulmonary artery.
- Pulmonary hypertension may arise with chronic emboli that are reorganized over time.

SYSTEMIC EMBOLISM

- Usually due to thromboembolus.
- Most commonly arise in the left heart.
- Travel down systemic circulation to occlude flow to organs, most commonly the lower extremities.

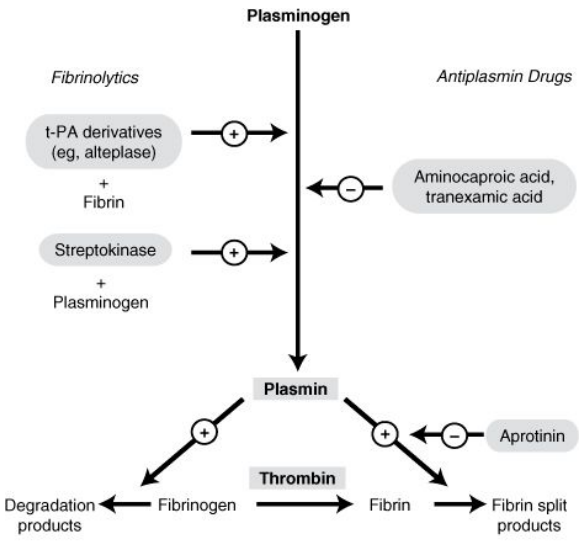
Thrombolytic Drugs

Introduction to Thrombolytics

Thrombolytics, also called fibrinolytics, are used to lyse active clots in the circulation.The goal of thrombolytic therapy is rapid restoration of blood flow in an occluded vessel by accelerating proteolysis of the already formed thrombus. Their basic mechanism is to increase formation of plasmin, the intrinsic enzyme responsible for degrading fibrin clots. Thrombolytics are highly indicated in cases of early MI and early thromboembolic (ischemic) stroke.

Types of Thrombolytic drugs

1) **Non-Fibrin Specific Agent**
   - It binds equally to circulating and non-circulating plasminogen
   - Activates plasminogen bound to clot surface (local fibrinolysis) as well as circulating plasminogen and other plasma proteins thus causing systemic fibrinolysis that leads to bleeding.
2) **Fibrin Specific Agent**
   - They are tissue plasminogen activators they act as tPA (human factor)
   - Selective in action (fibrin specific)
   - Bind to plasminogen at fibrin surface (non-circulating plasminogen)
   - Risk of bleeding is less than nonspecific agents
   - Activity is enhanced upon binding to fibrin



Thrombolytic Drugs

Non-Fibrin Specific Drugs

	Streptokinase	Anistreplase	Urokinase
Mechanism	Indirectly activates plasminogen. Streptokinase first binds plasminogen, forming a one-to-one complex. This active complex then catalyzes the formation of plasmin from another molecule of plasminogen.	It's an acylated plasminogen combined with streptokinase. It is a prodrug, de-acylated in circulation into the active plasminogen-streptokinase complex.	It is a direct plasminogen activator, high fibrin specificity. Human enzyme synthesized by the kidney. Obtained from either urine or cultures of human embryonic kidney cells.
Site	Free plasminogen and fibrin-bound plasminogen.		
Indication	Acute MI, stroke, PE.		Only approved for lysis of pulmonary emboli
Side effects	Hemorrhage (Systemic lysis) Antigenicity Allergic reaction		Hemorrhage (Systemic lysis)
Contraindica-tion	Pregnancy, and in patients with healing wounds, a history of cerebrovascular accident, brain tumor, head trauma, intracranial bleeding, and metastatic cancer.		

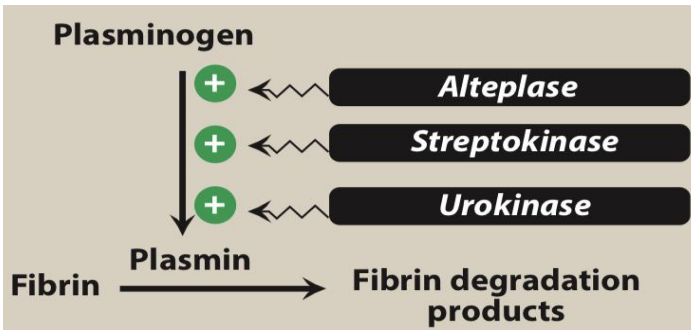


Figure A

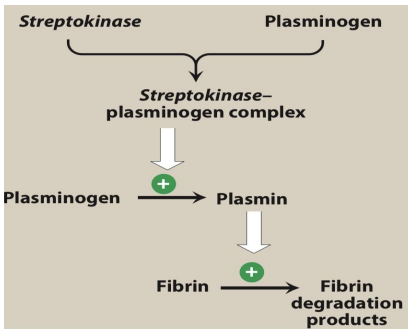


Figure B

Thrombolytic Drugs

Fibrin Specific Drugs (Tissue Plasminogen Activators)

	Alteplase	Reteplase	Tenecteplase
Mechanism	In contrast to streptokinase, tPA is **fibrin-specific**. Therefore it only activates plasminogen molecules that are bound to fibrin clots. It **directly** activates plasminogen.		
Site	Plasminogen bound to fibrin clots		
Indication	Acute MI, stroke, PE.	Acute MI, may be used off-label in DVT and massive PE	Acute MI
Side effects	Hemorrhage		
Contraindication	Pregnancy, and in patients with healing wounds, a history of cerebrovascular accident, brain tumor, head trauma, intracranial bleeding, and metastatic cancer.		

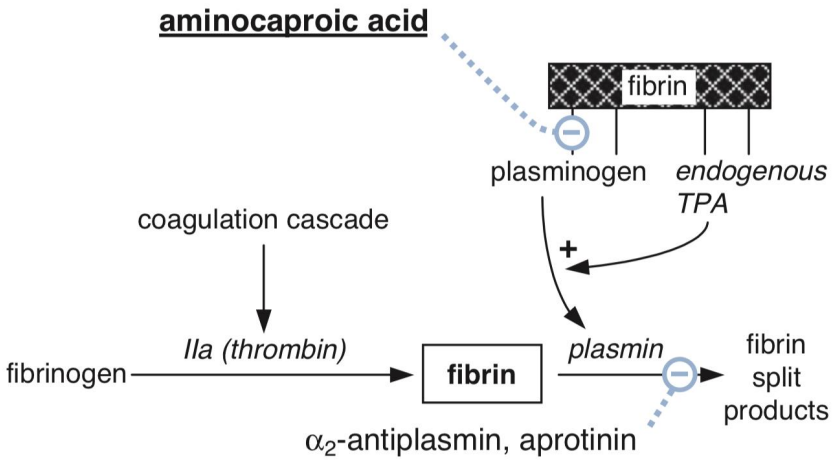
Fibrinolytic Inhibitors (Antiplasmin Drugs)

Overview

All thrombolytics can cause bleeding, which may be counteracted to some extent by administration of fibrinolytic inhibitors, such as aminocaproic acid. They possible antidotes in excessive bleeding.

Types of Thrombolytic drugs

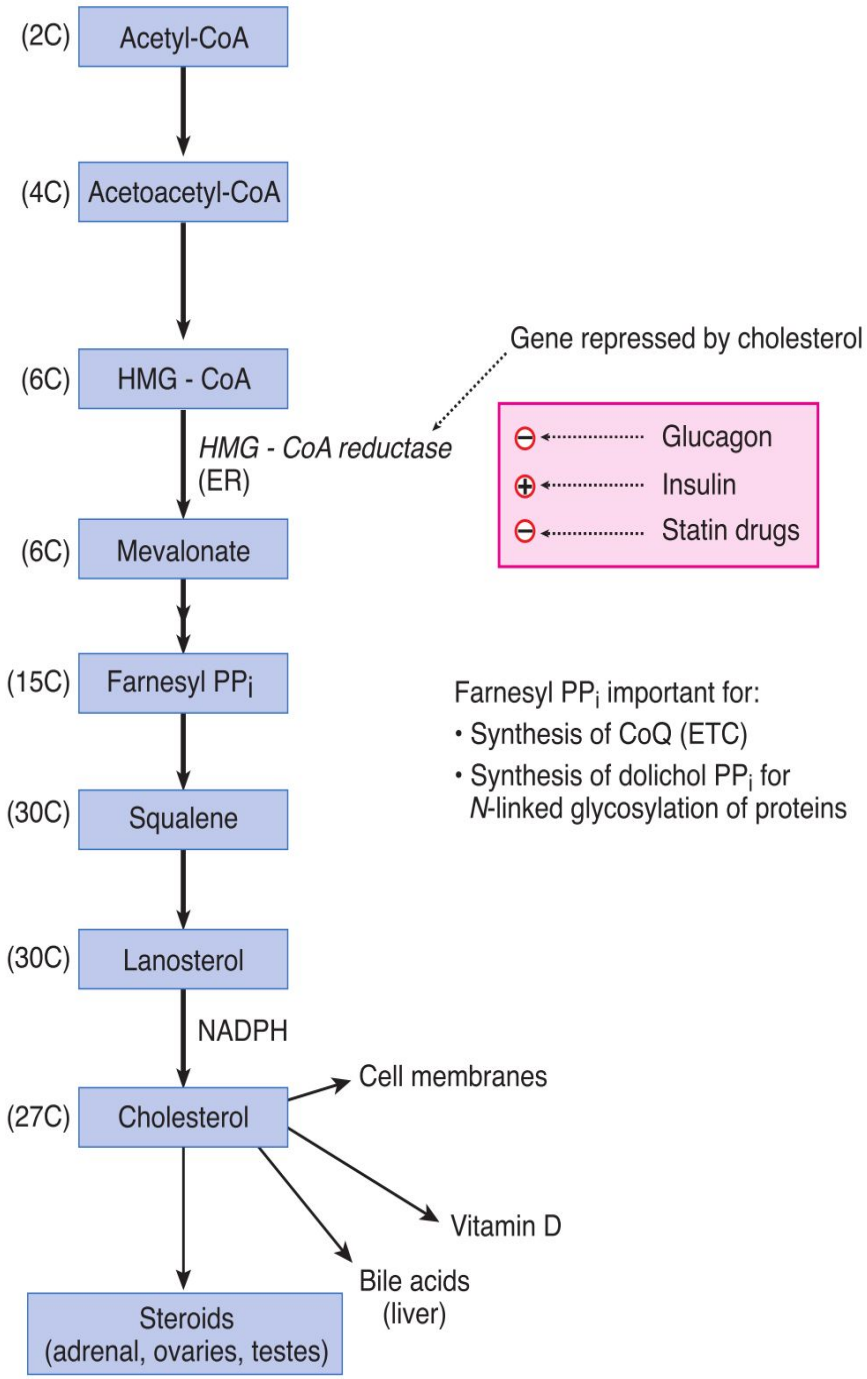
	Aminocaproic Acid	Tranexamic Acid	Aprotinin
Mechanism	Competitive inhibition of plasminogen activation. Tranexamic acid is 10 times more potent than aminocaproic acid.		Plasmin antagonist; Blocks the action of plasmin
Indication	1. Antidote for bleeding induced by fibrinolytic therapy 2. Post-surgical bleeding 3. Adjuvant therapy in hemophilia		
Side effects	Muscle necrosis Thrombosis CVA Seizure		Associated with an excess of presumably thrombotic end-organ dysfunction, including renal failure, myocardial infarction, stroke, and death.



