

HIGH-YIELD SYSTEMS

Cardiovascular

“As for me, except for an occasional heart attack, I feel as young as I ever did.”

—Robert Benchley

“Hearts will never be practical until they are made unbreakable.”

—The Wizard of Oz

“As the arteries grow hard, the heart grows soft.”

—H. L. Mencken

“Nobody has ever measured, not even poets, how much the heart can hold.”

—Zelda Fitzgerald

“The art of medicine has its roots in the heart.”

—Paracelsus

“It is not the size of the man but the size of his heart that matters.”

—Evander Holyfield

The cardiovascular system is one of the highest yield areas for the boards and, for some students, may be the most challenging. Focusing on understanding the mechanisms instead of memorizing the details can make a big difference. Pathophysiology of atherosclerosis and heart failure, mechanism of action of drugs (particularly, their interplay with cardiac physiology) and their adverse effects, ECGs of heart blocks, the cardiac cycle, and the Starling curve are some of the more high-yield topics. Differentiating between systolic and diastolic dysfunction is also very important. Heart murmurs and maneuvers that affect these murmurs have also been high yield and may be asked in a multimedia format.

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► CARDIOVASCULAR—EMBRYOLOGY

Heart morphogenesis First functional organ in vertebrate embryos; beats spontaneously by week 4 of development.

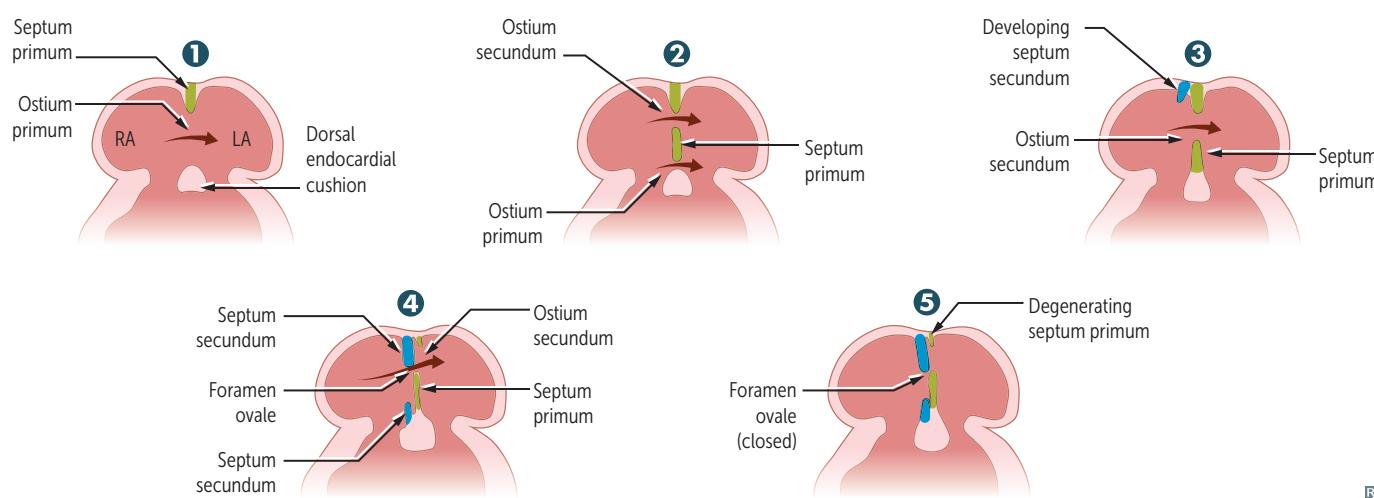
Cardiac looping	Primary heart tube loops to establish left-right polarity; begins in week 4 of development.	Defect in left-right dynein (involved in left-right asymmetry) can lead to dextrocardia, as seen in Kartagener syndrome.
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Septation of the chambers**Atria**

- ① Septum primum grows toward endocardial cushions, narrowing ostium primum.
- ② Ostium secundum forms in septum primum due to cell death (ostium primum regresses).
- ③ Septum secundum develops on the right side of septum primum, as ostium secundum maintains right-to-left shunt.
- ④ Septum secundum expands and covers most of ostium secundum. The residual foramen is the foramen ovale.
- ⑤ Remaining portion of septum primum forms the one-way valve of the foramen ovale.

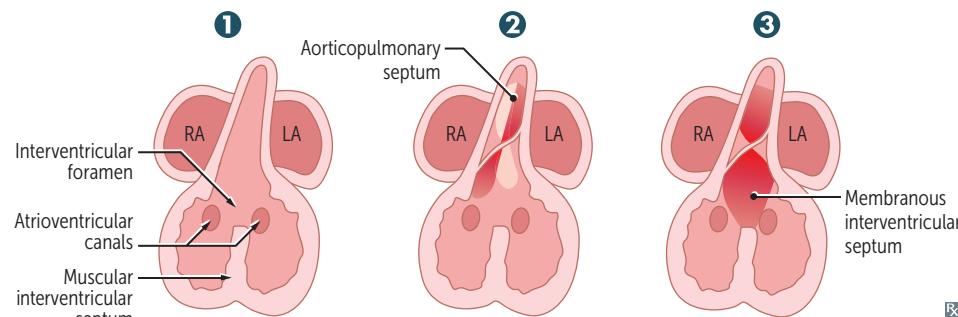
6. Septum primum closes against septum secundum, sealing the foramen ovale soon after birth because of ↑ LA pressure and ↓ RA pressure.
7. Septum secundum and septum primum fuse during infancy/early childhood, forming the atrial septum.

Patent foramen ovale—failure of septum primum and septum secundum to fuse after birth; seen in 25% of population. Most are asymptomatic and remain undetected. Can lead to paradoxical emboli (venous thromboemboli entering the systemic arterial circulation through right-to-left shunt) as can occur in atrial septal defect (ASD).



Heart morphogenesis (continued)**Ventricles**

- ① Muscular interventricular septum forms. Opening is called interventricular foramen.
- ② Aorticopulmonary septum rotates and fuses with muscular ventricular septum to form membranous interventricular septum, closing interventricular foramen.
- ③ Growth of endocardial cushions separates atria from ventricles and contributes to both atrial septation and membranous portion of the interventricular septum.

**Outflow tract formation**

Neural crest cell migrations → truncal and bulbar ridges that spiral and fuse to form aorticopulmonary septum → ascending aorta and pulmonary trunk.

Ventricular septal defect—most common congenital cardiac anomaly, usually occurs in membranous septum.

Atrioventricular septal defect (AVSD)—also known as endocardial cushion or AV canal defect. A cyanotic congenital heart defect with single common AV valve plus either ASD alone (partial AVSD) or both ASD and VSD (complete AVSD). Associated with Down syndrome, maternal diabetes, and obesity.

Valve development

Aortic/pulmonary: derived from endocardial cushions of outflow tract.
Mitral/tricuspid: derived from fused endocardial cushions of the AV canal.

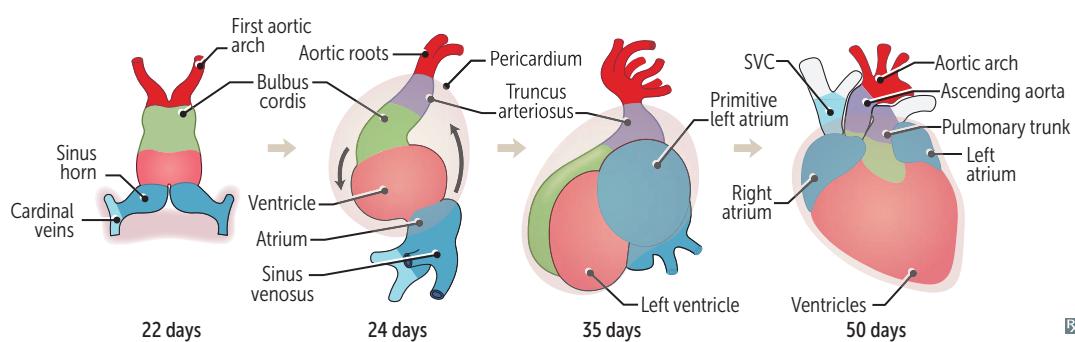
Conotruncal abnormalities associated with failure of neural crest cells to migrate:

- Transposition of great arteries (TGA).
- Tetralogy of Fallot.
- Persistent truncus arteriosus.

Valvular anomalies may be stenotic, regurgitant, atretic (eg, tricuspid atresia), or displaced (eg, Ebstein anomaly).

Heart embryology

EMBRYONIC STRUCTURE	GIVES RISE TO
Right common cardinal vein and right anterior cardinal vein	Superior vena cava (SVC)
Posterior cardinal, subcardinal, and supracardinal veins	Inferior vena cava (IVC)
Right horn of sinus venosus	Smooth part of right atrium (sinus venarum)
Left horn of sinus venosus	Coronary sinus
Primitive pulmonary vein	Smooth part of left atrium
Primitive atrium	Trabeculated part of left and right atria
Endocardial cushion	Atrial septum, membranous interventricular septum; AV and semilunar valves
Primitive ventricle	Trabeculated part of left and right ventricles
Bulbus cordis	Smooth parts (outflow tract) of left and right ventricles
Truncus arteriosus	Ascending aorta and pulmonary trunk

**Fetal-postnatal derivatives**

FETAL STRUCTURE	POSTNATAL DERIVATIVE	NOTES
Ductus arteriosus	Ligamentum arteriosum	Near the left recurrent laryngeal nerve
Ductus venosus	Ligamentum venosum	
Foramen ovale	Fossa ovalis	
Allantois → urachus	Median umbilical ligament	Urachus is part of allantois between bladder and umbilicus
Umbilical arteries	Medial umbilical ligaments	
Umbilical vein	Ligamentum teres hepatis (round ligament)	Contained in falciform ligament

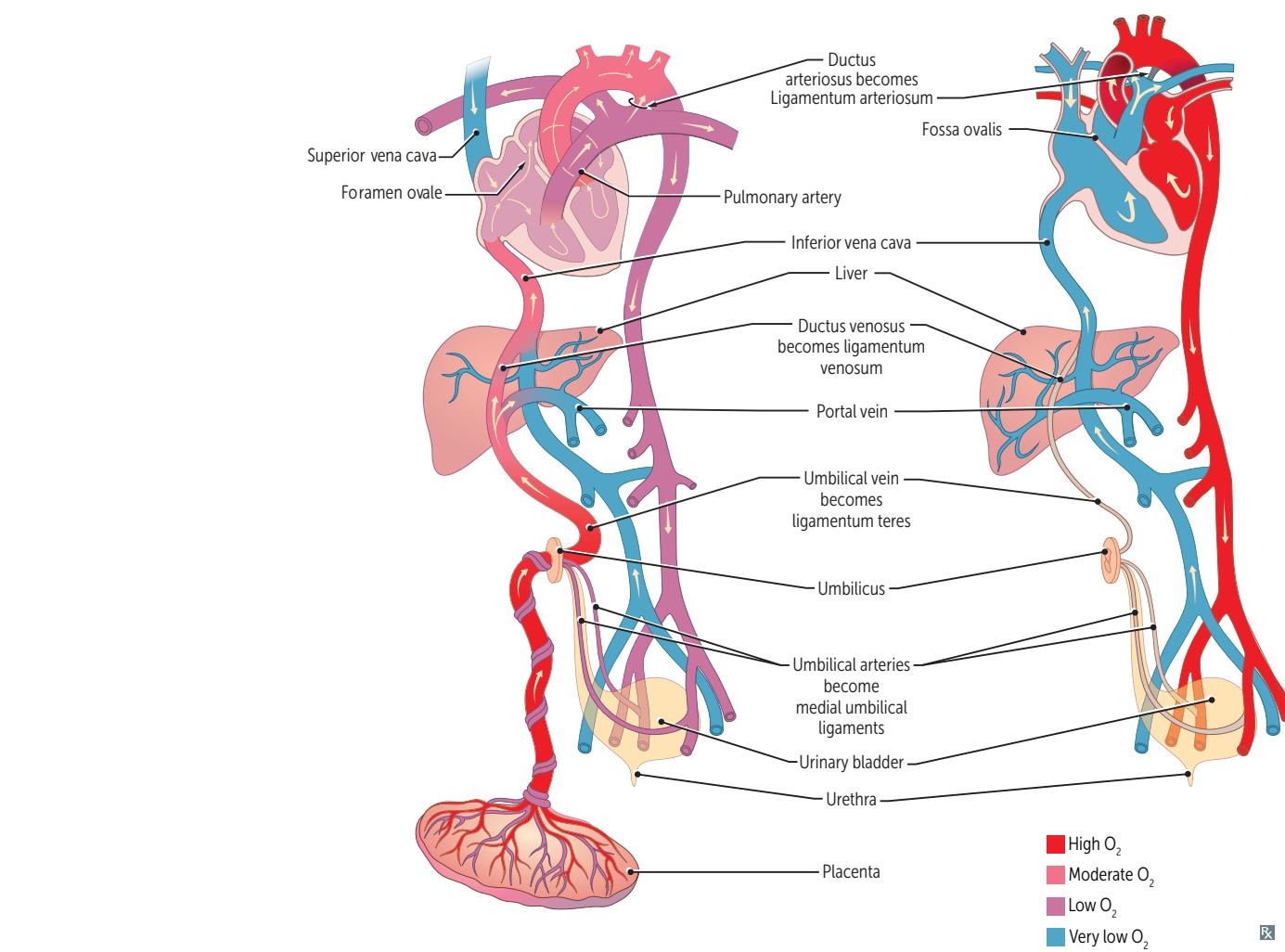
Fetal circulation

3 important shunts:

1. Umbilical vein → **ductus venosus** → IVC (bypassing hepatic circulation).
2. Most of the highly **oxygenated** blood from IVC → **foramen ovale** → LA.
3. Deoxygenated blood from SVC → RA → RV → main pulmonary artery → **ductus arteriosus** → descending aorta; shunt is due to ↑ fetal pulmonary artery resistance.

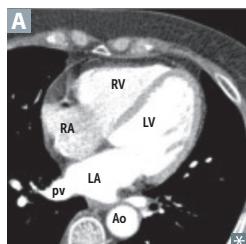
At birth, infant takes a breath → ↓ resistance in pulmonary vasculature → ↑ LA pressure vs RA pressure → foramen ovale closes (now called fossa ovalis); ↑ in O₂ (from respiration) and ↓ in prostaglandins (from placental separation) → closure of ductus arteriosus.

NSAIDs (eg, indomethacin, ibuprofen) or acetaminophen help close the patent ductus arteriosus (PDA) → ligamentum arteriosum (remnant of ductus arteriosus). “**End**omethacin” **end**s the PDA. Prostaglandins E₁ and E₂ **KEEP** PDA open.



► CARDIOVASCULAR—ANATOMY

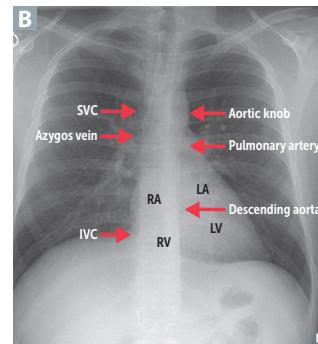
Heart anatomy



LA is the most posterior part of the heart **A**; LA enlargement (eg, in mitral stenosis) can lead to:

- Compression of esophagus → dysphagia
- Compression of left recurrent laryngeal nerve (branch of vagus nerve → hoarseness (**Ortner syndrome**)

RV is the most anterior part of the heart and most commonly injured in trauma. LV is about 2/3 and RV is about 1/3 of the inferior (diaphragmatic) cardiac surface **B**.



Pericardium

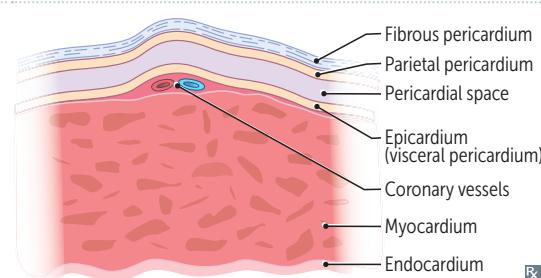
Consists of 3 layers (from outer to inner):

- Fibrous pericardium
- Parietal pericardium
- Epicardium (visceral pericardium)

Pericardial space lies between parietal pericardium and epicardium.

Pericardium innervated by phrenic nerve.

Pericarditis can cause referred pain to the neck, arms, or one or both shoulders (often left).



Coronary blood supply

LAD and its branches supply anterior 2/3 of interventricular septum, anterolateral papillary muscle, and anterior surface of LV. Most commonly occluded.