Hyperlipidemia

Cholesterol & Lipoprotein Metabolism

Cholesterol is essential for steroid, membrane, and vitamin D synthesis also it is important in the liver for bile acid synthesis. The vast majority of cells derive their cholesterol from LDL or HDL, however some cholesterol may be synthesized de novo. Most de novo synthesis happens in the liver, where cholesterol is synthesized from acetyl-CoA in the cytoplasm. The citrate shuttle carries mitochondrial acetyl-CoA into the cytoplasm, and NADPH is provided by the HMP shunt and malic enzyme.



Cholesterol & Lipoprotein Metabolism

Cholesterol Digestion

Triglycerides and cholesterol are transported in the blood as lipoproteins. Lipoproteins are named according to their density, which increases with the percentage of protein in the particle.
From least dense to most dense:

1-Chylomicrons 2-VLDL 3-IDL(intermediate-density lipoproteins) 4-LDL 5-HDL

Lipoprotein	Functions	Apoprotein	Functions
Chylomicrons	Transport dietary triglyceride and cholesterol from intestine to tissues	apo-48 apoC-II apoE	Secreted by intestine and activate lipoprotein lipase
VLDL	Transport triglyceride from liver to tissues	apoB-100 apoC-II apoE	Secreted by liver and activate lipoprotein lipase
IDL	Pick up cholesterol from HDL to become LDL	apoE apoB-100	Uptake by liver
LDL	Delivers Cholesterol into cells	apoB-100	Uptake by liver and other tissues by LDL receptor
HDL	Pick up Cholesterols from blood vessels to liver	apoA-1	Activate LCAT to produce cholesterol esters

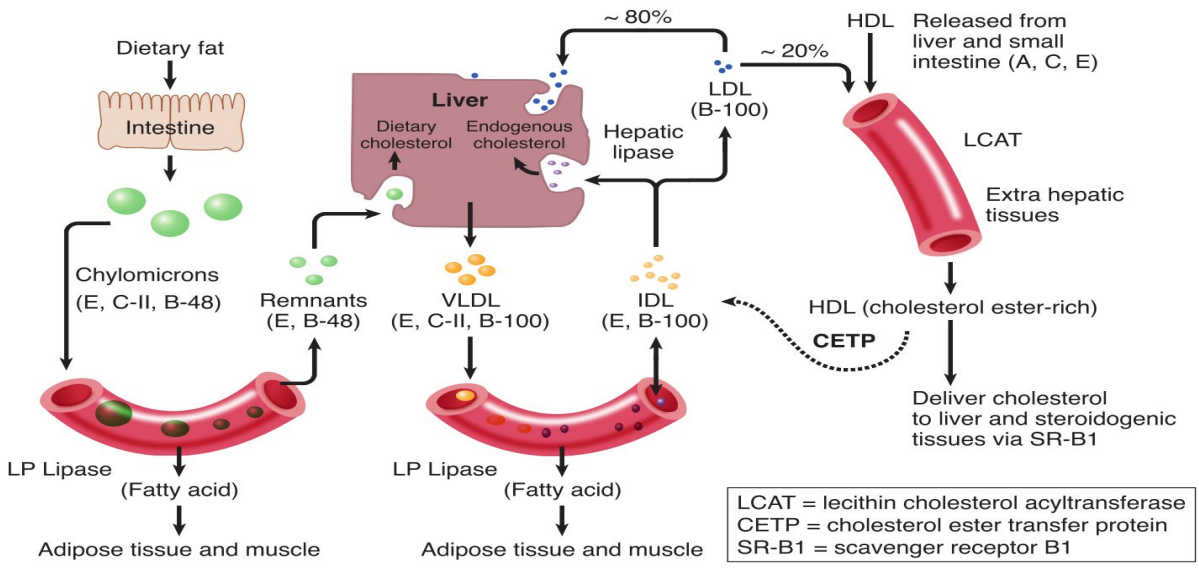


Figure I-15-5. Lipoprotein Metabolism

Atherosclerosis

Atherosclerosis is characterized by the presence of an atherosclerotic plaque in the walls of arterial vessels. Atherosclerotic plaque or atheroma is composed mainly of cholesterol, cholesterol esters, and necrotic derbies covered by fibrous caps.

Pathogenesis

- Injury to the endothelial cells will increase permeability, enhance leukocytes adhesion and monocytes migration into the intima,
- macrophages then activate and release cytokines that cause smooth muscles to migrate into the intima,
- macrophages engulf lipids forming into foam cells and become fatty streaks which enlarges over time
- smooth muscles will then proliferate and after some time a fibrous capsule will appear and fatty streak now changes into an atherosclerotic plaque.
- with time the plaque will increase in size and occlude the vessel.

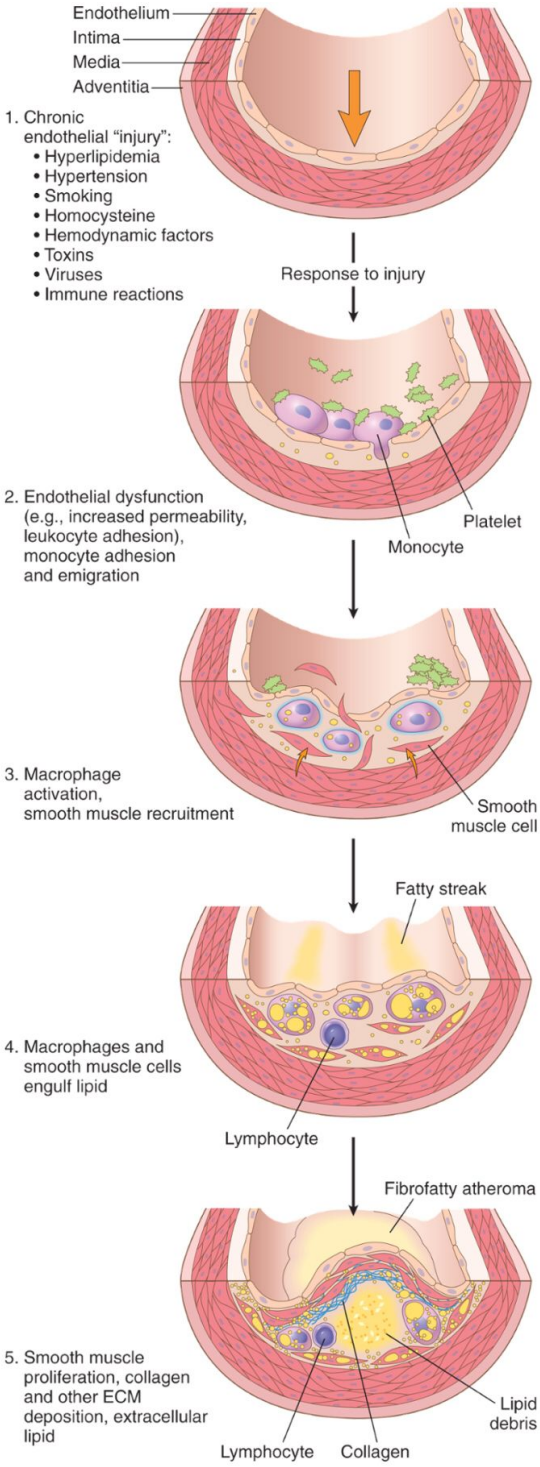


Image source: Robbins basic pathology ninth edition figure 9-10

Common sites affected by atherosclerosis:

The most commonly involved vessels are the large elastic arteries and large and medium sized muscular arteries:
abdominal aorta > coronary artery > popliteal artery > internal carotid artery > circle of Willis. The common carotid arteries are often spared

Atherosclerosis

Risk factors

Atherosclerosis risk factors are divided into modifiable and nonmodifiable risk factors listed in the table below:

Modifiable	Nonmodifiable
Hyperlipidemia Hypertension Cigarette Smoking Diabetes Inflammation Obesity Sedentary lifestyle Oral contraceptives	Age Male gender (men and postmenpausal women) Homocystinuria Family history/ genetic abnormalities (e.g. familial hypercholesterolemia)

Clinical consequences:

- plaques can obstruct the lumina of the vessels which compromises tissue perfusion and lead to ischemia (e.g. ischemic heart disease and Myocardial infarction)
- they are also prone to rupture causing the formation of a thrombus.
- cause weakening the underlying vessel wall leading to aneurysm.

Complications

- Ischemic heart disease (myocardial infarctions)
- Cerebrovascular accidents (stroke or transient ischemic attacks)
- Renal thrombosis leading to renal infarcts and activation of the renin-angiotensin- aldosterone system and hypertension
- Periphrastic vascular disease (claudications, aneurysms)

Drugs for Hyperlipidemia

Drugs	Examples	MOA	Side Effects
HMG-CoA reductase inhibitors (statins)	Atorvastatin Lovastatin Pravastatin Simvastatin	Inhibit rate-determining step in cholesterol synthesis, leading to increase LDL receptors **First line in hypercholesterolemia**	Increase LFTs, myositis
Bile acid resins	Cholestyramine Colestipol	Bind to bile salts in intestine and prevent their reabsorption	Cholesterol gallstone, bad taste, bloating, constipation, impair absorption of fat soluble vitamins
Cholesterol absorption inhibitors	Ezetimibe	Prevent absorption of cholesterol in the intestine	Diarrhea
Fibrates	Gemfibrozil Fenofibrate	Increase synthesis of lipoprotein lipase	Myositis, increase LFTs, Cholesterol gallstone
Niacin	Nicotinic acid Vitamin B_3	Decrease formation and secretion of VLDL	Flushed face; prevented by aspirin

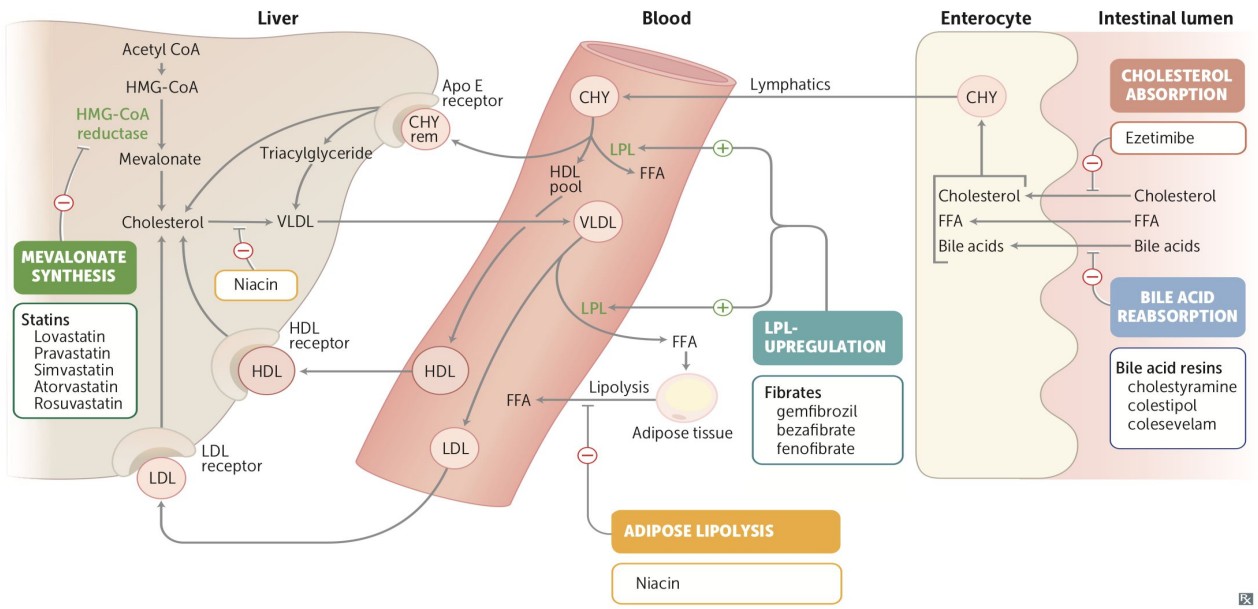


FIGURE 1-85. **Overview of mechanisms of various lipid-lowering agents.** CHY-rem, chylomicron remnant; FFA, free fatty acid; HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

Clinical integration

Hyperlipidemia

Hyperlipidemia is a medical term for elevated levels of lipids in the blood including elevated plasma triglyceride or cholesterol levels or both.

Types of cholesterol:

1- High-density lipoproteins (HDL), (good" cholesterol).
HDL carries cholesterol from body back to liver, which then removes it from your body. A higher level of HDL is better.
2- Low-density lipoproteins (LDL), (bad cholesterol).
LDL causes the buildup of plaque in blood vessels. A lower level of LDL is better.

Types of Hyperlipidemia :

1- Primary Hyperlipidemia
such as a familial dyslipidemia syndrome

2- Secondary hyperlipidemia
a. Endocrine disorders—hypothyroidism, DM, Cushing syndrome
b. Renal disorders—nephrotic syndrome, uremia
c. Chronic liver disease

Risk factor

- Diet
- Alcohol intake
- Age
- Inactive lifestyle, abdominal obesity
- Family history of hyperlipidemia
- Gender: men generally

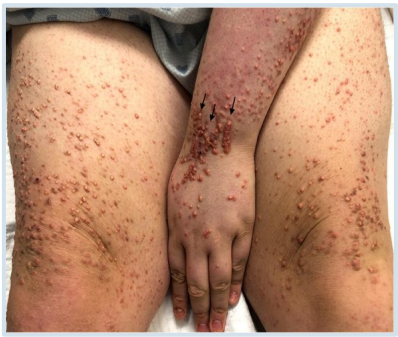
History:

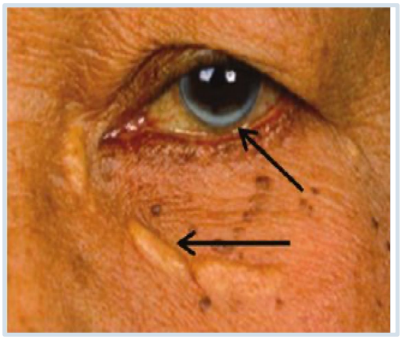
Hyperlipidemia is usually asymptomatic, sign and symptoms are usually related to complication such as

- Heart attack
- Stroke
- Peripheral artery disease

Physical exam:

On examination, findings may be normal, or they may include the following





Physical finding	Xanthomas	Xanthelasmas
Explanation	hard, yellowish masses found on tendons (finger extensors, Achilles tendon, plantar tendons).	Yellow plaques on eyelids.

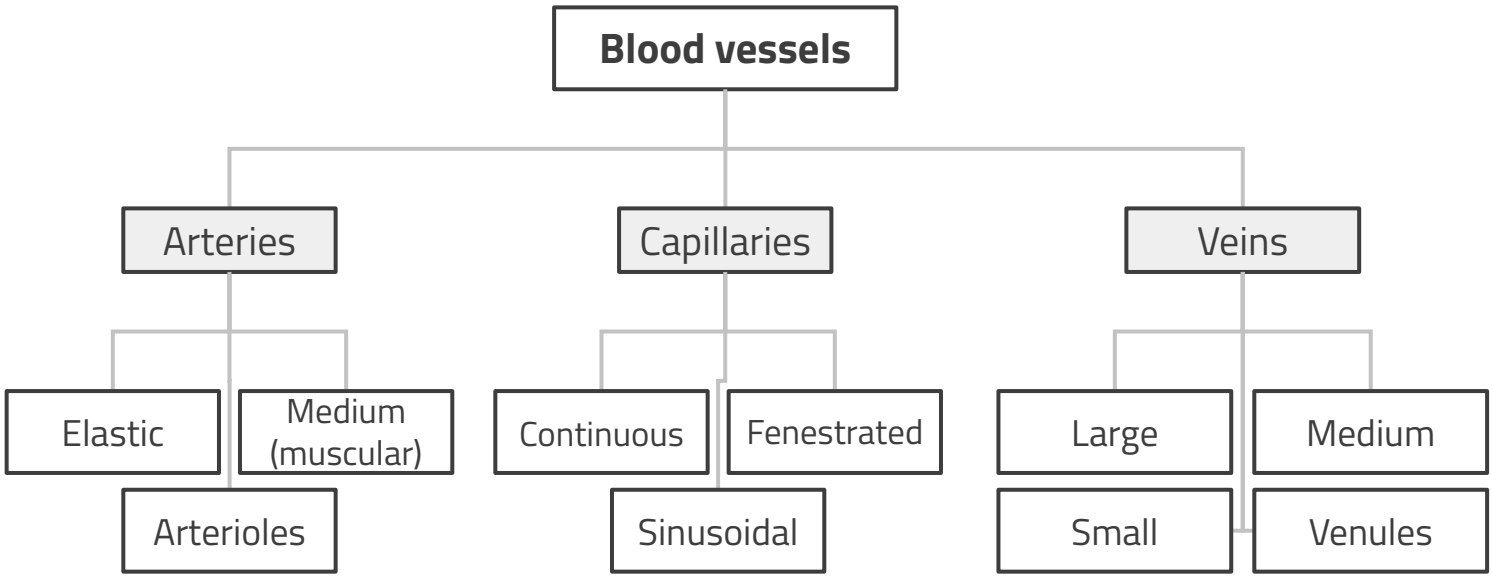
How to diagnose ?

1. A full lipid profile includes TG levels and calculation of LDL levels.
2. Consider checking laboratory tests to exclude secondary causes of hyperlipidemia.

a. TSH (hypothyroidism).
b. LFTs (chronic liver disease).
c. BUN and Cr, urinary proteins (nephrotic syndrome).
d. Glucose levels (diabetes).

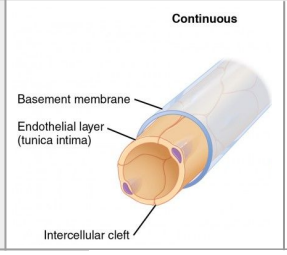
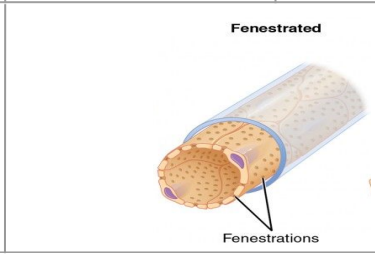
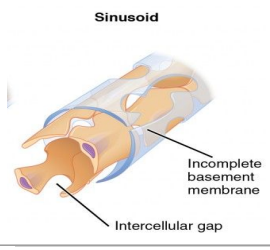
Hypertension

Blood vessels



	Elastic arteries (large)	Muscular arteries (medium)
Examples	Aorta, common carotid artery, subclavian artery, common iliac artery, pulmonary Trunk	Brachial, Ulnar, Renal arteries.
Tunica intima (interna)	▪Endothelium ▪Subendothelial C.T. ▪Internal elastic lamina: **not prominent** & indistinct	▪Endothelium ▪Subendothelial C.T. ▪Internal elastic lamina: **prominent** and Displays an undulating surface.
Tunica media	▪Fenestrated elastic membranes: sheets & lamellae. ▪In between: 1- Elastic fibers (**main**) 2- Collagen fibers (type I collagen) 3- Reticular fibers (type III collagen) 4- Smooth muscle cells	▪Smooth muscle cells (**main**) ▪In between SMCs: 1- Elastic fibers 2- Collagen fibers (type I collagen) 3- Reticular fibers (type III collagen) ▪External elastic lamina: may be identifiable.
Tunica adventitia (externa)	▪Much thinner than tunica media (T.M.) ▪It is composed of loose connective tissue ▪Contains vasa vasorum that send branches to the outer part of T.M.	▪thinner or similar in thickness to T.M. ▪ composed of loose connective

	Medium sized veins thinner than the accompanying artery
Tunica intima (interna)	• no internal elastic lamina • usually forms **valves**: composed of 2 leaflets each has a thin fold of the T. Intima. Components: - Endothelium - Core of C.T.
Tunica media	• Fewer SMCs. • Types I & III Collagen fibers
Tunica adventitia (externa)	• thicker than T. Media

Blood capillaries	Continuous	Fenestrated		Sinusoidal
Microscopic structure	1. Single layer of squamous endothelial cells. 2. Basal lamina: surrounds the external surface of the endothelial cells. 3. Pericytes: Have processes, share the basal lamina of the endothelial cells.			
	No pores or fenestrae in walls	Walls of their endothelial cells have pores (fenestrae) **with diaphragm**	Walls of their endothelial cells have pores (fenestrae) **without diaphragm**	▪Their endothelial cells have "large" fenestrae **without diaphragms.** ▪ possess discontinuous endothelial cells & discontinuous basal lamina. ▪Macrophages may be located in or along the outside of the endothelial wall. ▪Diameter: irregular
Distribution	muscles, nervous tissue, C.T. Pulmonary capillaries	intestine, pancreas and endocrine glands	In renal glomerulus	Red bone marrow, liver, spleen and certain endocrine glands
				

Picture source: https://courses.lumenlearning.com/suny-ap2/chapter/structure-and-function-of-blood-vessels/.

Major arteries of the body

General principles of arteries & Arterial Anastomosis

- **Arteries:**

  Blood vessels that carry blood from the heart to the body. All arteries carry oxygenated blood, **except** the Pulmonary artery which carries deoxygenated blood to the lungs. The flow of blood depends on the pumping action of the heart.

- **Free anastomosis:**

  normally in branches of arteries supplying adjacent areas, providing backup routes for blood to flow if one artery is blocked. E.g. **arteries of limbs**

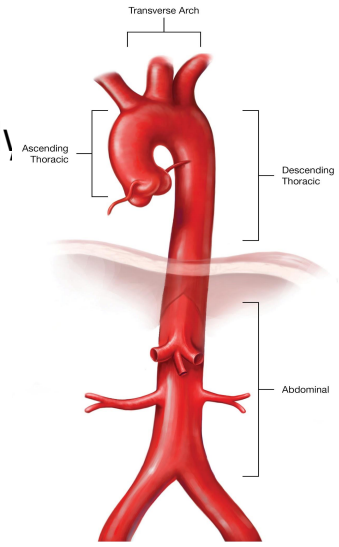
- **End arteries:**

  whose terminal branches do not anastomose with branches of adjacent arteries.