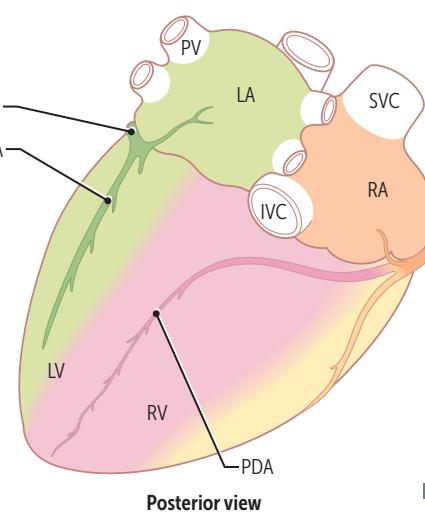
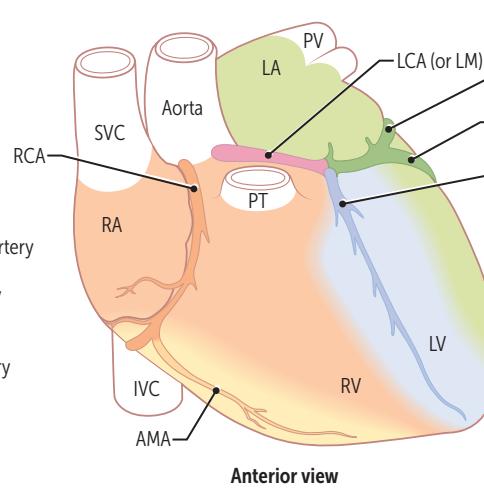
Posterior descending artery (PDA) supplies posterior 1/3 of interventricular septum, posterior 2/3 of ventricular walls, posteromedial papillary muscle, and SA and AV nodes (as determined by dominance). Infarct may cause nodal dysfunction (bradycardia or heart block). Right (acute) marginal artery supplies RV.

Dominance:

- Right-dominant circulation (most common) = PDA arises from RCA
- Left-dominant circulation = PDA arises from LCX (~5%–10% of patients)
- Codominant circulation = PDA arises from both LCX and RCA (~10%–20% of patients)

Coronary blood flow to LV and interventricular septum peaks in early diastole.
Coronary sinus runs in the left AV groove and drains into the RA.

Key:	
AMA	= Acute marginal artery
LAD	= Left anterior descending artery
LCA (or LM)	= Left (main) coronary artery
LCX	= Left circumflex artery
OMA	= Obtuse marginal artery
PDA	= Posterior descending artery
PT	= Pulmonary trunk
PV	= Pulmonary vein
RCA	= Right coronary artery



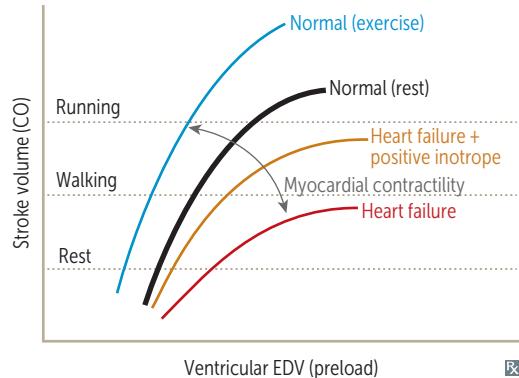
► CARDIOVASCULAR—PHYSIOLOGY

Cardiac output variables

Stroke volume	Stroke Volume affected by Contractility, Afterload, and Preload. ↑ SV with: <ul style="list-style-type: none">■ ↑ Contractility (eg, anxiety, exercise)■ ↑ Preload (eg, early pregnancy)■ ↓ Afterload	SV CAP. Stroke work (SW) is work done by ventricle to eject SV. $SW \propto SV \times MAP$ A failing heart has ↓ SV (systolic and/or diastolic dysfunction).
Contractility	Contractility (and SV) ↑ with: <ul style="list-style-type: none">■ Catecholamine stimulation via β_1 receptor:<ul style="list-style-type: none">■ Activated protein kinase A<ul style="list-style-type: none">→ phospholamban phosphorylation→ active Ca^{2+} ATPase \rightarrow ↑ Ca^{2+} storage in sarcoplasmic reticulum■ Activated protein kinase A \rightarrow Ca^{2+} channel phosphorylation \rightarrow ↑ Ca^{2+} entry \rightarrow ↑ Ca^{2+}-induced Ca^{2+} release■ ↑ intracellular Ca^{2+}■ Digoxin (blocks Na^+/K^+ pump<ul style="list-style-type: none">→ ↑ intracellular Na^+ \rightarrow ↓ Na^+/Ca^{2+} exchanger activity \rightarrow ↑ intracellular Ca^{2+})	Contractility (and SV) ↓ with: <ul style="list-style-type: none">■ β_1-blockade (↓ cAMP)■ Heart failure (HF) with systolic dysfunction■ Acidosis■ Hypoxia/hypercapnia (↓ Po_2/↑ Pco_2)■ Nondihydropyridine Ca^{2+} channel blockers
Preload	Preload approximated by ventricular end-diastolic volume (EDV); depends on venous tone and circulating blood volume, both of which affect venous return.	Venous vasodilators (eg, nitroglycerin) ↓ preload.
Cardiac oxygen demand	Myocardial O_2 demand is ↑ by: <ul style="list-style-type: none">■ ↑ contractility■ ↑ afterload (proportional to arterial pressure)■ ↑ heart rate■ ↑ diameter of ventricle (↑ wall tension) Coronary sinus contains most deoxygenated blood in body.	Wall tension follows Laplace's law: Wall tension = pressure × radius Wall stress = $\frac{\text{pressure} \times \text{radius}}{2 \times \text{wall thickness}}$
Afterload	Afterload approximated by MAP. ↑ pressure \rightarrow ↑ wall tension per Laplace's law \rightarrow ↑ afterload. LV compensates for ↑ afterload by thickening (hypertrophy) in order to ↓ wall stress.	Arterial vasodilators (eg, hydralazine) ↓ afterload. ACE inhibitors and ARBs ↓ both preload and afterload. Chronic hypertension (↑ MAP) \rightarrow LV hypertrophy.

Cardiac output equations

	EQUATION	NOTES
Stroke volume	$SV = EDV - ESV$	$ESV = \text{end-systolic volume}$.
Ejection fraction	$EF = \frac{SV}{EDV} = \frac{EDV - ESV}{EDV}$	EF is an index of ventricular contractility (\downarrow in systolic HF; usually normal in diastolic HF). Normal EF is 50%–70%.
Cardiac output	$CO = \dot{Q} = SV \times HR$ Fick principle: $CO = \frac{\text{rate of O}_2 \text{ consumption}}{(\text{arterial O}_2 \text{ content} - \text{venous O}_2 \text{ content})}$	In early stages of exercise, CO maintained by \uparrow HR and \uparrow SV. In later stages, CO maintained by \uparrow HR only (SV plateaus). Diastole is shortened with $\uparrow\uparrow$ HR (eg, ventricular tachycardia) \rightarrow \downarrow diastolic filling time \rightarrow \downarrow SV \rightarrow \downarrow CO.
Pulse pressure	$PP = \text{systolic blood pressure (SBP)} - \text{diastolic blood pressure (DBP)}$	PP directly proportional to SV and inversely proportional to arterial compliance. \uparrow PP in aortic regurgitation, aortic stiffening (isolated systolic hypertension in older adults), obstructive sleep apnea (\uparrow sympathetic tone), high-output state (eg, anemia, hyperthyroidism), exercise (transient). \downarrow PP in aortic stenosis, cardiogenic shock, cardiac tamponade, advanced HF.
Mean arterial pressure	$MAP = CO \times \text{total peripheral resistance (TPR)}$	$MAP (\text{at resting HR}) = \frac{2}{3} DBP + \frac{1}{3} SBP = DBP + \frac{1}{3} PP$.

Starling curves

Force of contraction is proportional to end-diastolic length of cardiac muscle fiber (preload).

- ↑ contractility with catecholamines, positive inotropes (eg, dobutamine, milrinone, digoxin).
- ↓ contractility with loss of functional myocardium (eg, MI), β-blockers (acutely), nondihydropyridine Ca^{2+} channel blockers, HF.

Resistance, pressure, flow

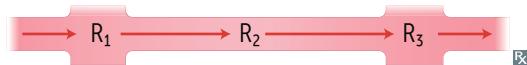
Volumetric flow rate (\dot{Q}) = flow velocity (v) × cross-sectional area (A)

Resistance (R)

$$= \frac{\text{driving pressure } (\Delta P)}{\dot{Q}} = \frac{8\eta \text{ (viscosity)} \times \text{length}}{\pi r^4}$$

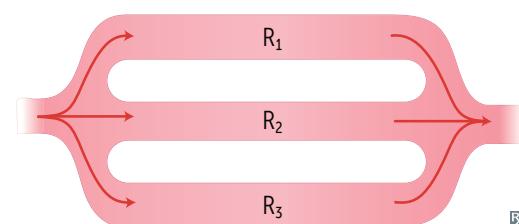
Total resistance of vessels in series:

$$R_T = R_1 + R_2 + R_3 \dots$$



Total resistance of vessels in parallel:

$$\frac{1}{R_T} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} \dots$$



$\Delta P = \dot{Q} \times R$ is analogous to Ohm's Law for electrical circuits ($V = I \times R$).

$$\dot{Q} \propto r^4$$

$$R \propto 1/r^4$$

Capillaries have highest total cross-sectional area and lowest flow velocity.

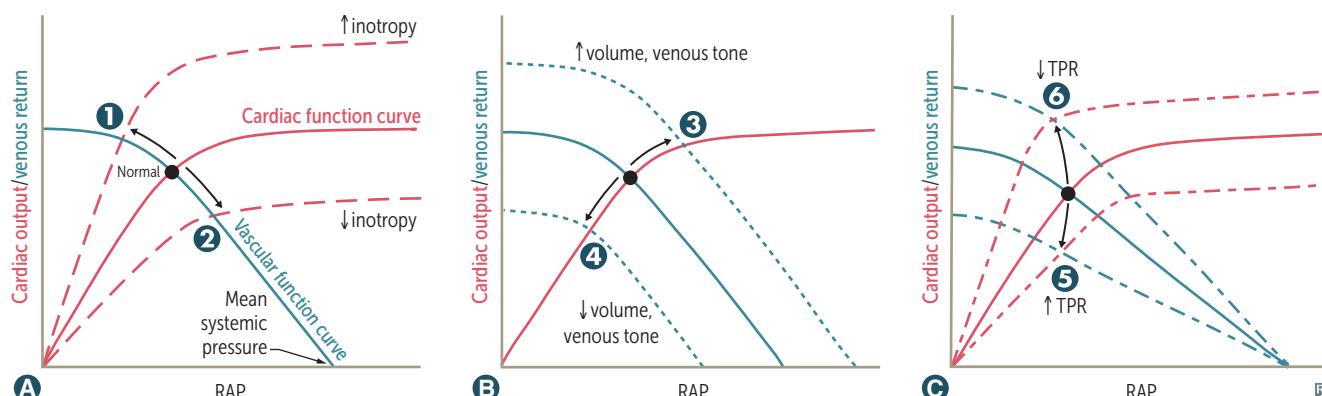
Pressure gradient drives flow from high pressure to low pressure.

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

Viscosity depends mostly on hematocrit.

Viscosity ↑ in hyperproteinemic states (eg, multiple myeloma), polycythemia.

Viscosity ↓ in anemia.

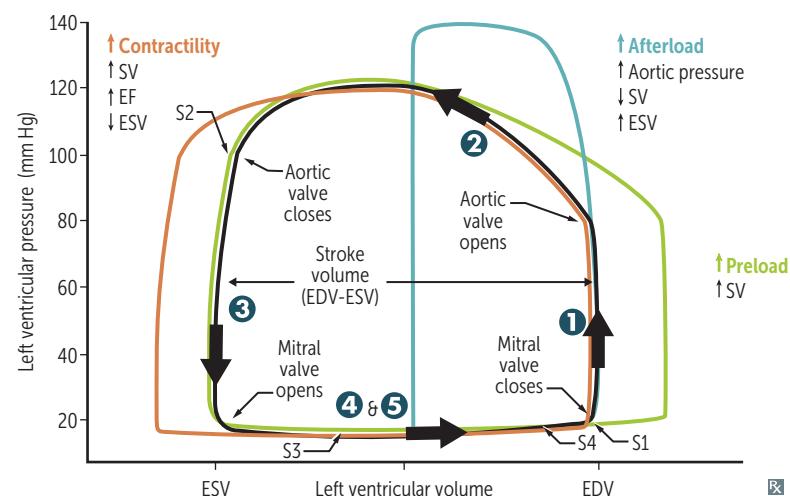
Cardiac and vascular function curves

Intersection of curves = operating point of heart (ie, venous return and CO are equal, as circulatory system is a closed system).

GRAPH	EFFECT	EXAMPLES
A Inotropy	Changes in contractility → altered SV → altered CO/venous return (VR) and RA pressure (RAP)	<p>① Catecholamines, dobutamine, digoxin, exercise ⊕</p> <p>② HF with reduced EF, narcotic overdose, sympathetic inhibition ⊖</p>
B Venous return	Changes in circulating volume → altered RAP → altered SV → change in CO	<p>③ Fluid infusion, sympathetic activity, arteriovenous shunt ⊕</p> <p>④ Acute hemorrhage, spinal anesthesia ⊖</p>
C Total peripheral resistance	Changes in TPR → altered CO Change in RAP unpredictable	<p>⑤ Vasopressors ⊕</p> <p>⑥ Exercise, arteriovenous shunt ⊖</p>

Changes often occur in tandem, and may be reinforcing (eg, exercise ↑ inotropy and ↓ TPR to maximize CO) or compensatory (eg, HF ↓ inotropy → fluid retention to ↑ preload to maintain CO).

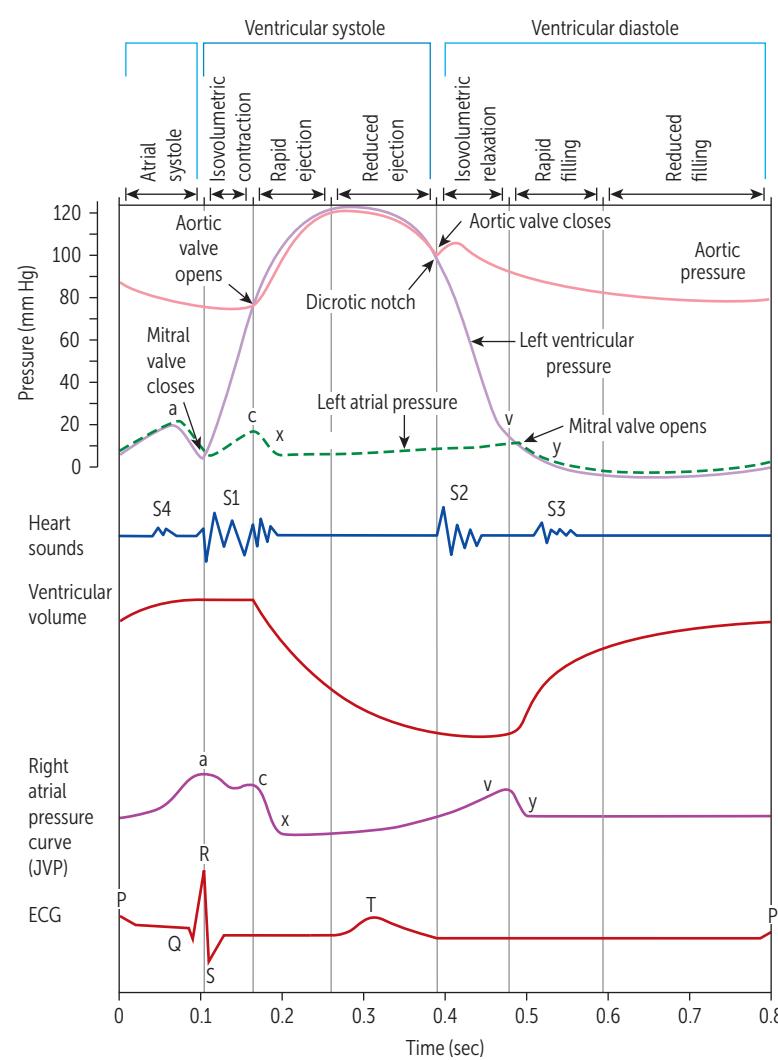
Pressure-volume loops and cardiac cycle



The black loop represents normal cardiac physiology.

Phases—left ventricle:

- ① Isovolumetric contraction—period between mitral valve closing and aortic valve opening; period of highest O₂ consumption
- ② Systolic ejection—period between aortic valve opening and closing
- ③ Isovolumetric relaxation—period between aortic valve closing and mitral valve opening
- ④ Rapid filling—period just after mitral valve opening
- ⑤ Reduced filling—period just before mitral valve closing



Heart sounds:

S1—mitral and tricuspid valve closure. Loudest at mitral area.

S2—aortic and pulmonary valve closure. Loudest at left upper sternal border.

S3—in early diastole during rapid ventricular filling phase. Best heard at apex with patient in left lateral decubitus position. Associated with ↑ filling pressures (eg, MR, AR, HF, thyrotoxicosis) and more common in dilated ventricles (but can be normal in children, young adults, athletes, and pregnancy). Turbulence caused by blood from LA mixing with ↑ ESV.