A. **Anatomic (True) End Artery:** When NO anastomosis exists. E.g. **artery of retina.**
B. **Functional End Artery:** When an anastomosis exists but is incapable of providing a sufficient supply of blood. E.g. **splenic artery, renal artery.**

Aorta

- The largest artery in the body.
- Carries oxygenated blood to all parts of the body
- divided into 4 parts:
  1. Ascending aorta
  2. Arch of aorta
  3. Descending thoracic aorta
  4. Abdominal aorta



Ascending aorta

- Originates from left ventricle.
- Has three dilatations at its base: **aortic sinuses.**
- **Branches**: Right & Left coronary arteries (supplying heart) , arise from aortic sinuses.
- Continues as the **arch of aorta.**

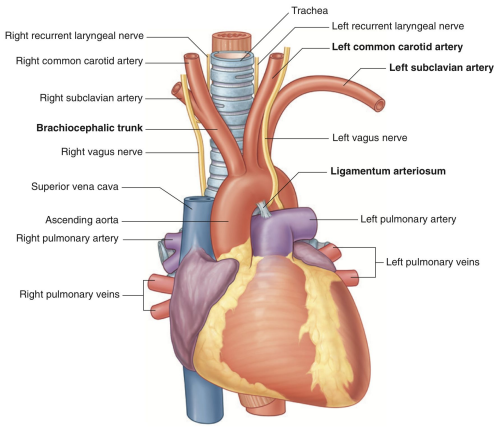
Arch of aorta

- Continuation of the ascending aorta.
- Leads to **descending aorta.**
- Located behind the lower part of manubrium sterni and on the left side of trachea.
- **Branches**:

  1. Brachiocephalic trunk.

  2. Left common carotid artery.

  3. Left subclavian artery.



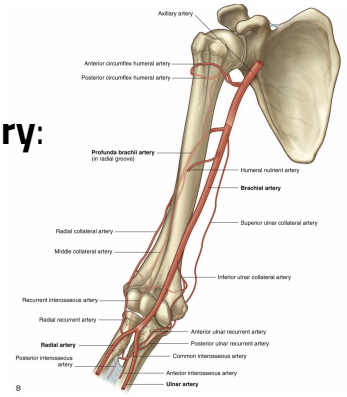
Common Carotid artery

- Origin: **Left** from aortic arch. **Right** from brachiocephalic trunk.
- Each common carotid divides into two branches:

Internal carotid artery (right & left)	External carotid artery (right & left)
Enters the cranial cavity, joins the basilar artery (formed by the union of two vertebral arteries) and forms "arterial circle of Willis"	Divides behind neck of mandible into: Superficial temporal & Maxillary arteries
Supplies: -brain (by circle of Willis) -nose -scalp -eye	**Supplies:** -Scalp: Superficial temporal, occipital, posterior auricular. -Face: Facial artery -Maxilla & mandible: Maxillary artery -Tongue: Lingual artery -Pharynx: ascending pharyngeal artery -Thyroid gland: Superior thyroid artery

Subclavian artery

- Origin: **Left** from arch of aorta, **Right** from brachiocephalic trunk.
- Main **branches**:
- Vertebral artery: supplies brain & spinal cord
- Internal thoracic artery: supplies thoracic wall
- It continues at lateral border of first rib as **axillary artery**: artery of upper limb.



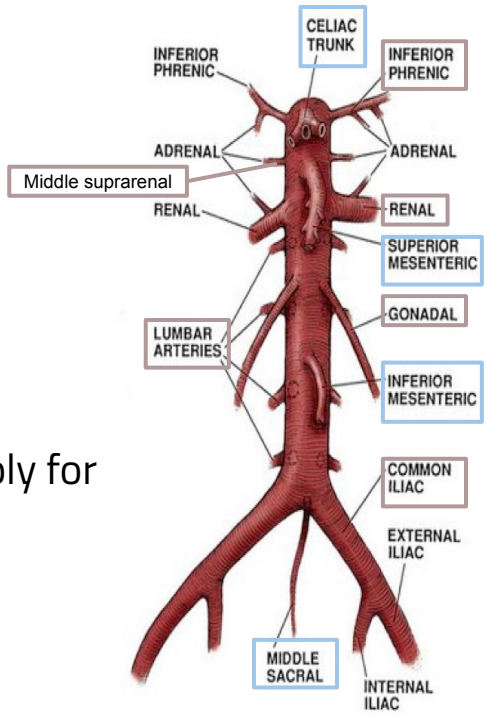
Descending thoracic aorta

- It is the continuation of aortic arch.
- **Branches**: Bronchial, Esophageal, Pericardial, Posterior intercostal.
  Mnemonic: BE Pery Positive
- At the level of the **12th thoracic** vertebra, it passes through the diaphragm and continues as the **abdominal aorta**.

Abdominal aorta

- It enters the abdomen through the aortic opening of diaphragm.
- At the level of lower border of **L4**,
- It divides into two **common Iliac** arteries.
- **Branches** divided into two groups:

  1-Single branches 2-Paired branches



Branches of common iliac artery

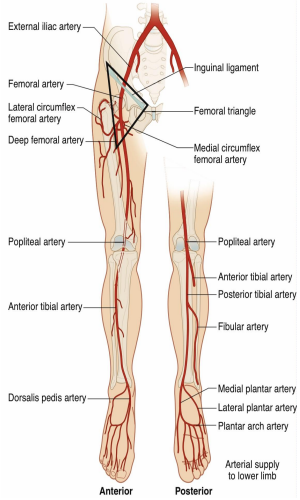
1-**External iliac artery:** continues (at midpoint of inguinal ligament) as femoral artery the main supply for lower limb.

2-**Internal iliac artery:** supplies pelvis.

Arteries of lower limb

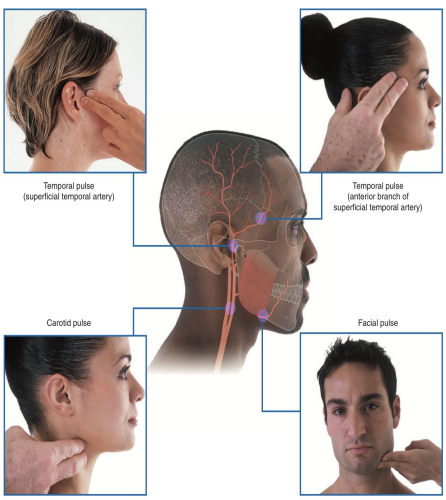
1-**Femoral Artery:** Passes through adductor hiatus and continues as:

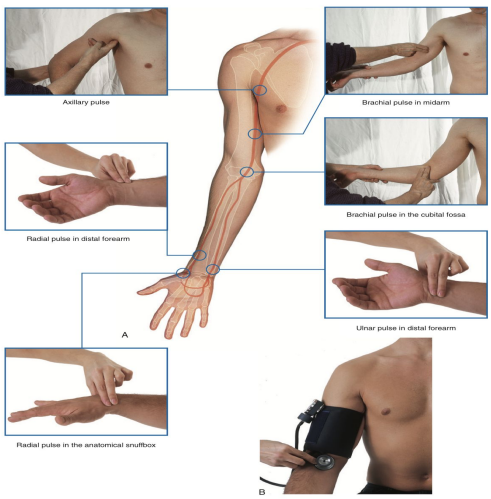
2-**Popliteal Artery:** Deeply placed in the popliteal fossa. Divides, at lower end of popliteal fossa into:
A- Anterior Tibial Artery (continues as Dorsalis Pedis Artery).
B- Posterior Tibial Artery (divides into Medial & Lateral Plantar Arteries)

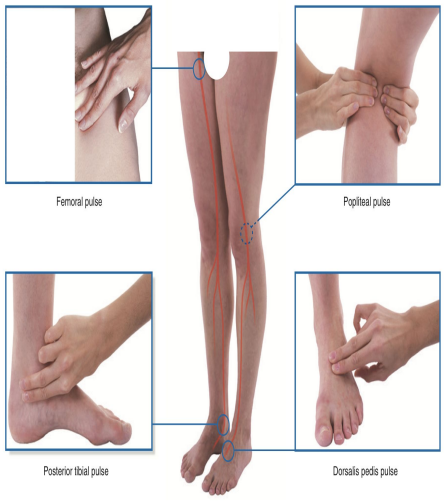


Pulse points

Head & neck **Upper limb** **Lower limb**







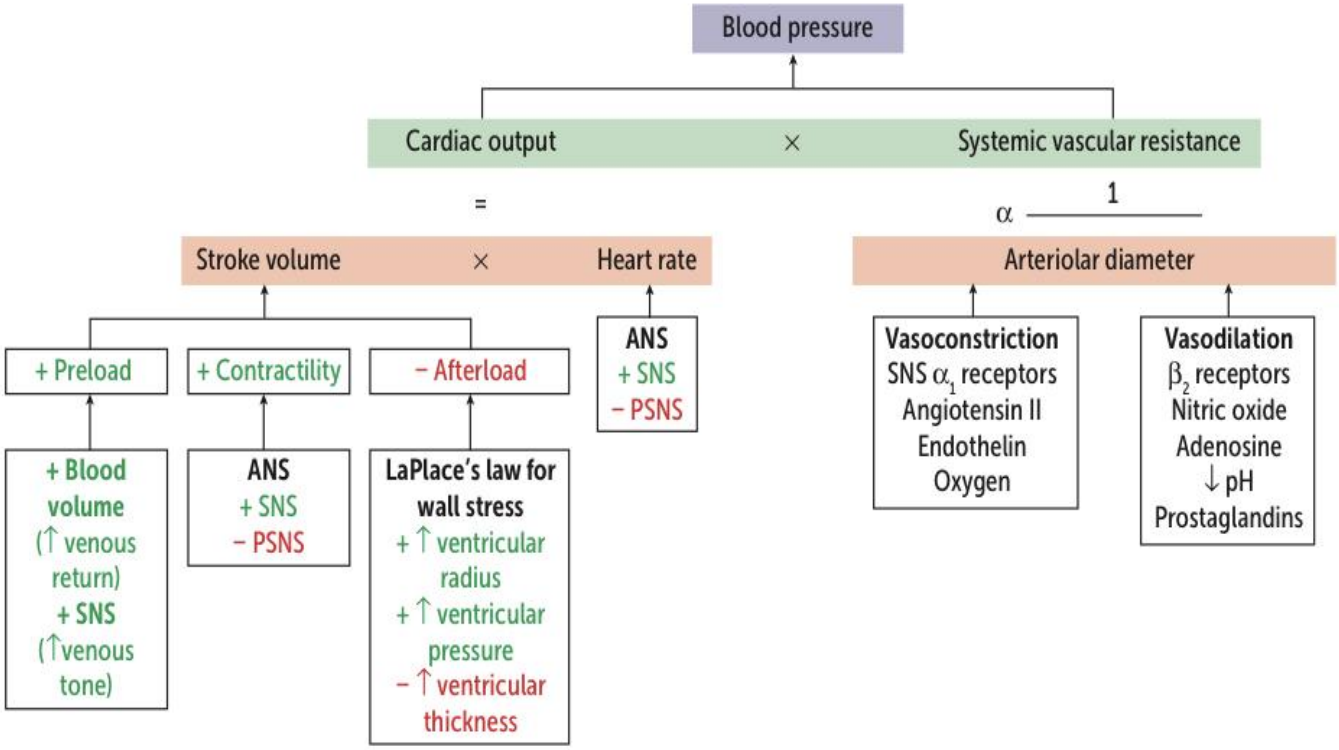
Arterial Blood Pressure

	Definition	Normal range	formulas
Arterial Blood Pressure	It is the lateral pressure force exerted by the blood flow on the arterial wall against any unit area of the vessel wall.***	120 mmHg systolic /80 mmHg diastolic	-
Systolic	The maximum force exerted by the blood flow against any unit area of the vessel wall while the heart is maximally contracting***	90 – 120 mmHg	-
Diastolic	The minimum force exerted by the blood flow against any unit area of the vessel wall while the heart is maximally relaxing ***	60 – 80 mmHg	-
Mean Blood Pressure	average pressure in a patient's arteries during one cardiac cycle.*	-	-**MAP =** diastolic pressure + 1/3 × (pulse pressure) ** -**MAP =** ⅓Systolic BP + ⅔Diastolic BP
Pulse Pressure.	Difference between systolic and diastolic pressure **	-	**Pulse pressure =** Systolic P – Diastolic P

Physiological Factors Affecting Arterial Blood Pressure :

- **Sex** →Male > Female (equal at menopause)
- **Age** →BP rises with age (elderly > children)
- **Body mass index** →BP rises with body size.
- **Emotions** →BP ↑ due to neural & hormonal factors
- **Exercise** → BP ↑ due to ↑ venous return.
- **Hormones** →adrenaline, noradrenaline & thyroid H ↑BP.
- **Gravity** →BP is higher in lower limbs than upper limbs.
- **Race, dietary factors, stress.**
- **Sleep** →BP ↓ due to↓venous return.
- **Pregnancy** →BP ↑ due to ↑ in metabolism.
- **Temperature** → BP ↓ with Heat due to vasodilatation, & ↑ with Cold due to vasoconstriction.