S4—in late diastole (“atrial kick”). Turbulence caused by blood entering stiffened LV. Best heard at apex with patient in left lateral decubitus position. High atrial pressure. Associated with ventricular noncompliance (eg, hypertrophy). Considered abnormal if palpable. Common in older adults.

Jugular venous pulse (JVP):

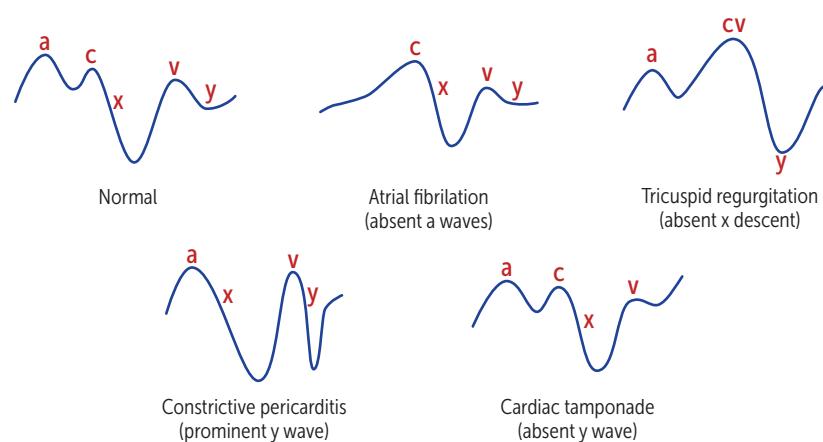
a wave—atrial contraction. Prominent in AV dissociation (cannon a wave) and ↑ RV end-diastolic pressure from any cause. Absent in atrial fibrillation.

c wave—RV contraction (closed tricuspid valve bulging into atrium).

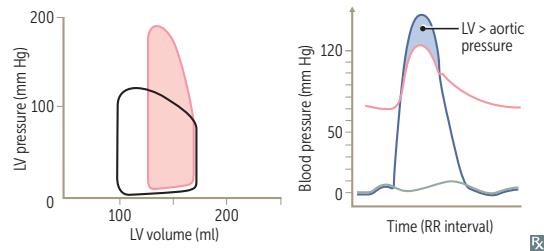
x descent—atrial relaxation and downward displacement of closed tricuspid valve during rapid ventricular ejection phase. Reduced or absent in tricuspid regurgitation and right HF because pressure gradients are reduced.

v wave—↑ RA pressure due to ↑ volume against closed tricuspid **v** valve.

y descent—RA emptying into RV. Prominent in constrictive pericarditis, absent in cardiac tamponade.

Jugular venous pressure tracings

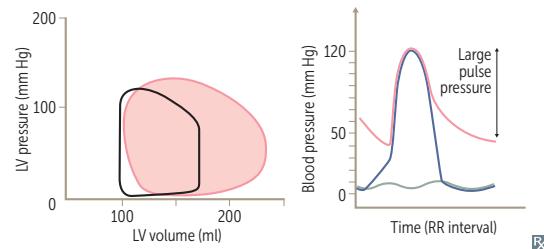
Rx

Pressure-volume loops and valvular disease**Aortic stenosis**

- ↑ LV pressure
- ↑ ESV
- No change in EDV (if mild)
- ↓ SV

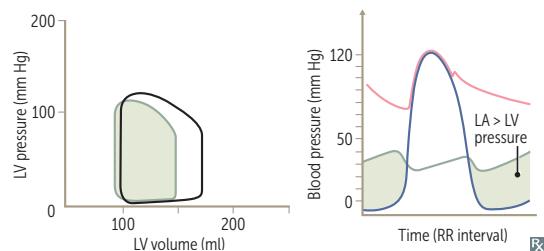
Ventricular hypertrophy → ↓ ventricular compliance → ↑ EDP for given EDV

Rx

Aortic regurgitation

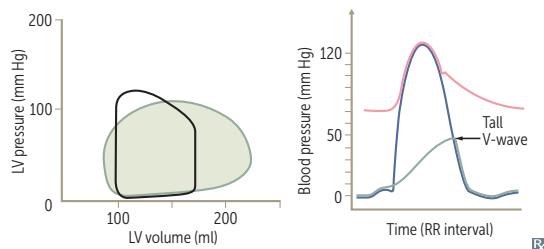
- No true isovolumetric phase
- ↑ EDV
- ↑ SV
- Loss of dicrotic notch

Rx

Mitral stenosis

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

Rx

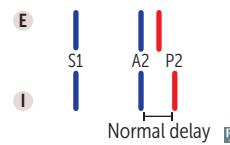
Mitral regurgitation

- No true isovolumetric phase
- ↓ ESV due to ↓ resistance and ↑ regurgitation into LA during systole
- ↑ EDV due to ↑ LA volume/pressure from regurgitation → ↑ ventricular filling
- ↑ SV (forward flow into systemic circulation plus backflow into LA)

Rx

Splitting of S2**Physiologic splitting**

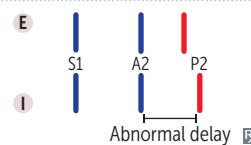
Inspiration → drop in intrathoracic pressure
 → ↑ venous return → ↑ RV filling → ↑ RV stroke volume → ↑ RV ejection time
 → delayed closure of pulmonic valve.
 ↓ pulmonary impedance (↑ capacity of the pulmonary circulation) also occurs during inspiration, which contributes to delayed closure of pulmonic valve.



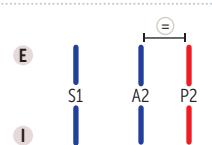
E = Expiration
 I = Inspiration

Wide splitting

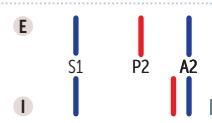
Seen in conditions that delay RV emptying (eg, pulmonic stenosis, right bundle branch block). Causes delayed pulmonic sound (especially on inspiration). An exaggeration of normal splitting.

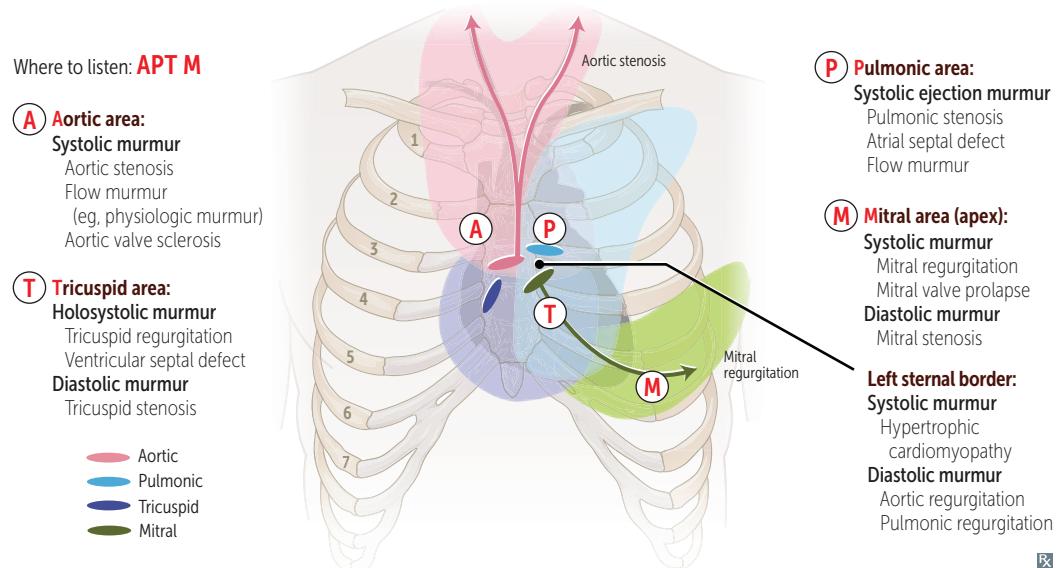
**Fixed splitting**

Heard in ASD. ASD → left-to-right shunt
 → ↑ RA and RV volumes → ↑ flow through pulmonic valve → delayed pulmonic valve closure (independent of respiration).

**Paradoxical splitting**

Heard in conditions that delay aortic valve closure (eg, aortic stenosis, left bundle branch block). Normal order of semilunar valve closure is reversed: in paradoxical splitting P2 occurs before A2. On inspiration, P2 closes later and moves closer to A2, “paradoxically” eliminating the split. On expiration, the split can be heard (opposite to physiologic splitting).



Auscultation of the heart

MANEUVER	CARDIOVASCULAR CHANGES	MURMURS THAT INCREASE WITH MANEUVER	MURMURS THAT DECREASE WITH MANEUVER
Standing, Valsalva (strain phase)	↓ preload (↓ LV volume)	MVP (↓ LV volume) with earlier midsystolic click HCM (↓ LV volume)	Most murmurs (↓ flow through stenotic or regurgitant valve)
Passive leg raise	↑ preload (↑ LV volume)		MVP (↑ LV volume) with later midsystolic click
Squatting	↑ preload, ↑ afterload (↑ LV volume)	Most murmurs (↑ flow through stenotic or regurgitant valve)	HCM (↑ LV volume)
Hand grip	↑↑ afterload → ↑ reverse flow across aortic valve (↑ LV volume)	Most other left-sided murmurs (AR, MR, VSD)	AS (↓ transaortic valve pressure gradient) HCM (↑ LV volume)
Inspiration	↑ venous return to right heart, ↓ venous return to left heart	Most right-sided murmurs (increase with inspiration)	Most left-sided murmurs (increase with expiration)

Heart murmurs

	AUSCULTATION	CLINICAL ASSOCIATIONS	NOTES
Systolic			
Aortic stenosis	Crescendo-decrescendo ejection murmur, loudest at heart base, radiates to carotids Soft S2 +/- ejection click “Pulsus parvus et tardus”— weak pulses with delayed peak	Age-related calcification (> 60 years old) Early-onset calcification of bicuspid aortic valve (~ 50–60 years old)	Can lead to Syncope , Angina , Dyspnea on exertion (SAD) LV pressure > aortic pressure during systole
Mitral/tricuspid regurgitation	Holosystolic, high-pitched “blowing” murmur MR: loudest at apex, radiates toward axilla TR: loudest at tricuspid area	MR: often due to ischemic heart disease (post-MI), MVP, LV dilatation, rheumatic fever (RF) TR: often due to RV dilatation; may be 2° to permanent pacemaker placement MR or TR: infective endocarditis	
Mitral valve prolapse	Late crescendo murmur with midsystolic click (MC) that occurs after carotid pulse Best heard over apex Loudest just before S2	Usually benign, but can predispose to infective endocarditis Can be caused by RF, chordae rupture, mitral annular disjunction, or myxomatous degeneration (1° or 2° to connective tissue disease)	MC due to sudden tensing of chordae tendineae as mitral leaflets prolapse into LA (chordae cause crescendo with click)
Ventricular septal defect	Holosystolic, harsh-sounding murmur Loudest at tricuspid area	Congenital	Larger VSDs have lower intensity murmur than smaller VSDs
Diastolic			
Aortic regurgitation	Early diastolic, decrescendo, high-pitched “blowing” murmur best heard at base (aortic root dilation) or left sternal border (valvular disease)	Causes include BEAR : Bicuspid aortic valve, Endocarditis , Aortic root dilation , RF Wide pulse pressure, pistol shot femoral pulse, pulsing nail bed	Hyperdynamic pulse and head bobbing when severe and chronic Can progress to left HF
Mitral stenosis	Follows opening snap (OS) Delayed rumbling mid-to-late murmur (↓ interval between S2 and OS correlates with ↑ severity)	Late and highly specific sequelae of RF Chronic MS can result in LA dilation and pulmonary congestion, atrial fibrillation, Ortner syndrome, hemoptysis, right HF	OS due to abrupt halt in leaflet motion in diastole after rapid opening due to fusion at leaflet tips LA >> LV pressure during diastole
Continuous			
Patent ductus arteriosus	Continuous machine like murmur, best heard at left infraclavicular area Loudest at S2	Often due to congenital rubella or prematurity	You need a patent for that machine .

Myocardial action potential

Phase 0 = rapid upstroke and depolarization—fast voltage-gated Na^+ channels open.

Phase 1 = initial repolarization—inactivation of voltage-gated Na^+ channels. Transient outward voltage-gated K^+ channels begin to open.

Phase 2 = plateau (“platwo”)— Ca^{2+} influx through voltage-gated Ca^{2+} channels balances K^+ efflux. Ca^{2+} influx triggers Ca^{2+} release from sarcoplasmic reticulum and myocyte contraction (excitation-contraction coupling).

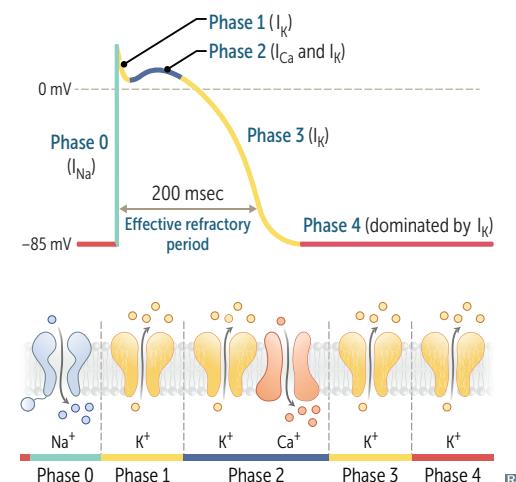
Phase 3 = rapid repolarization— K^+ efflux due to opening of voltage-gated slow delayed-rectifier K^+ channels and closure of voltage-gated Ca^{2+} channels.

Phase 4 = resting potential—high K^+ permeability through K^+ channels.

In contrast to skeletal muscle, cardiac muscle has the following characteristics:

- Action potential has a plateau due to Ca^{2+} influx and opposing K^+ efflux.
- Contraction requires Ca^{2+} influx from ECF to induce Ca^{2+} release from sarcoplasmic reticulum (Ca^{2+} -induced Ca^{2+} release).
- Myocytes conduct excitation throughout the heart via gap junctions.

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



Pacemaker action potential

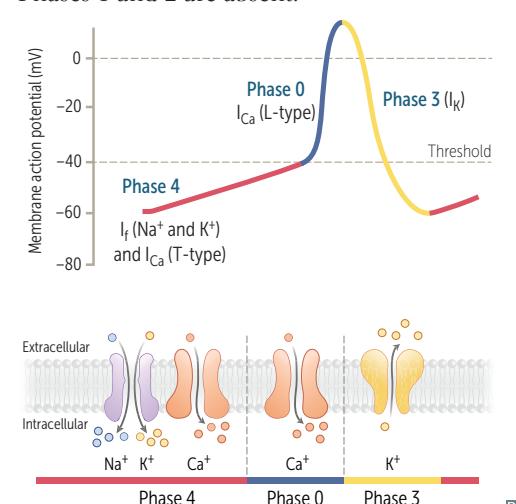
Key differences from the ventricular action potential include:

Phase 4 = slow spontaneous diastolic depolarization due to I_f (“funny current”). HCN channels are responsible for a slow, mixed Na^+/K^+ inward current; different from I_{Na} in phase 0 of ventricular action potential. Accounts for automaticity of SA and AV nodes. The slope of phase 4 in the SA node determines HR. ACh/adenosine \downarrow the rate of diastolic depolarization and \downarrow HR, while catecholamines \uparrow depolarization and \uparrow HR. Sympathetic stimulation \uparrow the chance that HCN channels are open and thus \uparrow HR.

Phase 0 = upstroke—opening of voltage-gated Ca^{2+} channels. Fast voltage-gated Na^+ channels are permanently inactivated due to the less negative resting potential of these cells \rightarrow slow conduction velocity, used by AV node to prolong transmission from atria to ventricles.

Phase 3 = repolarization—inactivation of Ca^{2+} channels and \uparrow activation of K^+ channels \rightarrow \uparrow K^+ efflux.

Occurs in the SA and AV nodes. Phases 1 and 2 are absent.



Electrocardiogram

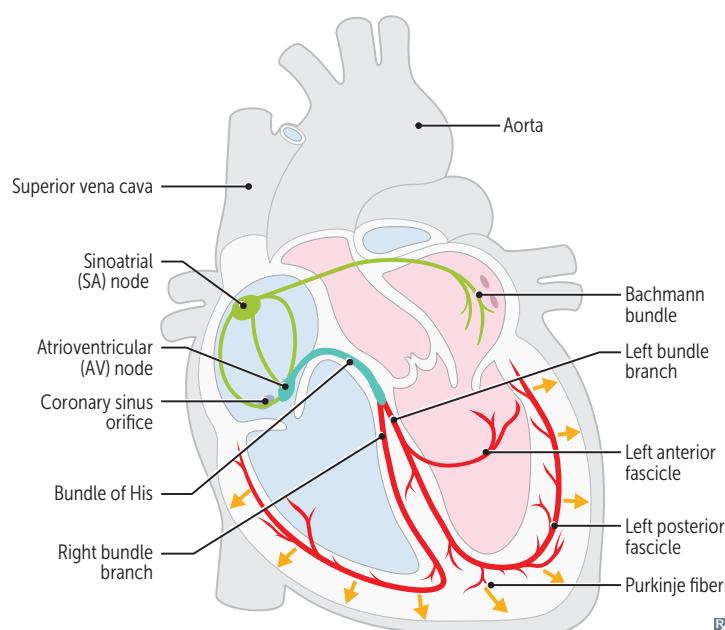
Conduction pathway: SA node → atria
→ AV node → bundle of His → right bundle branch and left bundle branch (which divides into left anterior and posterior fascicles) → Purkinje fibers → ventricles; left bundle branch divides into left anterior and posterior fascicles.