Factors Determining Arterial Blood Pressure :



Relationship between CO, BP and total peripheral resistance:

Q = ΔP / R		
Q (Generally is equal to the Cardiac output (CO))	**ΔP**	**R**
• Blood flow is the amount of blood moving through a vessel in a given time period.	• Directly proportional to the flow	• Resistance :tendency of vascular system to oppose flow. • Inversely proportional to the flow • influenced by:Length of the tube ,radius of the tube ,& viscosity of the blood

Regulation of Blood pressure

- Maintaining MAP within normal range is important to keep a steady blood flow (perfusion) to the tissues.

- In order to maintain the blood pressure, regulating its determining factors is necessary:
  1- Cardiac output 2- Peripheral Resistance 3-Blood Volume

Mechanism In Regulating Mean Arterial Pressure

Short term regulation:

Fast response (acts within sec/min).

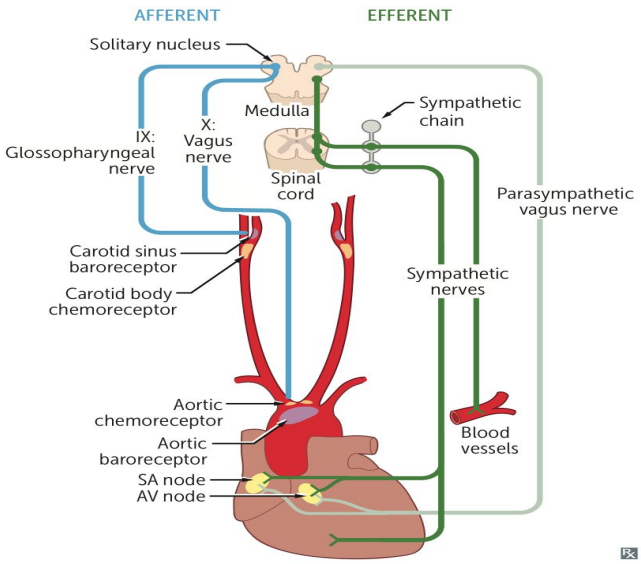
It is mainly made up of reflex mechanisms that act through autonomic nervous system (Centers in Medulla Oblongata) that is:

1- Baroreceptors: They are mechano-stretch receptors found in the walls of the aortic arch and carotid sinus, and they're stimulated in response to rapid blood pressure changes i.e: standing up.

2- Chemoreceptors: Receptors found peripherally in carotid and aortic bodies, **or** centrally in the brainstem, and they detect changes in O2,CO2,H. when Mean Arterial Pressure is less than 60 mmHg.

- Receptors are activated

- They reduce blood flow to unessential areas and protect vital tissues like brain and heart.



3- Atrial stretch volume receptors: They are receptors found in the walls of the atria

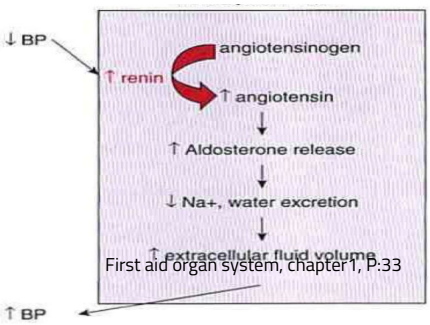
As blood volume in the atria increases, the atrial wall is stretched, which activates the receptors, Causes vasodilation and decrease Na reabsorption at the renal collecting tubule which will decrease the blood volume.

4- CNS ischemic response: Emergency pressure control mechanism that acts rapidly with very powerful sympathetic activity when blood flow to the brain decreases significantly.

Intermediate term regulation:

1- Renin-Angiotensin mechanism:

Decrease in BP activates RAAS, renin converts Angiotensinogen to Ag1 and then to Ag2 in the lungs by ACE.



First aid organ system, chapter 1, P:33

2- Capillary fluid shift mechanism: Shifting of fluid from the interstitial space to the capillaries or the opposite in response to decrease/increase in BP respectively.

Long term regulation:

1- Aldosterone mechanism

2- Antidiuretic hormone

3- Erythropoietin

Hypertension

Hypertension : a sustained systolic pressure in excess of 140 mm Hg or a sustained diastolic pressure more than 90 mm Hg (>140/90)

- Factors which contributes in development of hypertension

Coronary heart disease.

- Cerebrovascular accidents (stroke)
- Cardiac hypertrophy
- Congestive heart failure.
- Aortic dissection.
- Renal failure.
- Retinopathy

- Risk factors for Hypertension

- Hereditary,Genetics- family history
- Race. African-Americans
- Gender. Men & postmenopausal women
- Age
- Obesity
- Diet, particularly sodium intake
- Lifestyle-stressful
- Heavy alcohol consumption
- Diabetes
- Use of oral contraceptives
- Sedentary or inactive lifestyle

Classification of Hypertension

- Based on etiology or cause
- Based on clinical features

Classification: based on etiology/cause

1. Primary/Essential Hypertension (95%) : Mechanisms largely unknown. It is idiopathic.
2. Secondary Hypertension (5-10%): it can be due to pathology in the renal, endocrine, vascular or neurogenic systems

Pathophysiology

- There will be decrease blood flow to the glomerular capillaries because of arterial stenosis
- Because of decrease blood flow, the juxtaglomerular aperture will release renin. Renin will convert angiotensinogen into angiotensin I. By ACE angiotensin I will convert into angiotensin II
- Angiotensin II is a strong vasoconstrictor. Vasoconstriction of the peripheral arteries lead to increase blood pressure. Other way for the angiotensin II to increase the blood pressure is by activating aldosterone which will increase Na and water reabsorption → increase blood volume → ↑ blood pressure
- The arterial stenosis happen in unilateral fashion, so the decrease blood flow will be unilateral. The low perfusion of the kidney will lead to atrophy. Unilateral kidney atrophy is feature of renal arterial stenosis and not found in Primary/Essential Hypertension
- Causes of renal arterial stenosis are: in elderly it is commonly caused by atherosclerosis. In young female it is commonly caused by fibromuscular dysplasia

Classification of Hypertension

Other causes of secondary hypertension

Renal	• Glomerulonephritis • Renal vasculitis • Adult polycystic disease • Chronic renal disease • Renin producing tumors
Endocrine	• Adrenocortical hyperfunction (Cushing syndrome, primary aldosteronism, congenital adrenal hyperplasia) • Hyperthyroidism/Thyrotoxicosis • Hypothyroidism/ Myxedema • Pheochromocytoma • Acromegaly • Exogenous hormones (glucocorticoids, estrogen e.g. oral contraceptives) • Pregnancy-induced
Vascular	• Coarctation of aorta • Vasculitis e.g.Polyarteritis nodosa • Increased intravascular volume • Increased cardiac output • Rigidity of the aorta
Neurogenic	• Psychogenic • Increased intracranial pressure • Sleep apnea • Acute stress, including surgery

Classification of Hypertension

Classification based on clinical feature

1. Benign
    - The BP is at modest level (not very high).
    - It can be idiopathic HTN or secondary HTN
    - Fairly stable over years to decades.
    - Compatible with long life.

2. Malignant (5%)
    - there is rapidly rising BP which often leads to end organ damage
    - It can be a complication of any type of HTN (i.e. essential or secondary)
    - It is seen in 5% of HTNsive patients.
    - The diastolic pressure is usually over 120 mmHg
    - It is associated with:
        - Widespread arterial necrosis and thrombosis
        - Rapid development of renal failure
        - Retinal hemorrhage and exudate, with/without papilledema
        - Hypertensive encephalopathy
        - Left ventricular failure
        - Leads to death in 1 or 2 years if untreated.

Regulation of Blood Pressure (BP)

- There are 2 hemodynamic variables that are involved in the regulation of BP. They are cardiac output and peripheral vascular resistance

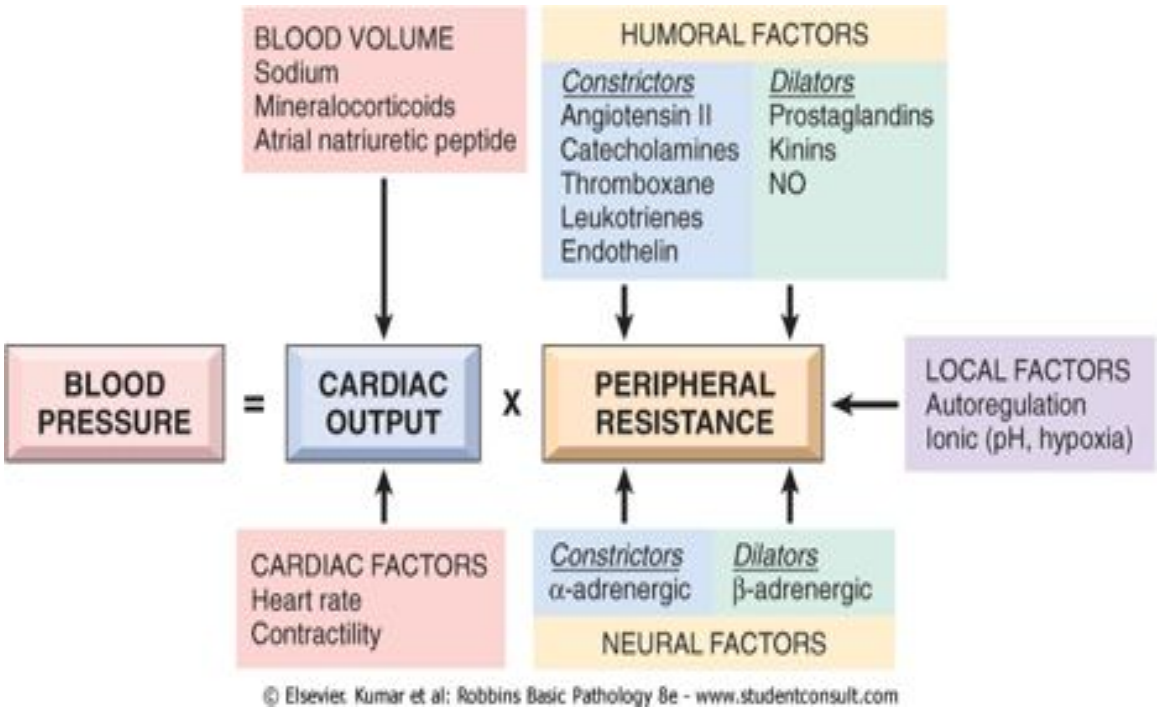
  BP = Cardiac Output x Peripheral Resistance

- Cardiac output is affected by blood volume and is dependent on sodium concentrations.