SA node—located in upper crista terminalis near SVC; typically serves as dominant "pacemaker" for HR, with slow phase of upstroke.

AV node—located in interatrial septum near coronary sinus opening. Blood supply via PDA. 100-msec delay allows time for ventricular filling.

Pacemaker rates: SA > atria > AV > bundle of His/Purkinje/ventricles.

Speed of conduction: **His-Purkinje > Atria > Ventricles > AV node. He Parks At Ventura Avenue.**



P wave—atrial depolarization.

PR interval—time from start of atrial depolarization to start of ventricular depolarization (normally 120-200 msec).

QRS complex—ventricular depolarization (normally ≤ 100 msec).

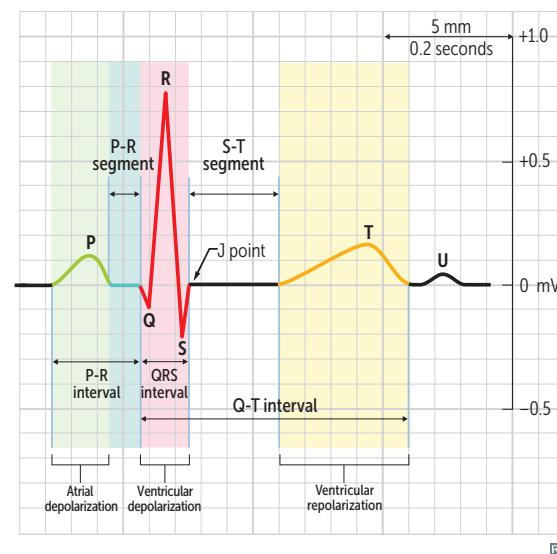
QT interval—ventricular depolarization, contraction, repolarization.

T wave—ventricular repolarization. Inversion may indicate ischemia or recent MI.

J point—junction between end of QRS complex and start of ST segment.

ST segment—isoelectric, ventricles depolarized.

U wave—prominent in hypokalemia (think hyp“U”kalemia), bradycardia.

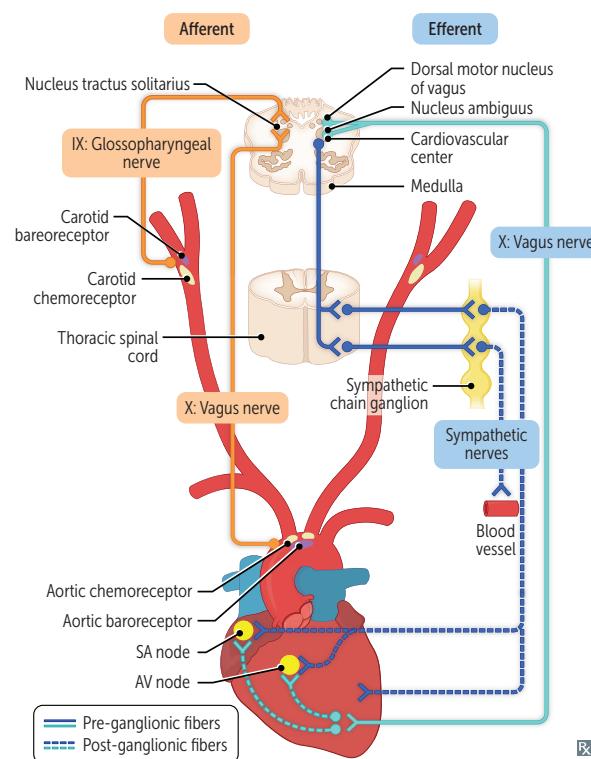


Atrial natriuretic peptide

Released from atrial myocytes in response to ↑ blood volume and atrial pressure. Acts via cGMP. Causes vasodilation and ↓ Na⁺ reabsorption at the renal collecting tubule. Dilates afferent renal arterioles and constricts efferent arterioles, promoting diuresis and contributing to “aldosterone escape” mechanism.

B-type (brain) natriuretic peptide

Released from ventricular myocytes in response to ↑ tension. Similar physiologic action to ANP, with longer half-life. BNP blood test used for diagnosing HF (very good negative predictive value).

Baroreceptors and chemoreceptors**Receptors:**

- Aortic arch transmits via vagus nerve to nucleus tractus solitarius of medulla (responds to changes in BP).
- Carotid sinus (dilated region superior to bifurcation of carotid arteries) transmits via glossopharyngeal nerve to nucleus tractus solitarius of medulla (responds to changes in BP).

Chemoreceptors:

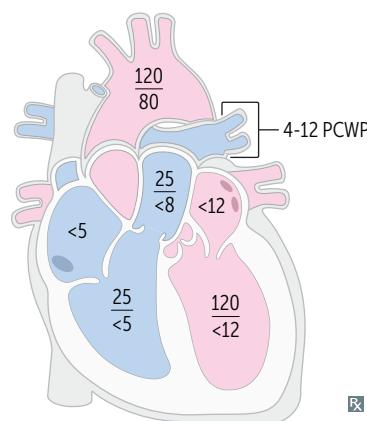
- Peripheral—carotid and aortic bodies are stimulated by ↑ PCO₂, ↓ pH of blood, and ↓ PO₂ (< 60 mm Hg).
- Central—are stimulated by changes in pH and PCO₂ of brain interstitial fluid, which in turn are influenced by arterial CO₂ as H⁺ cannot cross the blood-brain barrier. Do not respond to PO₂. Central chemoreceptors become less sensitive with chronically ↑ PCO₂ (eg, COPD) → ↑ dependence on peripheral chemoreceptors to detect ↓ O₂ to drive respiration.

Baroreceptors:

- Hypotension—↓ arterial pressure → ↓ stretch → ↓ afferent baroreceptor firing → ↑ efferent sympathetic firing and ↓ efferent parasympathetic stimulation → vasoconstriction, ↑ HR, ↑ contractility, ↑ BP. Important in the response to hypovolemic shock.
- Carotid sinus hypersensitivity—elicited by carotid massage, shaving, tight necktie or shirt collar → ↑ carotid sinus pressure → ↑ afferent baroreceptor firing → ↑ AV node refractory period → ↓ HR → ↓ CO. Also leads to peripheral vasodilation. Can cause presyncope/syncope. Exaggerated in underlying atherosclerosis, prior neck surgery, older age.
- Component of Cushing reflex (triad of hypertension, bradycardia, and respiratory depression)—↑ intracranial pressure constricts arterioles → cerebral ischemia → ↑ pCO₂ and ↓ pH → central reflex sympathetic ↑ in perfusion pressure (hypertension) → ↑ stretch → peripheral reflex baroreceptor-induced bradycardia.

Normal resting cardiac pressures

Pulmonary capillary wedge pressure (PCWP; in mm Hg) is a good approximation of left atrial pressure, except in mitral stenosis when PCWP > LV end diastolic pressure. PCWP is measured with pulmonary artery catheter (Swan-Ganz catheter).

**Autoregulation**

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

ORGAN	FACTORS DETERMINING AUTOREGULATION	
Lungs	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
Heart	Local metabolites (vasodilatory): NO, CO ₂ , ↓ O ₂	
Brain	Local metabolites (vasodilatory): CO ₂ (pH)	
Kidneys	Myogenic (stretch-dependent response of afferent arteriole) and tubuloglomerular feedback	
Skeletal muscle	Local metabolites during exercise (vasodilatory): CO ₂ , H ⁺ , Adenosine, Lactate, K ⁺ At rest: sympathetic tone in arteries	CHALK
Skin	Sympathetic vasoconstriction most important mechanism for temperature control	

Capillary fluid exchange

Starling forces determine fluid movement through capillary walls:

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

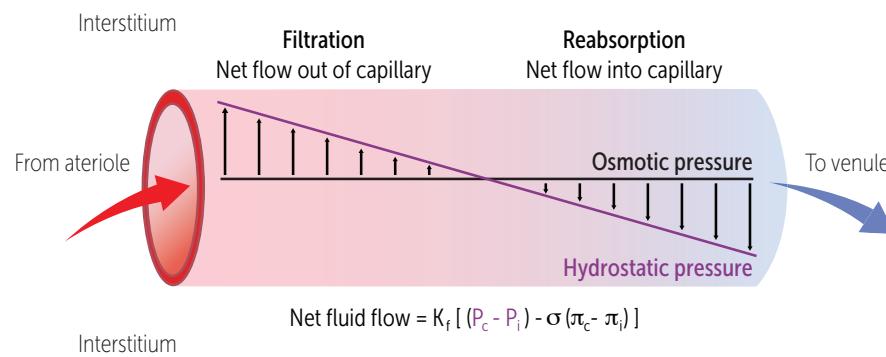
$$J_v = \text{net fluid flow} = K_f [(P_c - P_i) - \sigma(\pi_c - \pi_i)]$$

K_f = capillary permeability to fluid

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

Edema—excess fluid outflow into interstitium commonly caused by:

- ↑ capillary hydrostatic pressure ($\uparrow P_c$; eg, HF)
- ↑ capillary permeability ($\uparrow K_f$; eg, toxins, infections, burns)
- ↑ interstitial fluid oncotic pressure ($\uparrow \pi_i$; eg, lymphatic blockage)
- ↓ plasma proteins ($\downarrow \pi_c$; eg, nephrotic syndrome, liver failure, protein malnutrition)



► CARDIOVASCULAR—PATHOLOGY

Congenital heart diseases**RIGHT-TO-LEFT SHUNTS**

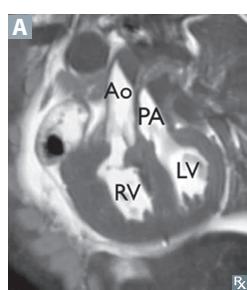
Early cyanosis—"blue babies." Often diagnosed prenatally or become evident immediately after birth. Usually require urgent surgical treatment and/or maintenance of a PDA via prostaglandin therapy.

The **5 T's**:

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

Persistent truncus arteriosus

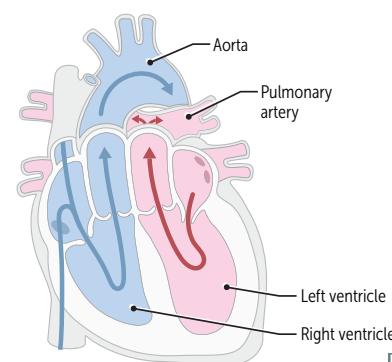
Truncus arteriosus fails to divide into pulmonary trunk and aorta due to failure of aorticopulmonary septum formation; most patients have accompanying VSD.

D-transposition of great arteries

Aorta leaves RV (anterior) and pulmonary trunk leaves LV (posterior) → separation of systemic and pulmonary circulations **A**. Not compatible with life unless a shunt is present to allow mixing of blood (eg, VSD, PDA, or patent foramen ovale).

Due to failure of the aorticopulmonary septum to spiral (narrow superior mediastinum causes "egg on a string" appearance on CXR).

Without surgical intervention, most infants die within the first few months of life.

**Tricuspid atresia**

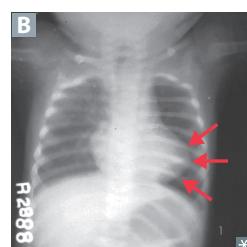
Absence of tricuspid valve, hypoplastic RV; requires both ASD and VSD/PDA for viability.

ECG shows hypertrophy of RA (tall P-waves) and LV (left axis deviation).

PROVe.

Squatting: ↑ SVR, ↓ right-to-left shunt, improves cyanosis.

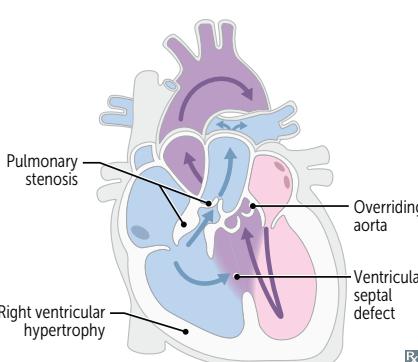
Associated with 22q11 syndromes.

Tetralogy of Fallot

Caused by anterosuperior displacement of the infundibular septum. Most common cause of early childhood cyanosis.

- ① Pulmonary infundibular stenosis (most important determinant for prognosis)
- ② Right ventricular hypertrophy (RVH)—boot-shaped heart on CXR **B**
- ③ Overriding aorta—straddles VSD, receives blood from both LV and RV
- ④ VSD

Pulmonary stenosis forces right-to-left flow across VSD → RVH, "tet spells" (often caused by crying, fever, and exercise due to exacerbation of RV outflow obstruction).

**Total anomalous pulmonary venous return**

Pulmonary veins drain into right heart circulation (SVC, coronary sinus, etc); associated with ASD and sometimes PDA to allow for right-to-left shunting to maintain CO.

Rare. Can be caused by lithium exposure in utero.

Ebstein anomaly

Displacement of tricuspid valve leaflets downward into RV, artificially "atrializing" the ventricle. Associated with tricuspid regurgitation, accessory conduction pathways, right-sided HF.

Congenital heart diseases (continued)**LEFT-TO-RIGHT SHUNTS**

Acyanotic at presentation; cyanosis may occur years later. Frequency: VSD > ASD > PDA.

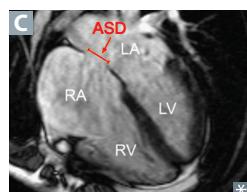
Right-to-left shunts: early cyanosis.

Left-to-right shunts: “later” cyanosis.

Ventricular septal defect

Asymptomatic at birth, may manifest weeks later or remain asymptomatic throughout life. Most smaller defects self-resolve; larger defects, if left surgically untreated, cause ↑ pulmonary blood flow and LV overload (Eisenmenger syndrome), which may progress to HF.

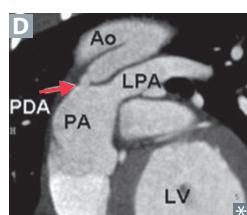
O₂ saturation ↑ in RV and pulmonary artery.

Atrial septal defect

Defect in interatrial septum **C**; systolic ejection murmur with wide, fixed split S2. Ostium secundum defects most common and usually an isolated finding; ostium primum defects rarer and usually occur with other cardiac anomalies. Symptoms range from none to HF. Distinct from patent foramen ovale, which is due to failed fusion.

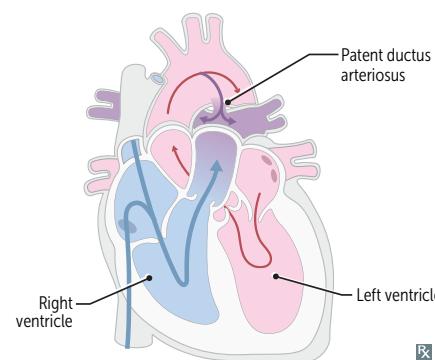
O₂ saturation ↑ in RA, RV, and pulmonary artery. May lead to paradoxical emboli (systemic venous emboli use ASD to bypass lungs and become systemic arterial emboli) in the setting of temporary shunt reversal (eg, when lifting weights or in Eisenmenger syndrome).

Associated with Down syndrome.

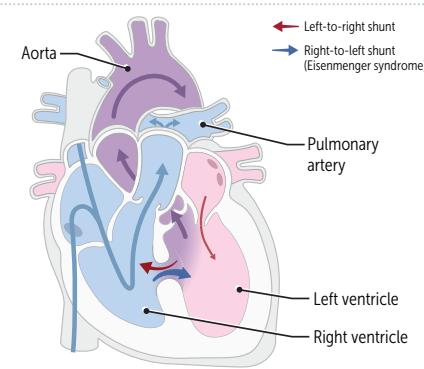
Patent ductus arteriosus

In fetal period, shunt is right to left (normal). In neonatal period, ↓ pulmonary vascular resistance → shunt becomes left to right → progressive RVH and/or LVH and HF. Associated with a continuous, “machinelike” murmur. Patency is maintained by PGE synthesis and low O₂ tension. Uncorrected PDA **D** can eventually result in late cyanosis in the lower extremities (differential cyanosis).

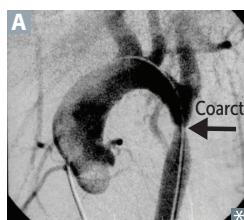
PDA is normal in utero and normally closes soon after birth.

**Eisenmenger syndrome**

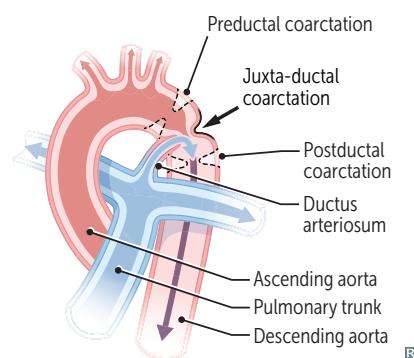
Uncorrected left-to-right shunt (VSD, ASD, PDA) → ↑ pulmonary blood flow → pathologic remodeling of vasculature → pulmonary arterial hypertension. RVH occurs to compensate → shunt becomes right to left when RV > LV pressure (see illustration). Causes late cyanosis, clubbing, and polycythemia. Age of onset varies depending on size and severity of initial left-to-right shunt.



Eisenmenger syndrome from chronic VSD

Coarctation of the aorta

Aortic narrowing **A** near insertion of ductus arteriosus ("juxtaductal"). Associated with bicuspid aortic valve, other heart defects, and Turner syndrome. Hypertension in upper extremities. Cyanosis, claudication, coolness, and weak, delayed pulses (brachiofemoral delay) in lower extremities. With age, intercostal arteries enlarge due to collateral circulation → rib-notching on x-ray. Complications include HF, ↑ risk of cerebral hemorrhage (berry aneurysms), aortic rupture, and infective endocarditis.

**Persistent pulmonary hypertension of the newborn**

Persistence of ↑ pulmonary vascular resistance after birth. Associated with abnormal development and postpartum adaptation of pulmonary vasculature. Risk factors include aspiration of meconium-stained amniotic fluid and neonatal pneumonia. Leads to right-to-left shunt through foramen ovale and ductus arteriosus. Preductal O₂ saturation is often > postductal. Newborn presents with signs of respiratory distress (eg, tachypnea) and (often differential) cyanosis. Equal pulses (no delay).

Congenital cardiac defect associations

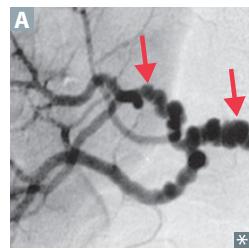
ASSOCIATION	DEFECT
Prenatal alcohol exposure (fetal alcohol syndrome)	VSD, PDA, ASD, tetralogy of Fallot
Congenital rubella	PDA, pulmonary artery stenosis, septal defects
Down syndrome	AVSD, VSD, ASD
Infant of patient with diabetes during pregnancy	TGA, truncus arteriosus, tricuspid atresia, VSD
Marfan syndrome	MVP, thoracic aortic aneurysm/dissection, AR
Prenatal lithium exposure	Ebstein anomaly
Turner syndrome	Bicuspid aortic valve, aortic coarctation/dissection
Williams syndrome	Supravalvular aortic stenosis
22q11 syndromes	Truncus arteriosus, tetralogy of Fallot

Hypertension

Persistent systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 80 mm Hg.

RISK FACTORS

↑ age, obesity, diabetes, physical inactivity, high-sodium diet, excess alcohol intake, tobacco smoking, family history; incidence greatest in Black > White > Asian populations.

FEATURES

90% of hypertension is 1° (essential) and related to ↑ CO or ↑ TPR. Remaining 10% mostly 2° to renal/renovascular diseases such as fibromuscular dysplasia (characteristic "string of beads" appearance of renal artery **A**, usually seen in adult females) and atherosclerotic renal artery stenosis, 1° hyperaldosteronism, or obstructive sleep apnea.

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

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

PREDISPOSES TO

CAD, concentric LVH (mediated by angiotensin II and endothelin), HF, atrial fibrillation; aortic dissection/aneurysm; stroke; CKD (hypertensive nephropathy); retinopathy.

Hyperlipidemia signs**Xanthomas**

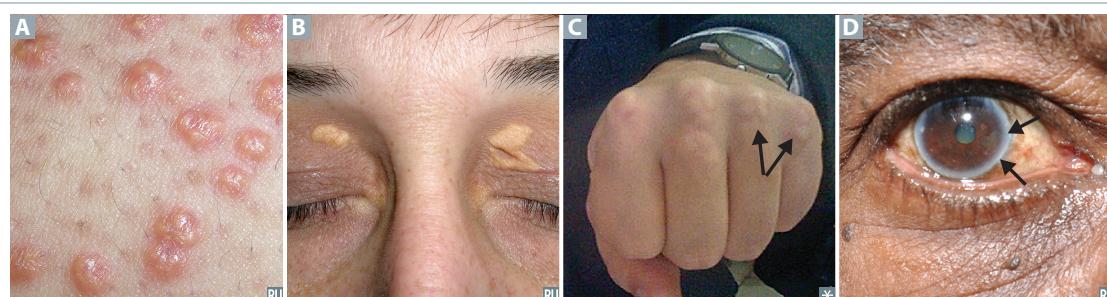
Plaques or nodules composed of lipid-laden histiocytes in skin **A**, especially the eyelids (xanthelasma **B**).

Tendinous xanthoma

Lipid deposit in tendon **C**, especially Achilles tendon and finger extensors. Associated with familial hypercholesterolemia.

Corneal arcus

Lipid deposit in cornea. Common in older adults (arcus senilis **D**), but appears earlier in life with hypercholesterolemia.

**Atherosclerosis**

Very common form of arteriosclerosis (hardening of arteries). Disease of elastic arteries and large- and medium-sized muscular arteries; caused by buildup of cholesterol plaques in tunica intima.

LOCATION

Abdominal aorta > coronary artery > popliteal artery > carotid artery > circle of **Willis**.
A copy cat named **Willis**.

RISK FACTORS

Modifiable: hypertension, tobacco smoking, dyslipidemia (\uparrow LDL, \downarrow HDL), diabetes.
Non-modifiable: age, male sex, postmenopausal status, family history.

SYMPTOMS

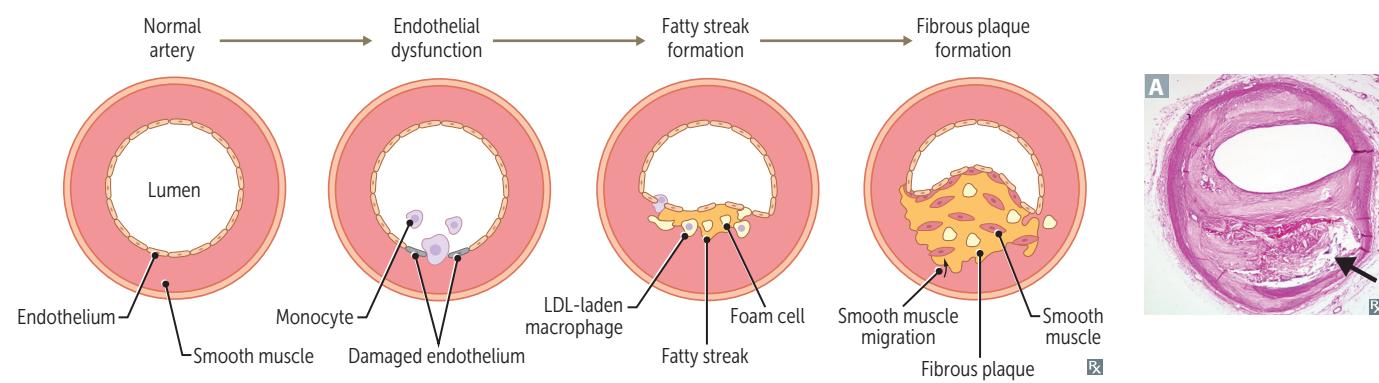
Angina, claudication, but can be asymptomatic.

PROGRESSION

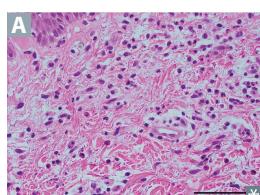
Inflammation important in pathogenesis: endothelial cell dysfunction \rightarrow macrophage and LDL accumulation \rightarrow foam cell formation \rightarrow fatty streaks \rightarrow smooth muscle cell migration (involves PDGF and FGF), proliferation, and extracellular matrix deposition \rightarrow fibrous plaque \rightarrow complex atheromas **A** \rightarrow calcification (calcium content correlates with risk of complications).

COMPLICATIONS

Ischemia, infarction, aneurysm formation, peripheral vascular disease, thrombosis, embolism, renovascular hypertension, coarctation of the aorta, subclavian steal syndrome.



Cholesterol emboli syndrome

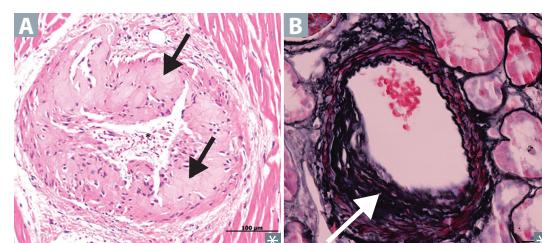


Microembolization of cholesterol displaced from atherosclerotic plaques **A** in large arteries (usually the aorta). Results in end-organ damage due to small artery emboli and an inflammatory response (eg, livedo reticularis, digital ischemia [blue toe syndrome], acute renal failure, cerebrovascular accident, gut ischemia). Pulses remain palpable because larger arteries are unaffected. May follow invasive vascular procedures (angiography, angioplasty, endovascular grafting).

Arteriolosclerosis

Common form of arteriosclerosis. Affects small arteries and arterioles. Two types:

- **Hyaline**—vessel wall thickening 2° to plasma protein leak into subendothelium in hypertension or diabetes mellitus **A**.
- **Hyperplastic**—“onion skinning” **B** in severe hypertension with proliferation of smooth muscle cells.



Aortic aneurysm

Localized pathologic dilation of the aorta. May cause abdominal and/or back pain, which is a sign of leaking, dissection, or imminent rupture.

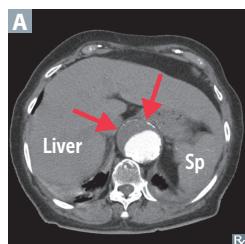
Thoracic aortic aneurysm

Associated with cystic medial degeneration. Risk factors include hypertension, bicuspid aortic valve, connective tissue disease (eg, Marfan syndrome). Also associated with 3° syphilis (obliterative endarteritis of the vasa vasorum). Aortic root dilatation may lead to aortic valve regurgitation.



- Ascending thoracic aorta
- Aortic arch
- Descending thoracic aorta
- Abdominal aorta

Abdominal aortic aneurysm

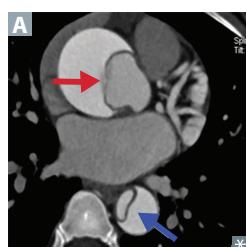


Associated with transmural (all 3 layers) inflammation and extracellular matrix degradation. Risk factors include tobacco smoking (strongest risk factor), ↑ age, male sex, family history. May present as palpable pulsatile abdominal mass (arrows in **A** point to outer dilated aortic wall). Rupture may present as triad of pulsatile abdominal mass, acute abdominal/back pain, and resistant hypotension. Most often infrarenal (distribution of vasa vasorum is reduced).

Traumatic aortic rupture

Due to trauma and/or deceleration injury (MVA or significant fall), most commonly at aortic isthmus (proximal descending aorta just distal to origin of left subclavian artery). X-ray may reveal widened mediastinum.

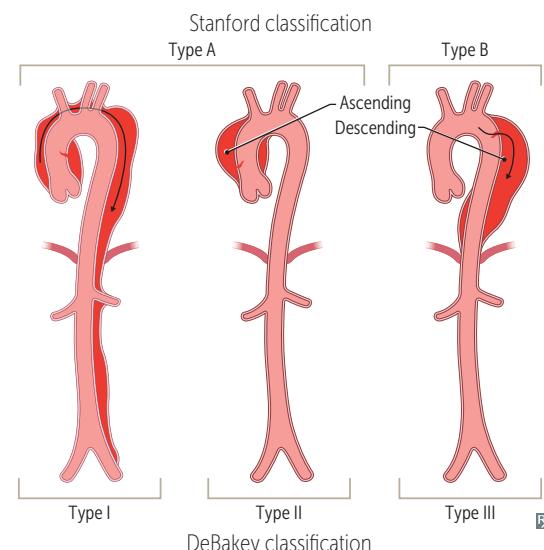
Aortic dissection



Longitudinal intimal tear forming a false lumen. Associated with hypertension (strongest risk factor), bicuspid aortic valve, inherited connective tissue disorders (eg, Marfan syndrome). Can present with tearing, sudden-onset chest pain radiating to the back +/− markedly unequal BP in arms. CXR can show mediastinal widening. Can result in organ ischemia, embolic stroke, aortic rupture, death.

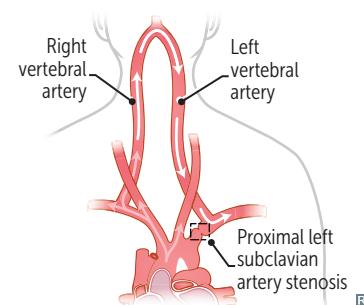
Stanford type **A** (proximal): involves Ascending aorta (red arrow in **A**). May extend to aortic arch or descending aorta (blue arrow in **A**). May result in acute aortic regurgitation or cardiac tamponade. Treatment: surgery.

Stanford type **B** (distal): involves only descending aorta (**B** Below left subclavian artery). Treatment: β -blockers, then vasodilators.



Subclavian steal syndrome

Stenosis of subclavian artery proximal to origin of vertebral artery → hypoperfusion distal to stenosis → reversed blood flow in ipsilateral vertebral artery → reduced cerebral perfusion on exertion of affected arm. Causes arm ischemia, pain, paresthesia, vertebrobasilar insufficiency (dizziness, vertigo), > 15 mm Hg difference in systolic BP between arms. Associated with atherosclerosis (most common cause), Takayasu arteritis, heart surgery.



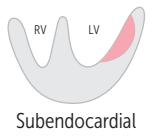
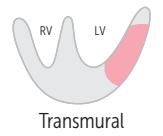
Coronary artery disease**Angina**

Chest pain due to ischemic myocardium 2° to coronary artery narrowing or spasm; no necrosis.

- **Stable**—usually 2° to atherosclerosis ($\geq 70\%$ occlusion); exertional chest pain in classic distribution resolving with rest or nitroglycerin.
- **Unstable**—thrombosis with incomplete coronary artery occlusion; ↑ in frequency or intensity of exertional chest pain or any chest pain at rest. No cardiac biomarker elevation (vs non-ST-segment elevation MI [NSTEMI]).
- **Vasospastic** (formerly Prinzmetal or variant)—occurs at rest 2° to coronary artery spasm; transient ischemic ST changes on ECG. Tobacco smoking is a major risk factor. Triggers include cocaine, amphetamines, alcohol, triptans. Treat with Ca^{2+} channel blockers, nitrates, and smoking cessation (if applicable).

Myocardial infarction

Most often due to an acute coronary syndrome (ACS): rupture of coronary artery atherosclerotic plaque → acute thrombosis. MI can also occur with prolonged supply-demand mismatch (eg, stable angina → prolonged tachycardia and hypotension from pneumonia → elevated troponin but no acute plaque rupture).

	Stable angina	Unstable angina	NSTEMI	STEMI
PAIN	On exertion	Mild exertion or at rest	At rest	At rest
TROPOBIN LEVEL	No elevation	No elevation	Elevated	Elevated
INFARCTION	None	None	 Subendocardial	 Transmural
ECG CHANGES	Possible ST depression and/or T-wave inversion	Possible ST depression and/or T-wave inversion	ST depression and/or T-wave inversion	ST elevation, pathologic Q waves

Ischemic heart disease manifestations**Coronary steal syndrome**

Distal to coronary stenosis, vessels are maximally dilated at baseline to compensate for reduced blood flow. Administration of vasodilators (eg, dipyridamole, adenosine, regadenoson) dilates normal vessels → ↓ hydrostatic pressure in normal coronary arteries → blood is shunted toward well-perfused areas → ↓ flow to myocardium perfused by stenosed vessels (“steal”) → ischemia of myocardium downstream to pathologically dilated vessels. Vasodilator stress tests rely on differential in flow to detect potential ischemia. Rarely, they can cause coronary steal and true ischemia. Vasodilation of healthy vessels **steals** blood from stenosed vessels.

Sudden cardiac death

Unexpected death due to cardiac causes within 1 hour of symptom onset or within 24 hours with no cardiovascular symptoms, most commonly due to lethal ventricular arrhythmia (eg, ventricular fibrillation) impairing blood flow to the brain. Associated with CAD (up to 70% of cases), cardiomyopathy (hypertrophic, dilated), myocarditis, coronary artery anomalies, and hereditary channelopathies (eg, long QT syndrome, Brugada syndrome). Prevent with implantable cardioverter-defibrillator.