Regulation of Blood Pressure (BP)

- Peripheral resistance: it is the resistance of the arteries to blood flow. When the arteries constrict the resistance increases and when they dilate the resistance decreases. Peripheral resistance is regulated at the level of the arterioles. Arterioles are also known as resistance vessels. Peripheral resistance is determined by three factors:
  1. Autonomic activity: sympathetic activity constricts peripheral arteries.
  2. Pharmacologic agents: vasoconstrictor drugs increase resistance while vasodilator drugs decrease it.
  3. Blood viscosity: increased viscosity increases resistance.
- Normal BP is maintained by a balance between factors that induce vasoconstriction (e.g. angiotensin II and catecholamines) and factors that induce vasodilation (e.g. kinins, prostaglandins, and nitric oxide).

NOTE: An increased blood flow in the arterioles induces vasoconstriction to protect tissues against hyperperfusion.



Pathogenesis of Essential Hypertension

- Essential HTN occurs when the relationship between cardiac output and peripheral resistance is altered. Multiple genetic and environmental factors ultimately increase the cardiac output and/or peripheral resistance

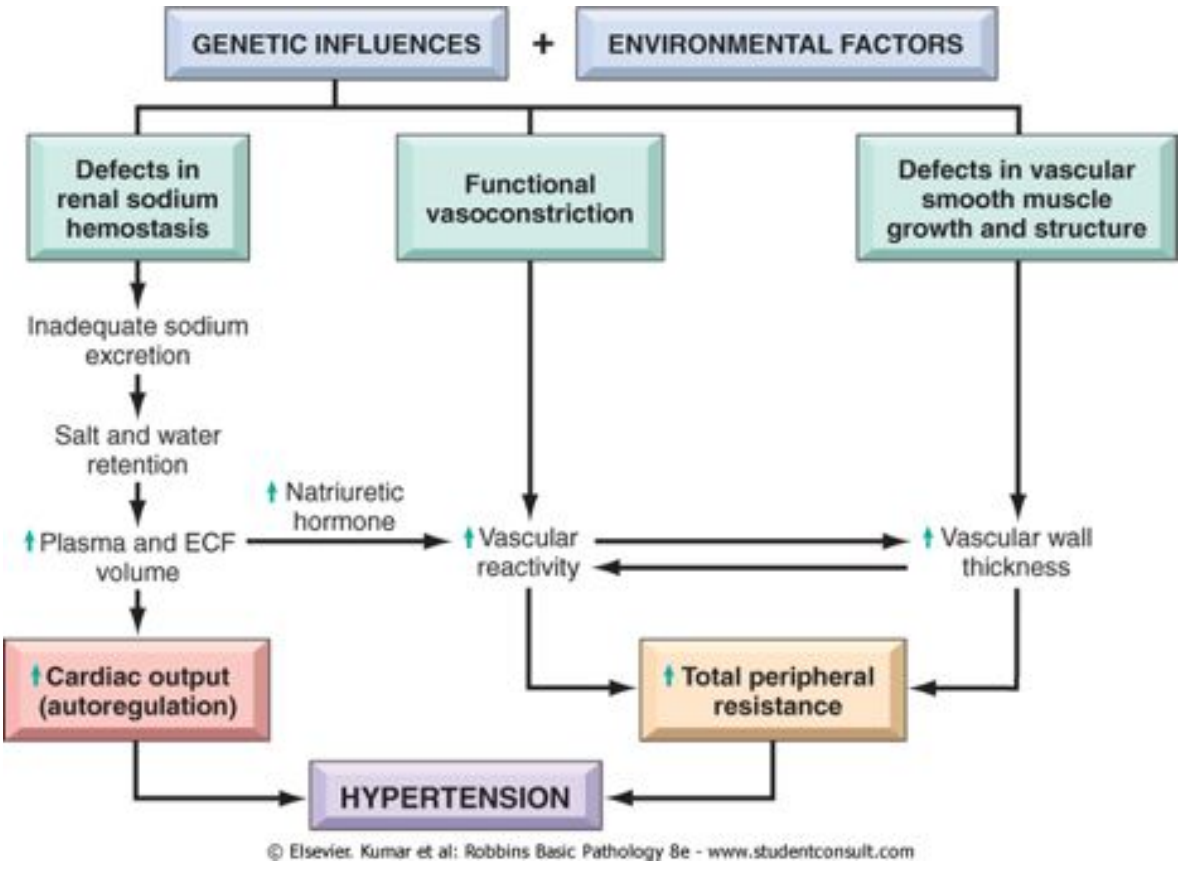
BP = Cardiac Output x Peripheral Resistance

1. Genetic factors: There is a strong genetic component (family history) e.g. a genetic effect is involved in making people more susceptible or less susceptible to high salt diet etc.
    - Defect in renal sodium homeostasis: reduced renal sodium excretion is a key initiating event in most forms of essential hypertension. Decreased sodium excretion → lead to increase in fluid volume and therefore → increase in cardiac output and therefore →elevated BP. This is usually due to defect in cell membrane function affecting the Na/Ca transport.
    - Functional vasoconstriction: abnormality in vascular tone such as increased sympathetic stimulation will cause vasoconstriction leading to increased peripheral resistance.
    - Structural abnormality in vascular smooth muscle also leads to increased peripheral resistance.
    - Also rare gene disorders can cause HTN by increasing renal sodium reabsorption e.g. Liddle syndrome. Liddle syndrome is an inherited autosomal dominant type of HTN, that begins in childhood. It is caused by mutations of the epithelial sodium channel protein (ENaC) which leads to increased sodium reabsorption in the renal tubules (followed by water), which leads to hypertension. Reabsorption of sodium is also correlates with potassium loss (hypokalemia).

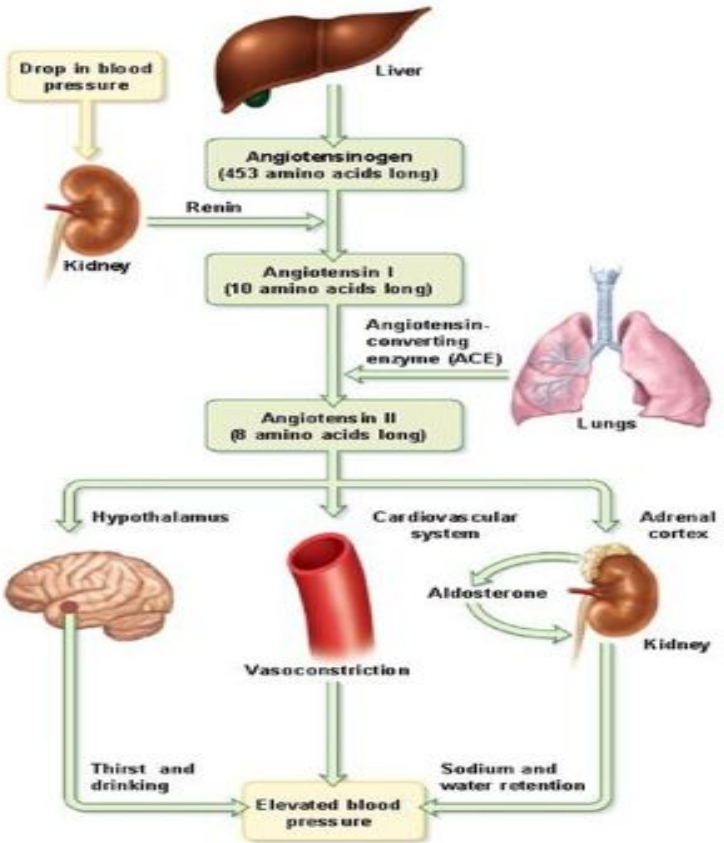
2. Environmental factors: stress, obesity, smoking, physical inactivity and heavy consumption of salt also play a role.

NOTE: In hypertension, both increased blood volume and increased peripheral resistance contribute to the increased pressure. However reduced renal sodium excretion in the presence of normal arterial pressure (initially) is probably a key initiating event.

Pathogenesis of Essential Hypertension



Endocrine Factors:
Role of renin- angiotensin- aldosterone in regulating BP



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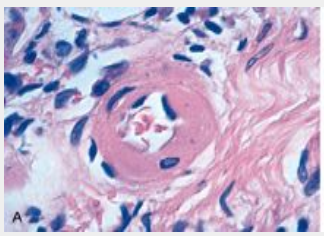
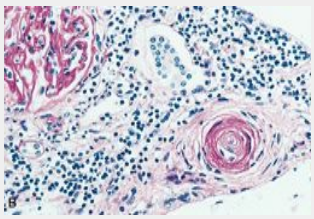
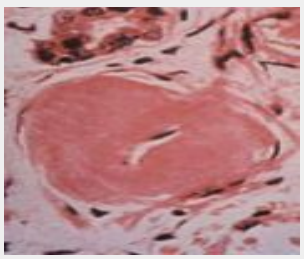
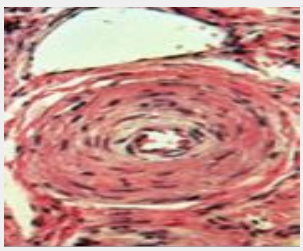
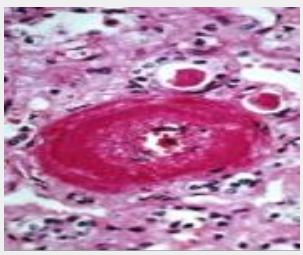
Morphology of Blood Vessels in Hypertension

- In large Blood Vessels (Macroangiopathy): Atherosclerosis. Hypertension is a major risk factor in Atherosclerosis.
- In small Blood Vessels (Microangiopathy): Arteriolosclerosis
  - Hyaline arteriolosclerosis

    Seen in benign hypertension
    - Can also be seen in elderly and diabetic patients even without hypertension.
    - Can cause diffuse renal ischemia which ultimately leads to benign nephrosclerosis
  - Hyperplastic arteriolosclerosis
    - Characteristic of malignant hypertension.
    - Can show onion-skinning on histology causing luminal obliteration of vascular lumen
    - May be associated with necrotizing arteriolitis and fibrinoid necrosis of the blood vessel.

	A. Hyaline arteriolosclerosis: hyalinosis of arteriolar wall with narrowing of lumen.
	B. Hyperplastic arteriolosclerosis (onionskinning) causing luminal obliteration of vascular lumen

		
Hyaline/ Benign hypertension	Hyperplastic/ Malignant hypertension showing onion skinning	Hyperplastic/ Malignant hypertension showing fibrinoid necrosis.