Chronic ischemic heart disease

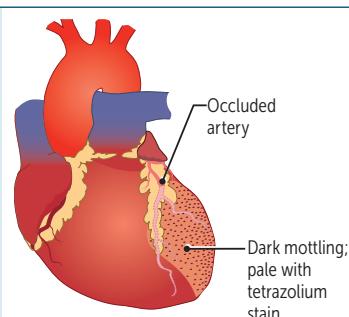
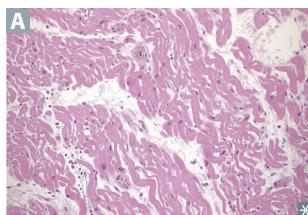
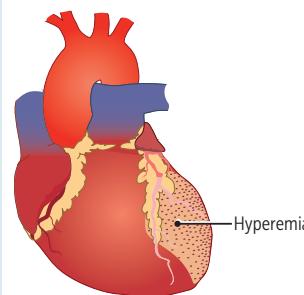
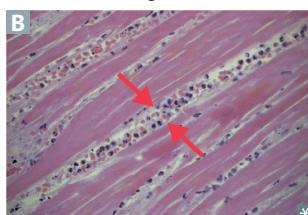
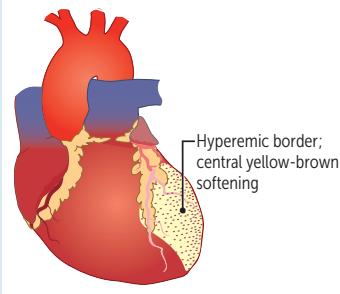
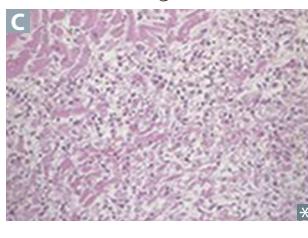
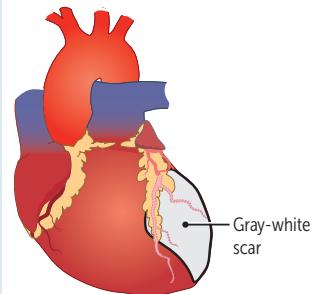
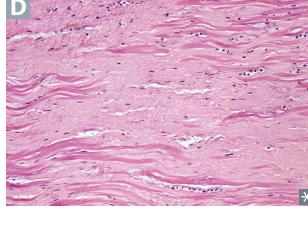
Progressive exertional symptoms and/or development of HF due to chronic ischemic myocardial damage.

Myocardial hibernation—LV systolic dysfunction in the setting of chronic ischemia. Potentially reversible with myocardial reperfusion. Seen in stable angina, acute MI, or HF. Contrast with **myocardial stunning**—transient, reversible LV systolic dysfunction after brief, acute ischemia.

Evolution of myocardial infarction

Commonly occluded coronary arteries: LAD > RCA > circumflex.

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

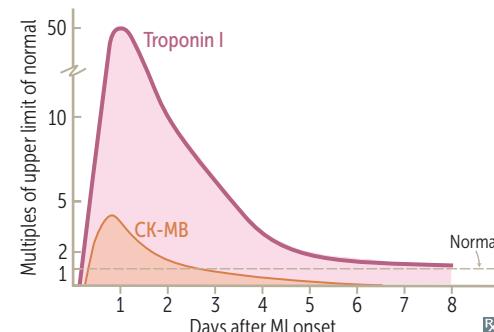
TIME	GROSS	LIGHT MICROSCOPE	COMPLICATIONS
0–24 hours	 <p>Occluded artery Dark mottling; pale with tetrazolium stain</p>	<p>Wavy fibers (0–4 hr), early coagulative necrosis (4–24 hr)</p> <p>A → cell content released into blood; edema, hemorrhage</p> <p>Reperfusion injury → free radicals and ↑ Ca²⁺ influx</p> <p>→ hypercontraction of myofibrils (dark eosinophilic stripes)</p> 	Ventricular arrhythmia, HF, cardiogenic shock
1–3 days	 <p>Hyperemia</p>	<p>Extensive coagulative necrosis</p> <p>Tissue surrounding infarct shows acute inflammation with neutrophils B</p> 	Postinfarction fibrinous pericarditis
3–14 days	 <p>Hyperemic border; central yellow-brown softening</p>	<p>Macrophages, then granulation tissue at margins C</p> 	Free wall rupture → tamponade; papillary muscle rupture → mitral regurgitation; interventricular septal rupture due to macrophage-mediated structural degradation → left-to-right shunt LV pseudoaneurysm (risk of rupture)
2 weeks to several months	 <p>Gray-white scar</p>	Contracted scar complete D 	Postcardiac injury syndrome, HF, arrhythmias, true ventricular aneurysm (risk of mural thrombus)

Diagnosis of myocardial infarction

In the first 6 hours, ECG is the gold standard. Cardiac troponin **I** rises after 4 hours (peaks at 24 hr) and is ↑ for 7–10 days; more specific than other protein markers.

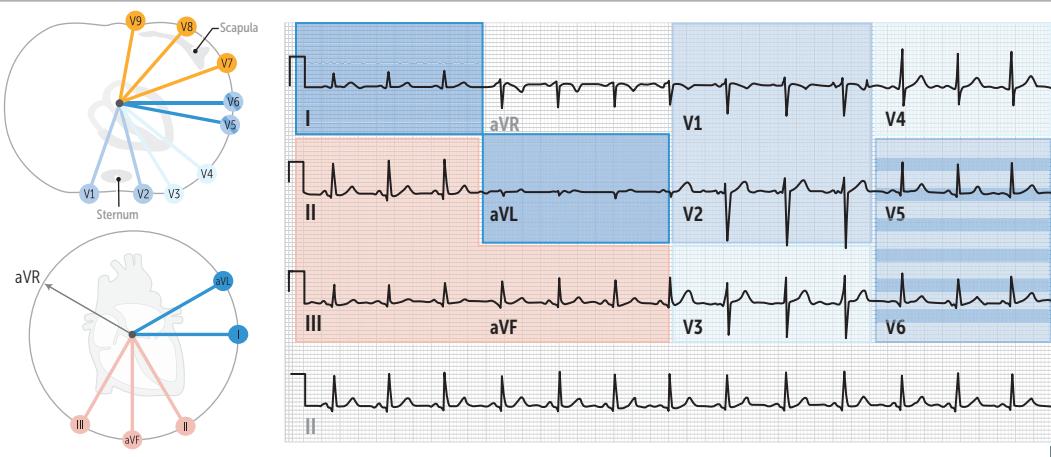
CK-MB increases after 6–12 hours (peaks at 16–24 hr) and is predominantly found in myocardium but can also be released from skeletal muscle. Useful in diagnosing reinfarction following acute MI because levels return to normal after 48 hours.

ECG changes can include ST elevation (STEMI, transmural infarct), ST depression (NSTEMI, subendocardial infarct), hyperacute (peaked) T waves, T-wave inversion, and pathologic Q waves or poor R wave progression (evolving or old transmural infarct).

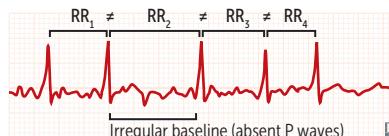
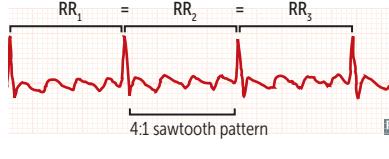


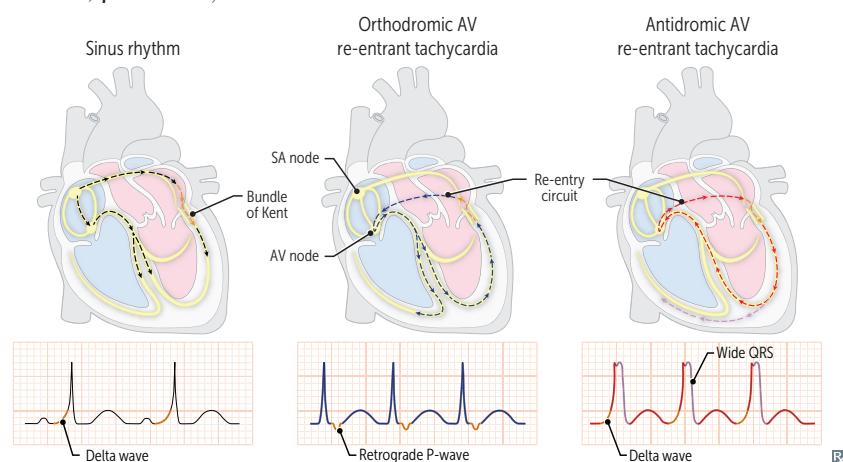
ECG localization of STEMI

INFARCT LOCATION	LEADS WITH ST-SEGMENT ELEVATIONS OR Q WAVES
Anteroseptal (LAD)	V ₁ –V ₂
Anteroapical (distal LAD)	V ₃ –V ₄
Anterolateral (LAD or LCX)	V ₅ –V ₆
Lateral (LCX)	I, aVL
InFerior (RCA)	II, III, aVF
Posterior (PDA)	V ₇ –V ₉ , ST depression in V ₁ –V ₃ with tall R waves

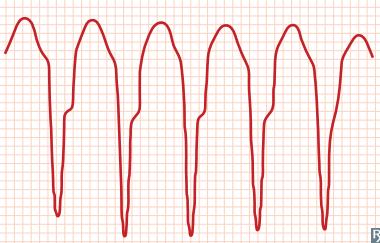
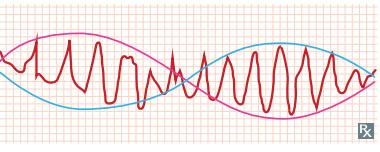
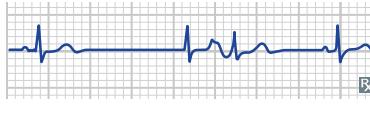


Narrow complex tachycardias Narrow QRS complex < 120 msec, rapid ventricular activation via normal ventricular conduction system, tachycardia originates within or above AV node (supraventricular arrhythmia).

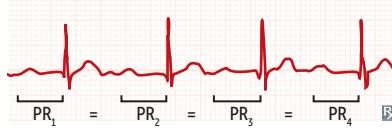
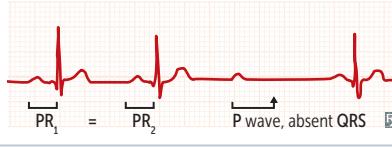
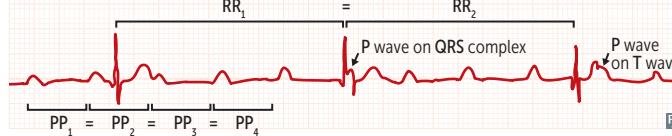
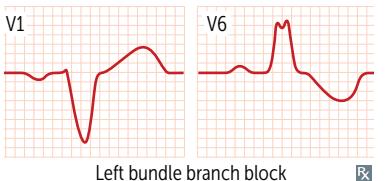
ARRHYTHMIA	DESCRIPTION	ECG FINDINGS
Atrial fibrillation	Irregularly irregular rate and rhythm with no discrete P waves. Arrhythmogenic activity usually originates from automatic foci near pulmonary vein ostia in left atrium. Common risk factors include hypertension, CAD, advanced age, atrial dilation. May predispose to thromboembolic events due to LA blood stasis, particularly stroke. LA appendage is the most common site of thrombus formation in atrial fibrillation. Management of Atrial fibrillation involves rate and rhythm control using Beta-Blockers, Calcium Channel blockers, and Digoxin (ABCD) and cardioversion.	
Multifocal atrial tachycardia	Irregularly irregular rate and rhythm with at least 3 distinct P wave morphologies, due to multiple ectopic foci in atria. Associated with underlying conditions such as COPD, pneumonia, HF.	
Atrial flutter	Rapid succession of identical, consecutive atrial depolarization waves → “sawtooth” appearance of P waves. Arrhythmogenic activity usually originates from reentry circuit around tricuspid annulus. Treat like atrial fibrillation +/- catheter ablation of region between tricuspid annulus and IVC.	
Paroxysmal supraventricular tachycardia	Most often due to a reentrant tract between atrium and ventricle, most commonly in AV node. Commonly presents with sudden-onset palpitations, lightheadedness, diaphoresis. Terminate by slowing AV nodal conduction (vagal maneuvers, adenosine). Definitively treat with catheter ablation.	
Wolff-Parkinson-White syndrome	Most common type of ventricular preexcitation syndrome. Abnormal fast accessory conduction pathway from atria to ventricle (bundle of Kent) bypasses rate-slowing AV node → ventricles partially depolarize earlier → characteristic delta wave with widened QRS complex and shortened PR interval. May result in reentry circuit → supraventricular tachycardia. Treatment: procainamide, ibutilide. Avoid AV nodal-blocking drugs (eg, adenosine, calcium channel blockers, β-blockers).	



Wide complex tachycardias Wide QRS complex \geq 120 msec, slow ventricular activation outside normal ventricular conduction system, tachycardia originates below AV node (ventricular arrhythmia).

ARRHYTHMIA	DESCRIPTION	ECG FINDINGS
Ventricular tachycardia	Typically regular rhythm, rate $>$ 100. Most commonly due to structural heart disease (eg, cardiomyopathy, scarring after myocardial infarction). High risk of sudden cardiac death.	
Torsades de pointes	Polymorphic ventricular tachycardia. Shifting sinusoidal waveforms. May progress to ventricular fibrillation. Long QT interval (eg, sinus bradycardia, congenital long QT syndromes) predisposes to torsades de pointes. Caused by drugs, $\downarrow K^+$, $\downarrow Mg^{2+}$, $\downarrow Ca^{2+}$. Torsades de pointes = twisting of the points Treatment: defibrillation for unstable patients, magnesium sulfate for stable patients. Drug-induced long QT (ABCDEF+NO): <ul style="list-style-type: none">▪ anti-Arrhythmics (Ia and III), Arsenic▪ anti-Biotics (macrolides, fluoroquinolones)▪ anti-Cychotics (haloperidol), Chloroquine▪ anti-Depressants (TCAs), Diuretics (thiazides)▪ anti-Emetics (ondansetron)▪ anti-Fungals (Fluconazole)▪ Navir (protease inhibitors)▪ Opioids (methadone)	
Ventricular fibrillation	Disorganized rhythm with no identifiable waves. Treatment: fatal without immediate CPR and defibrillation.	 No discernible rhythm
Hereditary channelopathies	Inherited mutations of cardiac ion channels \rightarrow abnormal myocardial action potential \rightarrow \uparrow risk of ventricular tachyarrhythmias and sudden cardiac death (SCD).	
Brugada syndrome	Autosomal dominant; most commonly due to loss of function mutation of Na^+ channels. \uparrow prevalence in Asian males. ECG pattern of pseudo-right bundle branch block and ST-segment elevations in leads V ₁ -V ₂ . Prevent SCD with ICD.	
Congenital long QT syndrome	Most commonly due to loss of function mutation of K^+ channels (affects repolarization). Includes: <ul style="list-style-type: none">▪ Romano-Ward syndrome—autosomal dominant, pure cardiac phenotype (no deafness).▪ Jervell and Lange-Nielsen syndrome—autosomal recessive, sensorineural deafness.	
Sick sinus syndrome	Age-related degeneration of SA node. ECG can show bradycardia, sinus pauses (delayed P waves), sinus arrests (dropped P waves), junctional escape beats.	

Conduction blocks

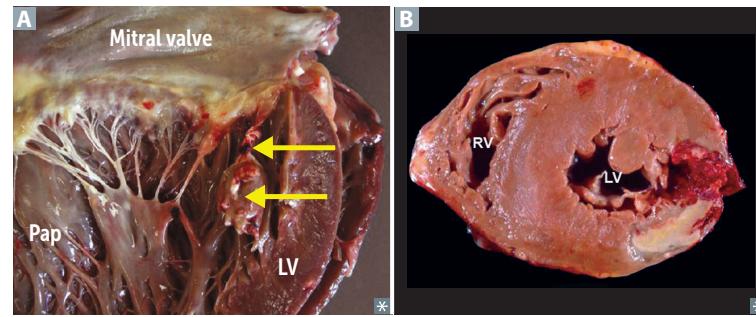
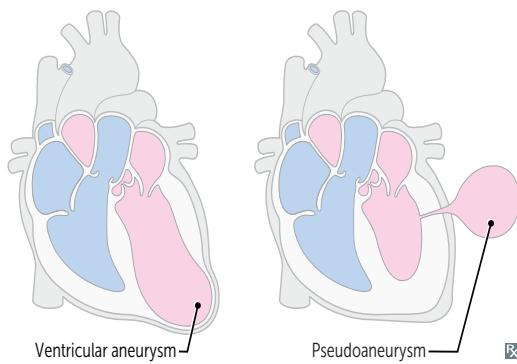
ARRHYTHMIA	DESCRIPTION	ECG FINDINGS
First-degree AV block	Prolonged PR interval (>200 msec). Treatment: none required (benign and asymptomatic).	
Second-degree AV block Mobitz type I (Wenckebach)	Progressive lengthening of PR interval until a beat is “dropped” (P wave not followed by QRS complex). Variable RR interval with a pattern (regularly irregular). Treatment: none required (usually asymptomatic)	
Second-degree AV block Mobitz type II	Dropped beats that are not preceded by a change in PR interval. May progress to 3rd-degree block, as it usually indicates a structural abnormality such as ischemia or fibrosis. Treatment: usually a pacemaker.	
Third-degree (complete) AV block	P waves and QRS complexes rhythmically dissociated. Atria and ventricles beat independently of each other. Atrial rate > ventricular rate. May be caused by Lym3 disease. Treatment: pacemaker.	
Bundle branch block	Interruption of conduction of normal left or right bundle branches. Affected ventricle depolarizes via slower myocyte-to-myocyte conduction from the unaffected ventricle, which depolarizes via the faster His-Purkinje system. Commonly due to degenerative changes (eg, cardiomyopathy, infiltrative disease).	