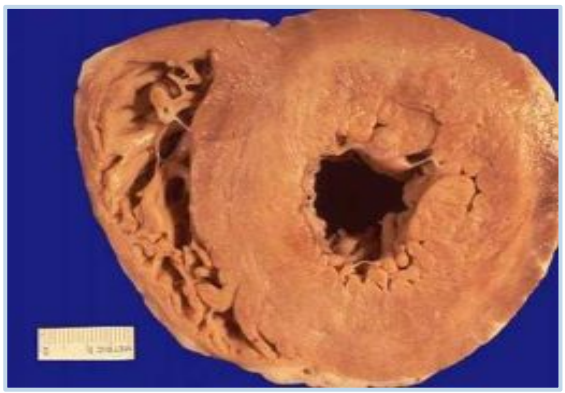
Hypertension complications

- The organs damaged in HTN are:

  - Cardiovascular

Left ventricular cardiac hypertrophy (left sided hypertensive cardiomyopathy/ hypertensive heart disease)

Hypertrophy of the heart is an adaptive response to pressure overload due to hypertension. hypertension induces left ventricular pressure overload which leads to hypertrophy of the left ventricle with increase in the weight of the heart and the thickness of the left ventricle wall.



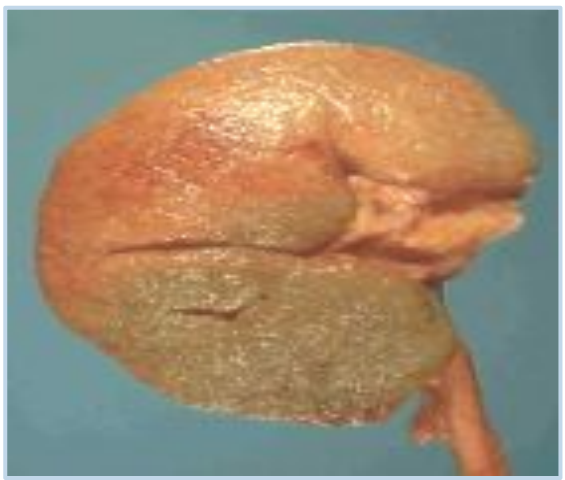
Coronary heart disease

Aortic dissection

  - Kidney

Benign nephrosclerosis

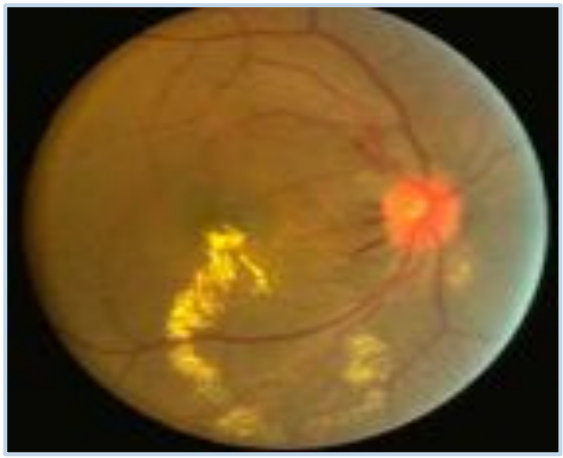
Renal failure in untreated or in malignant hypertension



Hypertension complications

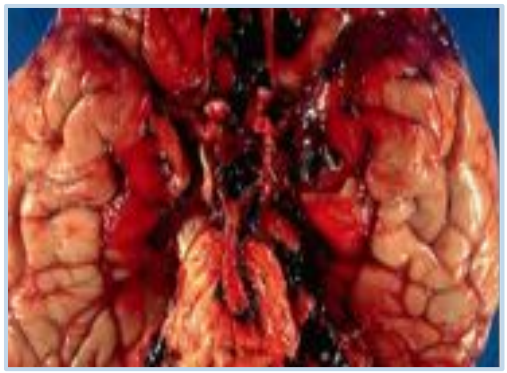
- Eyes

Hypertensive retinopathy is especially seen in malignant hypertension.

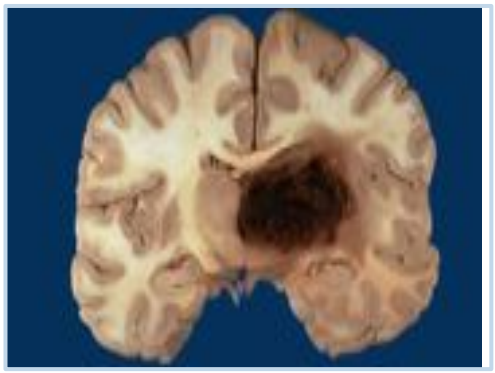


- Brain

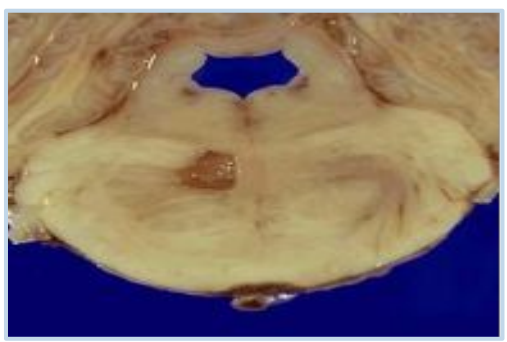
Hemorrhage, infarction leading to Cerebrovascular accidents



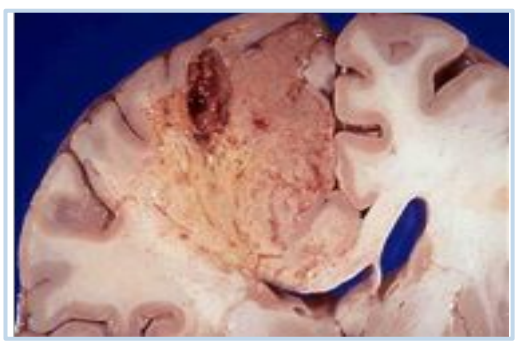
Subarachnoid Haemorrhage



Cerebral Hemorrhage



Lacunar Infarct



Cerebral Infarction

First-Line Antihypertensives

Class	Drug	MOA	Indication	ADRs	Contraindication
Thiazides	Hydrochlorothiazide Chlorthalidone Indapamide	Na/Cl transporter inhibition at the distal convoluted tubules.	-Hypertension -CHF -Nephrolithiasis -Nephrogenic Diabetes Insipidus	-hypercalcemia -Hypokalemia -Hyperglycemia -Hyperuricemia -Alkalosis	-
Loop diuretics	Furosemide	inhibit Na+ / K+ / 2Cl- cotransporter in the luminal membrane of the thick ascending loop of Henle (TAL). ▪ inhibit Ca++ and Mg ++ reabsorption.	-Acute pulmonary edema -Acute hyperkalaemia. -Acute hypercalcemia	-Hypocalcaemia -Hyperuricemia -Ototoxicity -Allergic reactions	-
ACEIs	Captopril, lisinopril, and other "-prils"	Block formation of angiotensin II	-Mild to moderate HTN (all) -CHF, & Protective of diabetic nephropathy (ACEIs/ARBs)	-Dry cough (ACEIs) -Angioedema. -Hyperkalemia. -Acute renal failure in renal artery stenosis/	Pregnancy
ARBs	Losartan, and other "-sartans"	Block angiotensin I receptors			
Renin Inhibitors	Aliskirin	Block formation of angiotensin I			
CCBs	Verapamil, diltiazem, and nifedipine	Block L-type Ca channels in heart & blood vessels	-HTN, Angina (all) -Antiarrhythmics (Verapamil, Diltiazem)	-Constipation (Verapamil) -Reflex tachycardia, Gingival hyperplasia ("-Dipines")	-

Antihypertensive Drugs in Comorbid Conditions

indication	Suitable drugs
Angina	Beta blocker , CCBs
Diabetes	ACEIs , ARBs
Heart failure	ACEIs , ARBs ,Beta blockers
post-MI	Beta blocker
BPH	Aloha blockers
Dyslipidemias	ACEI , ARBs

Drugs Altering Sympathetic Activity

Class	Drugs	MOA	ADRs	Indication
Beta Blockers	Propranolol, Atenolol	Prevent Beta receptors activation	-Sexual dysfunction. -Increase in LDL & TGs.	Caution in: -Asthma -Vasospastic disorders. -Diabetics.
Alpha-1 Blockers	Prazosin,Doxazosin, Terazosin	-Vasodilatation due to relaxation of arterial and venous smooth muscles -Reflex tachycardia.	-1st Dose Syncope. -Orthostatic Hypotension. -Urinary incontinence.	-HTN. -Benign Prostatic Hyperplasia.
Alpha-2 Agonists	Clonidine,Methyldopa	Decrease sympathetic outflow, TPR and HR.	-Positive Coombs Test (Methyldopa) -Edema, CNS Depression (Both).	-Mild to Moderate HTN (Both) -Opioid withdrawal (Clonidine) -HTN in Pregnancy (Methyldopa)

Direct Acting Vasodilators

Class	Drugs	MOA	ADRs	Indication
Through Nitric Oxide	-Nitroprusside.	-Decrease TPR via arteriolar dilation (Hydralazine) -Decrease TPR via arterioles & venules dilation (Nitroprusside)	-Cyanide Toxicity (Nitroprusside)	-Mild to moderate HTN (Hydralazine). -Hypertensive emergencies (Nitroprusside)
Potassium channel opener	-Hydralazine -Minoxidil -Diazoxide.	Open K channels causing hyperpolarization of smooth muscles.	-SLE Like Symptoms, Edem, Reflex tachycardia (Hydralazine). -Hypertrichosis (Minoxidil) -Hyperglycemia (Diazoxide)	-Insulinoma (Diazoxide) -Severe HTN,Baldness (Minoxidil)

Clinical integration Hypertension

Definition:

- **Systolic pressure above 140 mm Hg**
- **Diastolic pressure above 90 mm Hg**

Classification :

Category	Systolic (mmHg)		Diastolic (mmHg)
Normal	> 120	and	> 80
Elevated	120-129	and	> 80
High blood pressure stage 1	130-139	or	80-89
High blood pressure stage 2	≥ 140	or	≥ 90
Hypertensive crisis	> 180	and/or	> 120

Types of HTN:

1- primary HTN

most of hypertension has no clear etiology and can be called "essential hypertension."