Premature beats

ARRHYTHMIA	DESCRIPTION	ECG FINDINGS
Premature atrial contraction	Extra beats arising from ectopic foci in atria instead of the SA node. Often 2° to ↑ adrenergic drive (eg, caffeine consumption). Benign, but may increase risk for atrial fibrillation and flutter. Narrow QRS complex with preceding P wave on ECG.	
Premature ventricular contraction	Ectopic beats arising from ventricle instead of the SA node. Shortened diastolic filling time → ↓ SV compared to a normal beat. Prognosis is largely influenced by underlying heart disease. Wide QRS complex with no preceding P wave on ECG.	

Myocardial infarction complications

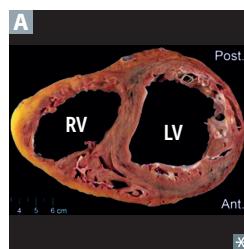
COMPLICATION	TIMEFRAME	FINDINGS	NOTES
Cardiac arrhythmia	First few days to several months	Can be supraventricular arrhythmias, ventricular arrhythmias, or conduction blocks.	Due to myocardial death and scarring. Important cause of death before reaching the hospital and within the first 48 hours post-MI.
Peri-infarction pericarditis	1–3 days	Pleuritic chest pain, pericardial friction rub, ECG changes, and/or small pericardial effusion.	Usually self-limited.
Papillary muscle rupture	2–7 days	Can result in acute mitral regurgitation → cardiogenic shock, severe pulmonary edema.	Posteromedial >> anterolateral papillary muscle rupture A , as the posteromedial has single artery blood supply (posterior descending artery) whereas anterolateral has dual (LAD, LCX).
Interventricular septal rupture	3–5 days	Symptoms can range from mild to severe with cardiogenic shock and pulmonary edema.	Macrophage-mediated degradation → VSD → ↑ O ₂ saturation and ↑ pressure in RV.
Ventricular pseudoaneurysm	3–14 days	May be asymptomatic. Symptoms may include chest pain, murmur, arrhythmia, syncope, HF, embolus from mural thrombus. Rupture → cardiac tamponade.	Free wall rupture contained by adherent pericardium or scar tissue—does not contain endocardium or myocardium. More likely to rupture than true aneurysm.
Ventricular free wall rupture	5–14 days	Free wall rupture B → cardiac tamponade or internal hemorrhage, often fatal.	LV hypertrophy and previous MI protect against free wall rupture.
True ventricular aneurysm	2 weeks to several months	Symptoms similar to pseudoaneurysm.	Outward bulge with contraction (“dyskinesia”). Associated with fibrosis.
Postcardiac injury syndrome	Weeks to several months	Pericarditis due to autoimmune reaction.	Also called Dressler syndrome. Cardiac antigens released after injury → deposition of immune complexes in pericardium → inflammation.



Acute coronary syndrome treatments

Unstable angina/NSTEMI—Anticoagulation (eg, heparin), antiplatelet therapy (eg, aspirin) + ADP receptor inhibitors (eg, clopidogrel), β -blockers, ACE inhibitors, statins. Symptom control with nitroglycerin +/- morphine.

STEMI—In addition to above, reperfusion therapy most important (percutaneous coronary intervention preferred over fibrinolysis). If RV affected (eg, RCA occlusion), support venous return/preload to maintain cardiac output (eg, IV fluids, avoiding nitroglycerin).

Cardiomyopathies**Dilated cardiomyopathy**

Most common cardiomyopathy (90% of cases). Often idiopathic or familial (eg, due to mutation of TTN gene encoding the sarcomeric protein titin). Other etiologies include drugs (eg, alcohol, cocaine, doxorubicin), infection (eg, coxsackie B virus, Chagas disease), ischemia (eg, CAD), systemic conditions (eg, hemochromatosis, sarcoidosis, thyrotoxicosis, wet beriberi), peripartum cardiomyopathy.

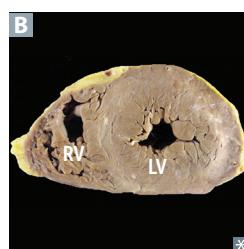
Findings: HF, S3, systolic regurgitant murmur, dilated heart on echocardiogram, balloon appearance of heart on CXR.

Treatment: Na⁺ restriction, ACE inhibitors/ARBs, β -blockers, sacubitril, diuretics, mineralocorticoid receptor blockers (eg, spironolactone), ICD, heart transplant.

Systolic dysfunction ensues.

Displays eccentric hypertrophy **A** (sarcomeres added in series). Compare to athlete's heart, where LV and RV enlargement facilitates ↑ SV and ↑ CO.

Stress cardiomyopathy (also called takotsubo cardiomyopathy, broken heart syndrome)—ventricular apical ballooning likely due to ↑ sympathetic stimulation (eg, stressful situations).

Hypertrophic cardiomyopathy

60–70% of cases are familial, autosomal dominant (most commonly due to mutations in genes encoding sarcomeric proteins, such as myosin binding protein C and β -myosin heavy chain). Causes syncope during exercise and may lead to sudden death (eg, in young athletes) due to ventricular arrhythmia.

Findings: S4, systolic murmur. May see mitral regurgitation due to impaired mitral valve closure.

Treatment: use of β -blockers or nondihydropyridine Ca²⁺ channel blockers (eg, verapamil) and, in some cases, cessation of high-intensity athletics. ICD if high risk. Avoid drugs that decrease preload (eg, diuretics, vasodilators).

Diastolic dysfunction ensues.

Displays ventricular concentric hypertrophy (sarcomeres added in parallel) **B**, often septal predominance. Myofibrillar disarray and fibrosis.

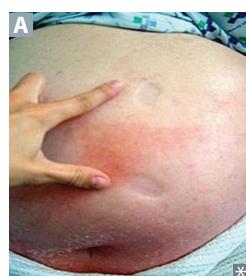
Classified as **hypertrophic obstructive cardiomyopathy** when LV outflow tract is obstructed. Asymmetric septal hypertrophy and systolic anterior motion of mitral valve → outflow obstruction → dyspnea, possible syncope.

Restrictive/infiltrative cardiomyopathy

Postradiation fibrosis, **Löffler endocarditis**, Endocardial fibroelastosis (thick fibroelastic tissue in endocardium of young children), **Amyloidosis**, **Sarcoidosis**, **Hemochromatosis** (**PLEASe Help!**).

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

Löffler endocarditis—associated with hypereosinophilic syndrome; histology shows eosinophilic infiltrates in myocardium.

Heart failure

Clinical syndrome of cardiac pump dysfunction → congestion and low perfusion. Symptoms include dyspnea, orthopnea, fatigue; signs include S3 heart sound, rales, jugular venous distention (JVD), pitting edema **A**.

Systolic dysfunction—heart failure with reduced ejection fraction (HFrEF), ↑ EDV; ↓ contractility often 2° to ischemia/MI or dilated cardiomyopathy.

Diastolic dysfunction—heart failure with preserved ejection fraction (HFpEF); ↓ compliance (↑ EDP) often 2° to myocardial hypertrophy.

Right HF most often results from left HF. Cor pulmonale refers to isolated right HF due to pulmonary cause.

ACE inhibitors, ARBs, angiotensin receptor–neprilysin inhibitors, β -blockers (except in acute decompensated HF), and aldosterone receptor antagonists ↓ mortality in HFrEF. Loop and thiazide diuretics are used mainly for symptomatic relief. Hydralazine with nitrates and SGLT2 inhibitors improve both symptoms and mortality in select patients.

Left heart failure

Orthopnea Shortness of breath when supine: ↑ venous return from redistribution of blood (immediate gravity effect) exacerbates pulmonary vascular congestion.

Paroxysmal nocturnal dyspnea Breathless awakening from sleep: ↑ venous return from redistribution of blood, reabsorption of peripheral edema, etc.

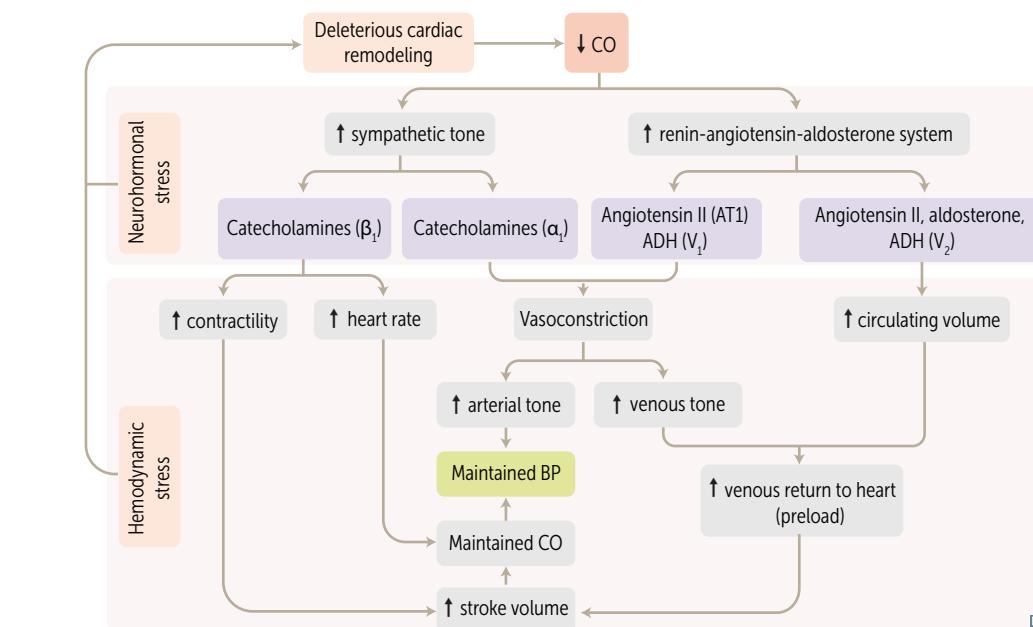
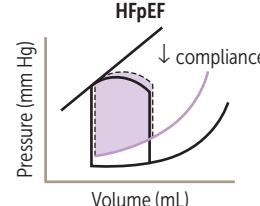
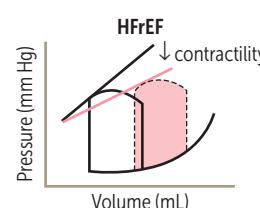
Pulmonary edema ↑ pulmonary venous pressure → pulmonary venous distention and transudation of fluid. Presence of hemosiderin-laden macrophages (“HF” cells) in lungs.

Right heart failure

Congestive hepatomegaly ↑ central venous pressure → ↑ resistance to portal flow. Rarely, leads to “cardiac cirrhosis.” Associated with nutmeg liver (mottled appearance) on gross exam.

Jugular venous distention ↑ venous pressure.

Peripheral edema ↑ venous pressure → fluid transudation.



High-output heart failure

Uncommon form of HF characterized by ↑ CO. High-output state is due to ↓ SVR from either vasodilation or arteriovenous shunting. Causes include severe obesity, advanced cirrhosis, severe anemia, hyperthyroidism, wet beriberi, Paget disease of bone.
Presents with symptoms and signs of pulmonary and/or systemic venous congestion.

Shock

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

TYPE	CAUSED BY	MECHANISM	SKIN	CVP	PCWP	CO	SVR	SVO ₂
Hypovolemic shock	Hemorrhage, dehydration, burns	Volume depletion		↓	↓	↓	↑	↓
Cardiogenic shock	MI, HF, valvular dysfunction, arrhythmia	Left heart dysfunction	Cold, clammy	↑	↑	↓	↑	↓
Obstructive shock	PE, tension pneumothorax	Impeded cardiopulmonary blood flow		↑	↓	↓	↑	↓
	Cardiac tamponade			↑	↑	↓	↑	↓
Distributive shock	Sepsis (early), anaphylaxis	Systemic vasodilation	Warm, dry	↓	↓	↑	↓	↑
	CNS injury			↓	↓	↓	↓	normal/↑

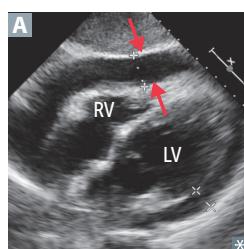
↓ = 1° disturbance driving the shock.

Cardiac tamponade

Compression of the heart by fluid (eg, blood, effusions) → ↓ CO. Equilibration of diastolic pressures in all 4 chambers.

Findings: Beck triad (hypotension, distended neck veins, distant heart sounds), ↑ HR, pulsus paradoxus. ECG may show low-voltage QRS and/or electrical alternans (due to “swinging” movement of heart in large effusion). Echocardiogram shows pericardial effusion (arrows in A), systolic RA collapse, diastolic RV collapse, and IVC plethora.

Treatment: pericardiocentesis or surgical drainage.

**Pulsus paradoxus**

↓ in amplitude of systolic BP by > 10 mm Hg during inspiration. ↑ venous return during inspiration → ↑ RV filling → interventricular septum bows toward LV (due to ↓ pericardial compliance) → ↓ LV ejection volume → ↓ systolic BP. Seen in constrictive pericarditis, obstructive pulmonary disease (eg, Croup, OSA, Asthma, COPD), cardiac Tamponade (pea COAT).

Syncope

Transient loss of consciousness caused by a period of ↓ cerebral blood flow. Types:

- Reflex (most common)—vasovagal (prodromal symptoms [eg, warmth, pallor, nausea]; episodes are short with rapid recovery), situational (eg, coughing/sneezing, swallowing, defecation, micturition), carotid sinus hypersensitivity (eg, wearing tight collar).
- Orthostatic—hypovolemia, drugs (eg, antihypertensives), autonomic dysfunction. Orthostatic hypotension is defined as a drop in systolic BP ≥ 20 mm Hg and/or diastolic BP ≥ 10 mm Hg within 3 minutes of standing.
- Cardiac—arrhythmias, structural (eg, aortic stenosis, HCM).

Infective endocarditis

Infection of the endocardial surface of the heart, typically involving ≥1 heart valves.

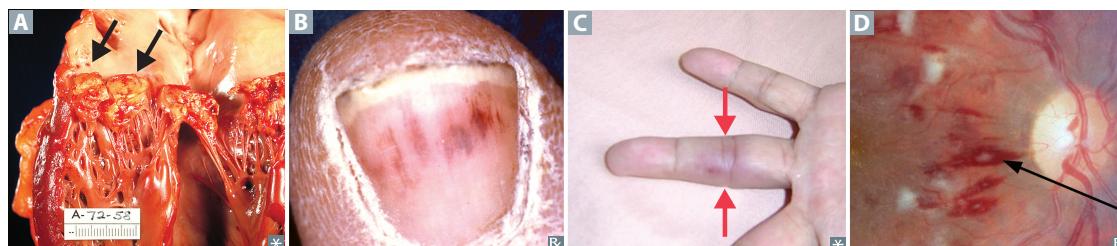
Caused by bacteria >> fungi. Forms:

- **Acute**—classically *S aureus* (high virulence). Large destructive vegetations **A** on previously normal valves. Rapid onset.
- **Subacute**—classically viridans streptococci (low virulence). Smaller vegetations on congenitally abnormal or diseased valves. Sequela of dental procedures. Gradual onset.

Presents with fever (most common), new murmur, vascular and immunologic phenomena.

Vascular phenomena—septic embolism, petechiae, splinter hemorrhages (linear hemorrhagic lesions on nail bed **B**), Janeway lesions (painless, flat, erythematous lesions on palms or soles).

Immunologic phenomena—immune complex deposition, glomerulonephritis, **Osler nodes** (painful ["Ouchy"], raised, violaceous lesions on finger or toe pads **C**), **Roth spots** (Retinal hemorrhagic lesions with pale centers **D**).

**Nonbacterial thrombotic endocarditis**

Also called marantic endocarditis. Rare, noninfective. Vegetations typically arise on mitral or aortic valve and consist of sterile, platelet-rich thrombi that dislodge easily. Usually asymptomatic until embolism occurs.

Mitral valve (most common) > aortic valve.

Tricuspid valve involvement is associated with injection drug use (don't "tri" drugs).

Common associations:

- Prosthetic valves—*S epidermidis*
- GI/GU procedures—*Enterococcus*
- Colon cancer—*S gallolyticus*
- Gram ⊥—**HACEK** organisms (*Haemophilus*, *Aggregatibacter* [formerly *Actinobacillus*], *Cardiobacterium*, *Eikenella*, *Kingella*)
- Culture ⊥—*Coxiella*, *Bartonella*
- Injection drug use—*S aureus*, *Pseudomonas*, *Candida*

Endothelial injury → formation of vegetations consisting of platelets, fibrin, and microbes on heart valves → valve regurgitation, septic embolism (systemic circulation in left-sided endocarditis, pulmonary in right-sided).