2- Secondary HTN

There is underlying pathology lead to Hypertension

- Renal artery stenosis
- Hyperaldosteronism
- Pheochromocytoma
- Glomerulonephritis
- Acromegaly
- Cushing syndrome

use of glucocorticoids

Sign and symptoms

- Headaches, especially early morning or waking headache
- Dizziness, tinnitus, blurred vision
- Flushed appearance
- Epistaxis
- Chest discomfort, palpitations; strong, bounding pulse on palpation
- Nervousness
- Fatigue, sleep disturbances
- Additional symptoms of an underlying disease in secondary hypertension
- Symptoms of end-organ damage (see "Complications" below)

History

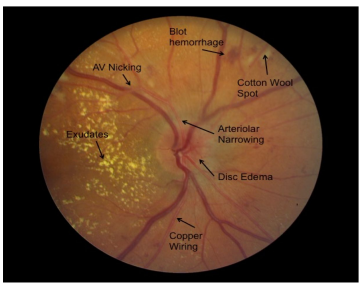
Totally asymptomatic

- Some patient complain from headache **-**occipital-
- Chest pain
- Present with complications like
- IHD
- Brain**:** stroke or transient ischemic attack.
- Chronic kidney disease
- Peripheral arterial disease
- Retinopathy

physical exam

Blood pressure measurements to detect and confirm the presence of high blood pressure

examination of the fundus for arteriolar narrowing, arteriovenous nicking, hemorrhages, exudates . heart for increased rate, increased size, precordial heave, clicks, murmurs, arrhythmias, and third(S3) and fourth (S4) sounds



Diagnosis

- Repeated measurements on both arms → Hypertension is diagnosed if the average blood pressure of **≥ 2 readings** obtained on **≥ 2 separate visits** is elevated

Rule out secondary causes

Diagnostic findings	Diagnostic findings
• Hypokalemia	• Conn syndrome • Renal artery stenosis
• Increased 24-hour urinary metanephrines	Pheochromocytoma
• ↑ Serum calcium, ↑ PTH level, ↓ serum phosphates	Hyperparathyroidism
• ↑ Serum cortisol	• Excess of glucocorticoids (e.g., Cushing syndrome)
• ↓TSH, ↑ free T4	• Hyperthyroidism

White coat hypertension (white coat effect)

- **Definition**: arterial hypertension detected only in **clinical settings** or during blood pressure measurement at a **physician's practice**
- **Etiology**: anxiety experienced by the patient
- **Clinical features**: consistently **normal blood pressure** measurements and normalization of elevated blood pressure **outside of a clinical setting**
- **Diagnostics**: **24-hour** blood pressure monitoring

That is why we need more than 2 reading for diagnosis

Management:

first : Lifestyle modification
Second : anti hypertensive drugs

Shock

Shock

Shock is generalized hypoperfusion of tissues and cells which the O_2 delivery can't meet O_2 demand. Initially, the injury is reversible, eventually it becomes permanent and lead to multiple organ dysfunction system (MODS). Frequently involves the lung, kidney, heart and liver.

Presentation:

They usually present with tachycardia, oliguria, weak pulse, hypotension, cool extremities and mental status change.

Stages of shock:

1- **Compensation:** which the reflex mechanism maintain the perfusion to the vital organs, these mechanisms are: increase heart rate, increase peripheral resistance, release of catecholamines and activation OF the Renin-Angiotensin-Aldosterone System (RAAS).
2- **Decompensation:** after loses of 15-20% of blood, compensation can no longer be maintained leading to: tissue hypoperfusion, reversible tissue injury and metabolic imbalance.
3- **Irreversible injury:** End organ damage and failure.

Types of shock:

Type	Causes	Skin	CVP	CO	SVR	Treatment
Hypovolemic	Hemorrhage, dehydration, burns	Cold, clammy	⇓⇓	⇓	⇑	I.V Fluid
Cardiogenic	Acute MI, HF, Valvular dysfunction, Arrhythmia	Cold, clammy	⇑	⇓⇓	⇑	Inotropes, Diuresis
Obstructive	Cardiac tamponade, PE	Cold, clammy	⇑	⇓⇓	⇑	Relieve obstruction
Distributive	Sepsis, CNS injury, anaphylaxis	Warm, Dry	⇓	⇑	⇓⇓	Pressor, I.V Fluid

Classes of hypovolemic shock:

	I	II	III	IIII
Blood loss(ml)	Up to 750	750-1500	1500-2000	>2000
Blood loss(% body volume)	Up to 15	15-30	30-40	>40
Pulse rate	<100	100-120	120-140	>140
Blood pressure	normal	normal	⬇	⬇
Pulse pressure(mm Hg)	Normal or ⬆	⬇	⬇	⬇
Respiratory rate	14-20	20-30	30-40	>35
Urine output(ml/hr)	>30	20-30	5-15	Negligible
Mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic

Vasculitis

Vasculitis

Vasculitis is inflammation of the blood vessels mainly caused by autoimmune.

Clinical features include:

- Non-specific inflammation symptoms (e.g. fever,weight loss and myalgia)
- Symptoms of organ ischemia secondary to narrowing of the lumina by inflammation

Vasculitis divided into :

1. Large vessel vasculitis involves the aorta and its major branches
2. Medium vessel vasculitis involves muscular arteries
3. Small vessel vasculitis involves atritioles, capillaries and venules

Large vessel vasculitis:

A. Temporal (Giant cell) Arteritis:

- It's a granulomatous vasculitis involving branches of carotid arteritis
- Most common affect adults >50 YO and females
- Patients present with headache, visual disturbance, jaw claudication and flu like symptoms
- Biopsy shows inflamed vessel wall with giant cells and intimal fibrosis
- Treatment is corticosteroid; there's high risk for blindness without treatment

B. Takayasu arteritis:

- Granulomatous vasculitis involving the aortic arch at branch points
- Most common in adult <50 YO
- Patients present with visual and neurological symptoms with weak or absent pulse in the upper extremities
- Treatment is corticosteroid

Medium vessel vasculitis:

A. Polyarteritis Nodosa:

- It's necrotizing vasculitis involving multiple organs but usually the lungs are spared.
- Usually present in young adults as hypertension, abdominal pain with melena, neurological disturbances and skin lesion.

- Early lesion shows transmural inflammation with fibrinoid necrosis, eventually it heels with fibrosis appeared as 'string-of-pearls' on imaging
- Treatment is by corticosteroid and cyclophosphamide

B. Kawasaki disease:

- Usually affect Asian children <4 years old, they present with nonspecific signs including erythematous rash of soles and palms, fever, conjunctivitis and enlarged cervical lymph nodes
- Coronary artery involvement is common increasing the risk of: 1- thrombosis with MI 2- aneurysm with rupture
- It's a self-limited disease, treated by IVIG and aspirin

C. Buerger disease:

- It's a necrotizing vasculitis involving the digits presents with ulceration, gangrene and autoamputation of fingers and toes, Raynaud phenomenon is often present
- It's associated with heavy smoking and the treatment is to stop smoking

Small cell vasculitis:

A. Wegener Granulomatosis:

- Usually involves nasopharynx, lungs and kidneys
- A middle age male with sinusitis, hemoptysis with bilateral lung infiltrates and hematuria is usually the classic presentation
- Serum c-ANCA levels correlates with disease activity
- Treatment is cyclophosphamide and steroid

B. Microscopic Polyangiitis:

- Involves multiple organ, typically the lungs and kidney
- Similar presentation to Wegener but with no nasophrangeal involvement and granulomas
- Serum p-ANCA correlates with disease activity
- Treatment is by cyclophosphamide and steroid

C. Churg-Strauss Syndrome:

- Eosinophilic inflammation involving multiple organ, typically the lung and heart
- Peripheral eosinophilia and asthma are usually present
- Serum p-ANCA correlates with disease activity

D. Henoch-Schonlein Purpura:

- The most common vasculitis in children, it's due to **IgA** immune complex deposition
- Present with palpable purpura in buttocks and legs, abdominal pain and GI bleeding and hematuria (IgA nephropathy)
- It's a self-limited disease

History and physical Examination

History Of CVS

Most common chief complaint of Cardiac diseases is: 1- Chest pain or heaviness 2-Dyspnea 3-Ankle swelling 4-palpitation

Chest pain: (SOCRATES)

- (Site): Where's the pain ?
- (Onset): When did it begin ?
- (character): How does it feel like ? continuous or intermittent ? is it progressive, constant or regressive ?
- (Radiation): Does it radiate to anywhere? If yes, to where ?
- (Alleviating factors): is the pain relieved by anything? Eg. Rest ?
- (Exacerbating factors): Does the pain increase with anything? Eg. Walking? Physical activity?
- (Time): Does the pain come at specific time in the day? If yes, when?
- (Severity): from 1 to 10 how severe is it?
- Associated symptoms: cough? Shortness of breath? Sweating? Dizziness? Nausea? Vomiting? Palpitation?

Dyspnea:

- Assess the severity by New York Heart Association Classification (NYHA):
  - Class I: only in heavy exertion
  - Class II: on moderate exertion
  - Class III: on minimal exertion (at usual activity)
  - Class IV: at rest
- Does the shortness of breath comes when you lie down? (Orthopnea), assess the severity by the number of pillows used on sleeping
- Do you wake up at night to catch your breath? (Paroxysmal Nocturnal Dyspnea (PND))

Ankle swelling (Edema):

- Unilateral or bilateral ?
- The level of the swelling: below the knee, to the middle of the thigh, the abdomen, the sacrum in bed ridden patients.
- The progression of the swelling:
    - From foot upward: Heart Failure
    - Ascites (Abdominal edema) then lower limb edema: Constrictive pericarditis
- Worsen at evening and improving during the night ?

Palpitation:

- Onset: when did it begin?
- Duration of the attack?
- How frequent is it?
- Rhythm, Is it regular or irregular?
- Specific triggers: Caffeine, exercise, alcohol
- Does it terminate by itself or by specific activity?
- Did you have syncope attack
- Associates symptoms ?

Other items of history:

Past history:

Past medical:

- Myocardial infarction
- Ischemic heart disease
- Rheumatic heart disease
- Recent dental work
- Transient ischemic attack
- Thyroid disease

Past surgical:

- Any previous surgery in the heart

Family history:

- Coronary heart disease, if yes. At what age?
- Hypertension, Diabetes mellitus or hyperlipidemia
- Familial hypercholesterolemia
- Systemic lupus erythematosus

Social history:

- Smoking, if yes. How many cigarettes daily and for how long ?
- Alcohol
- Caffeine consumption
- Drug abuse

Medication history

Blood transfusion

Allergies

Menstrual history

Systemic Review

Summary

Physical Examination of CVS

Vital signs

- Radial pulse: pulse rate and character
- Blood pressure

Precordium Examination

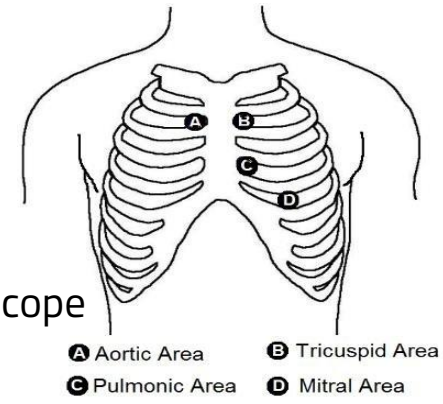
- Inspection
  - Shape of the chest and deformities: Eg. Pectus excavatum and carinatum
- Scars
- Devices: Holter monitoring and Pacemaker
- Apex beat

Palpation

- Apex beat: Palpable inferolateral above the mitral area
- Parasternal heaves: Place the heels of your hand above the right parasternal area and look for abnormal raising of your hand
- Thrills: abnormal palpable murmur felt above each valve area

Auscultation

- Start auscultation in the mitral are using the bell, then switch on diaphragm and hear the other area while you're feeling the pulse to know which sound is S1 and S2 and hear for any murmur
- Grades of murmur:
  - Grade 1: Very soft
  - Grade 2: Soft
  - Grade 3: Moderate without thrills
  - Grade 4: Moderate with thrills
  - Grade 5: Loud
  - Grade 6: Very loud; heard without stethoscope



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