Diagnosis requires multiple blood cultures and echocardiography.

Associated with the hypercoagulable state seen in advanced malignancy (especially pancreatic adenocarcinoma) or SLE (called **Libman-Sacks endocarditis** in this setting).

Rheumatic fever

A nonsuppurative consequence of pharyngeal infection with group A β -hemolytic streptococci. Late sequelae include **rheumatic heart disease**, which affects heart valves—**mitral > aortic >> tricuspid** (high-pressure valves affected most). Early valvular regurgitation, late valvular stenosis. Associated with Aschoff bodies (granuloma with giant cells), Anitschkow cells (enlarged macrophages with ovoid, wavy, rodlike nucleus), ↑ anti-streptolysin O (ASO) and ↑ anti-DNase B titers. Immune mediated (type II hypersensitivity); not a direct effect of bacteria. Antibodies to **M protein** cross-react with self antigens, often **myosin (molecular mimicry)**. Treatment/prophylaxis: penicillin.

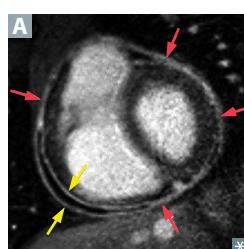
JONES (major criteria):

- Joint (migratory polyarthritis)
- Heart (pancarditis)
- Nodules in skin (subcutaneous)
- Erythema marginatum (evanescent rash with ring margin)
- Sydenham chorea (involuntary irregular movements of limbs and face)

Syphilitic heart disease

3° syphilis disrupts the vasa vasorum of the aorta with consequent atrophy of vessel wall and dilation of aorta and valve ring. May see calcification of aortic root, ascending aortic arch, and thoracic aorta. Leads to “tree bark” appearance of aorta.

Can result in aneurysm of ascending aorta or aortic arch, aortic insufficiency.

Acute pericarditis

Inflammation of the pericardium (red arrows in A). Commonly presents with sharp pain, aggravated by inspiration, and relieved by sitting up and leaning forward. Often complicated by pericardial effusion (between yellow arrows in A). Presents with friction rub. ECG changes include widespread/diffuse ST-segment elevation and/or PR depression. Usually idiopathic, but may be due to viral infections (eg, coxsackievirus B), malignancy (metastasis), cardiac surgery, thoracic radiotherapy (early), MI (eg, postcardiac injury syndrome), autoimmune diseases (eg, SLE, drug-induced lupus, rheumatoid arthritis), renal failure (uremia). Treatment: NSAIDs, colchicine, glucocorticoids, dialysis (uremia).

Constrictive pericarditis

Chronic inflammation of pericardium → pericardial fibrosis +/– calcification → limited space for expansion → ↓ ventricular filling. Usually idiopathic, but may be due to viral infections, cardiac surgery, thoracic radiotherapy (late). TB is the most common cause in resource-limited countries. ↓ EDV → ↓ CO → ↓ venous return. Presents with dyspnea, peripheral edema, jugular venous distention, Kussmaul sign, pulsus paradoxus, pericardial knock.

Kussmaul sign

Paradoxical ↑ in JVP on inspiration (normally, inspiration → negative intrathoracic pressure → ↑ venous return → ↓ JVP). Impaired RV filling → RV cannot accommodate ↑ venous return during inspiration → blood backs up into vena cava → Kussmaul sign. May be seen with constrictive pericarditis, restrictive cardiomyopathy, right HF, massive pulmonary embolism, right atrial or ventricular tumors.

Myocarditis

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

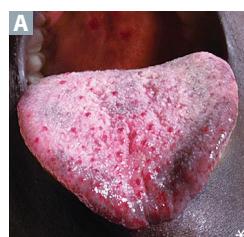
- Viral (eg, adenovirus, coxsackie B, parvovirus B19, HIV, HHV-6, COVID-19); lymphocytic infiltrate with focal necrosis highly indicative of viral myocarditis
- Parasitic (eg, *Trypanosoma cruzi*, *Toxoplasma gondii*)
- Bacterial (eg, *Borrelia burgdorferi*, *Mycoplasma pneumoniae*, *Corynebacterium diphtheriae*)
- Toxins (eg, carbon monoxide, black widow venom)
- RF
- Drugs (eg, doxorubicin, cocaine)
- Autoimmune (eg, Kawasaki disease, sarcoidosis, SLE, polymyositis/dermatomyositis)

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

Hereditary hemorrhagic telangiectasia

Also called Osler-Weber-Rendu syndrome. Autosomal dominant disorder of blood vessels. Findings: blanching lesions (eg, tongue telangiectasias A) on skin and mucous membranes, recurrent epistaxis, arteriovenous malformations (eg, brain, lung, liver), GI bleeding, hematuria.

Arteriovenous malformation—abnormal, high-flow connection between artery and vein. ↑ risk of high output cardiac failure. Most common cause of intracranial hemorrhage in children.

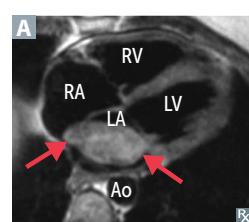
**Cardiac tumors**

Most common cardiac tumor is a metastasis (eg, melanoma).

Myxomas

Most common 1° cardiac tumor in adults (arrows in A). 90% occur in the atria (mostly left atrium). Myxomas are usually described as a “ball valve” obstruction in the left atrium (associated with multiple syncopal episodes). IL-6 production by tumor → constitutional symptoms (eg, fever, weight loss). May auscultate early diastolic “tumor plop” sound (mimics mitral stenosis). Histology: gelatinous material, myxoma cells immersed in glycosaminoglycans.

Adults make 6 myxed drinks.

**Rhabdomyomas**

Most frequent 1° cardiac tumor in children (associated with tuberous sclerosis). Histology: hamartomatous growths. More common in the ventricles.

Deep venous thrombosis

Blood clot within a deep vein → swelling, redness **A**, warmth, pain. Predisposed by Virchow triad (**SHE**):

- **S**tasis (eg, post-op, long drive/flight)
- **H**ypercoagulability (eg, defect in coagulation cascade proteins, such as factor V Leiden; oral contraceptive use; pregnancy)
- **E**ndothelial damage (exposed collagen triggers clotting cascade)

DVT of proximal deep veins of lower extremity (iliac, femoral, popliteal) → embolic source.

d-dimer test may be used clinically to rule out DVT if disease probability is low or moderate (high sensitivity, low specificity). Imaging test of choice is compression ultrasound with Doppler.

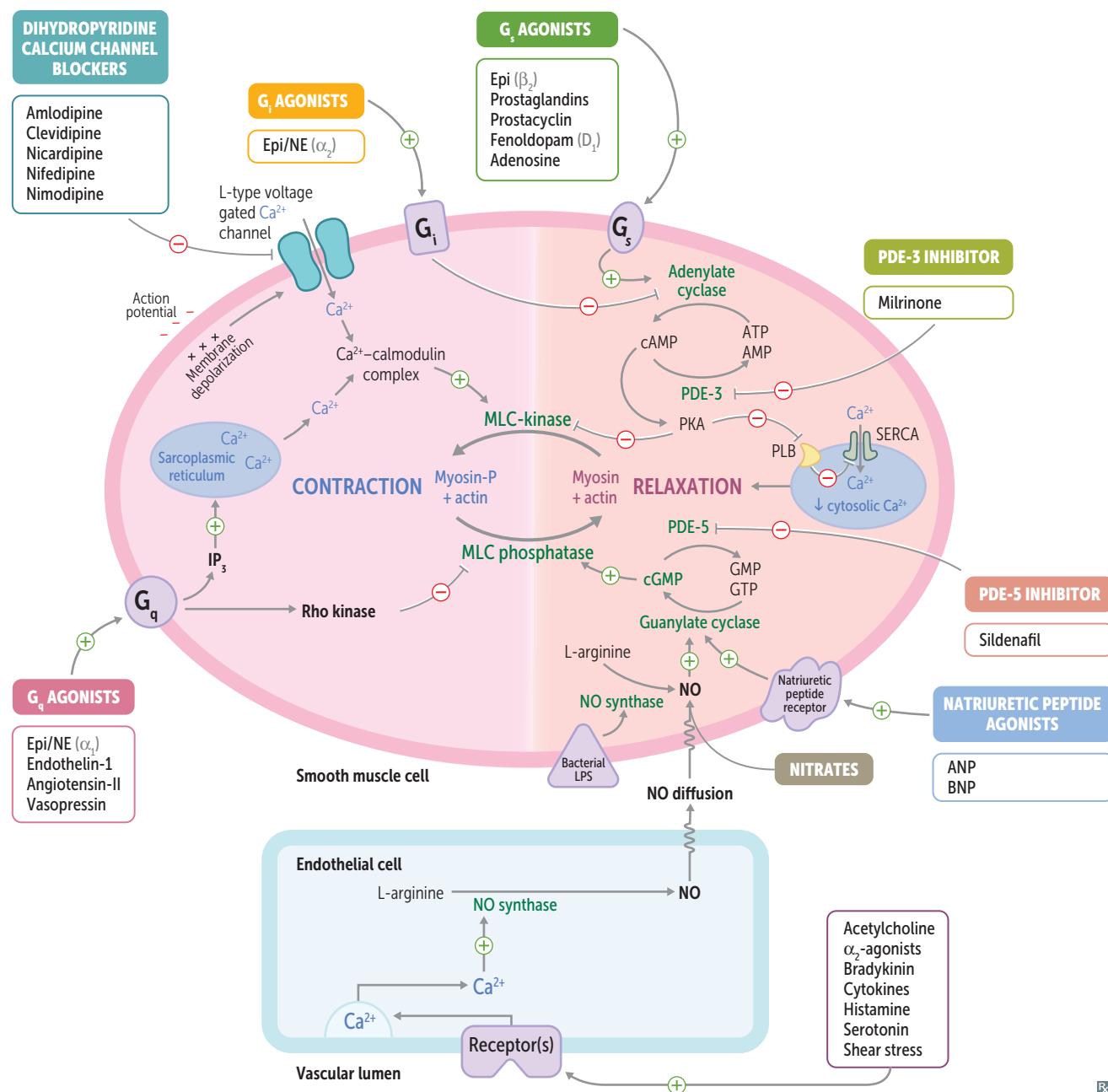
Use unfractionated heparin or low-molecular weight heparins (eg, enoxaparin) for prophylaxis and acute management. Use direct anticoagulants (eg, rivaroxaban, apixaban) for treatment and long-term prevention.

► CARDIOVASCULAR—PHARMACOLOGY

Hypertension treatment

Primary (essential) hypertension	Thiazide diuretics, ACE inhibitors, angiotensin II receptor blockers (ARBs), Ca^{2+} channel blockers.	
Hypertension with heart failure	ACE inhibitors/ARBs, β -blockers (compensated HF), aldosterone antagonists (mortality benefit), diuretics (improve symptoms and reduce hospitalization)	β -blockers must be used cautiously in decompensated HF and are contraindicated in cardiogenic shock.
Hypertension with diabetes mellitus	ACE inhibitors/ARBs, Ca^{2+} channel blockers, thiazide diuretics, β -blockers.	ACE inhibitors/ARBs are protective against diabetic nephropathy. β -blockers can mask hypoglycemia symptoms.
Hypertension with asthma	ARBs, Ca^{2+} channel blockers, thiazide diuretics, cardioselective β -blockers.	Avoid non-selective β -blockers to prevent β_2 -receptor-induced bronchoconstriction. Avoid ACE inhibitors to prevent confusion between drug- or asthma-related cough.
Hypertension with pregnancy	Hydralazine, methyldopa, labetalol, nifedipine.	Hypertensive moms love nifedipine.
Hypertension with gout	ACE inhibitors, Ca^{2+} channel blockers, ARBs (especially losartan).	Avoid loop and thiazide diuretics as these can cause gout flares.
Hypertension with osteoporosis	Thiazides preferred as monotherapy; combine with ACE inhibitors or ARBs if needed.	Thiazides preferred due to increased Ca^{2+} reabsorption.
Hypertension with pheochromocytoma	Phentolamine, phenoxybenzamine (α -blockade first) prior to resection and β -blockade.	Avoid β -blockade first to mitigate unopposed α -mediated hypertensive crisis.

Cardiovascular agents and molecular targets

**Nitrates**

Nitroglycerin, isosorbide dinitrate, isosorbide mononitrate.

MECHANISM

Vasodilate by ↑ NO in vascular smooth muscle → ↑ in cGMP and smooth muscle relaxation.
Dilate veins >> arteries. ↓ preload.

CLINICAL USE

Angina, ACS, pulmonary edema.

ADVERSE EFFECTS

Reflex tachycardia (treat with β -blockers), methemoglobinemia, hypotension, flushing, headache, “Monday disease” in industrial nitrate exposure: development of tolerance for the vasodilating action during the work week and loss of tolerance over the weekend → tachycardia, dizziness, headache upon reexposure. Contraindicated in right ventricular infarction, hypertrophic cardiomyopathy, and with concurrent PDE-5 inhibitor use.

Calcium channel blockers

Amlodipine, clevidipine, nicardipine, nifedipine, nimodipine (dihydropyridines, act on vascular smooth muscle); diltiazem, verapamil (nondihydropyridines, act on heart).

MECHANISM

Block voltage-dependent L-type calcium channels of cardiac and smooth muscle → ↓ muscle contractility.

Vascular smooth muscle—amlodipine = nifedipine > diltiazem > verapamil.
Heart—verapamil > diltiazem > amlodipine = nifedipine.

CLINICAL USE

Dihydropyridines (except nimodipine): hypertension, angina (including vasospastic type), Raynaud phenomenon. Dihydropyridine mainly dilates arteries.

Nimodipine: subarachnoid hemorrhage (prevents delayed ischemia).

Nicardipine, clevidipine: hypertensive urgency or emergency.

Nondihydropyridines: hypertension, angina, rate control in atrial fibrillation/flutter, prevention of nodal arrhythmias.

ADVERSE EFFECTS

Gingival hyperplasia.

Dihydropyridine: peripheral edema, flushing, dizziness.

Nondihydropyridine: cardiac depression, AV block, hyperprolactinemia (verapamil), constipation.

Hydralazine**MECHANISM**

↑ cGMP → smooth muscle relaxation. Hydralazine vasodilates arterioles > veins; afterload reduction.

CLINICAL USE

Severe hypertension (particularly acute), HF (with organic nitrate). Safe to use during pregnancy. Frequently coadministered with a β-blocker to prevent reflex tachycardia.

ADVERSE EFFECTS

Compensatory tachycardia (contraindicated in angina/CAD), fluid retention, headache, angina, drug-induced lupus.

Hypertensive emergency

Treat with labetalol, clevidipine, fenoldopam, nicardipine, nitroprusside.

Nitroprusside

Short acting vasodilator (arteries = veins); ↑ cGMP via direct release of NO. Can cause cyanide toxicity (releases cyanide).

Fenoldopam

Dopamine D₁ receptor agonist—coronary, peripheral, renal, and splanchnic vasodilation. ↓ BP, ↑ natriuresis. Also used postoperatively as an antihypertensive. Can cause hypotension, tachycardia, flushing, headache, nausea.

Antianginal therapy

Goal is reduction of myocardial O₂ consumption (MVO₂) by ↓ 1 or more of the determinants of MVO₂: end-diastolic volume, BP, HR, contractility.

COMPONENT	NITRATES	β-BLOCKERS	NITRATES + β-BLOCKERS
End-diastolic volume	↓	No effect or ↑	No effect or ↓
Blood pressure	↓	↓	↓
Contractility	↑ (reflex response)	↓	Little/no effect
Heart rate	↑ (reflex response)	↓	No effect or ↓
Ejection time	↓	↑	Little/no effect
MVO ₂	↓	↓	↓↓

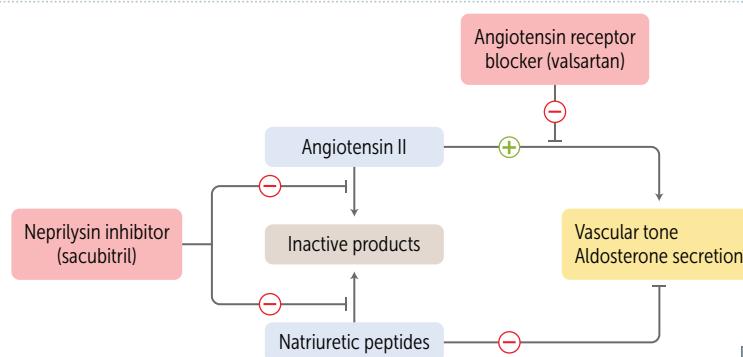
Nondihydropyridine calcium channel blockers (verapamil, diltiazem) are similar to β-blockers in effect.

Ranolazine

MECHANISM	Inhibits the late phase of inward sodium current thereby reducing diastolic wall tension and oxygen consumption. Does not affect heart rate or blood pressure.
CLINICAL USE	Refractory angina.
ADVERSE EFFECTS	Constipation, dizziness, headache, nausea, QT prolongation.

Sacubitril

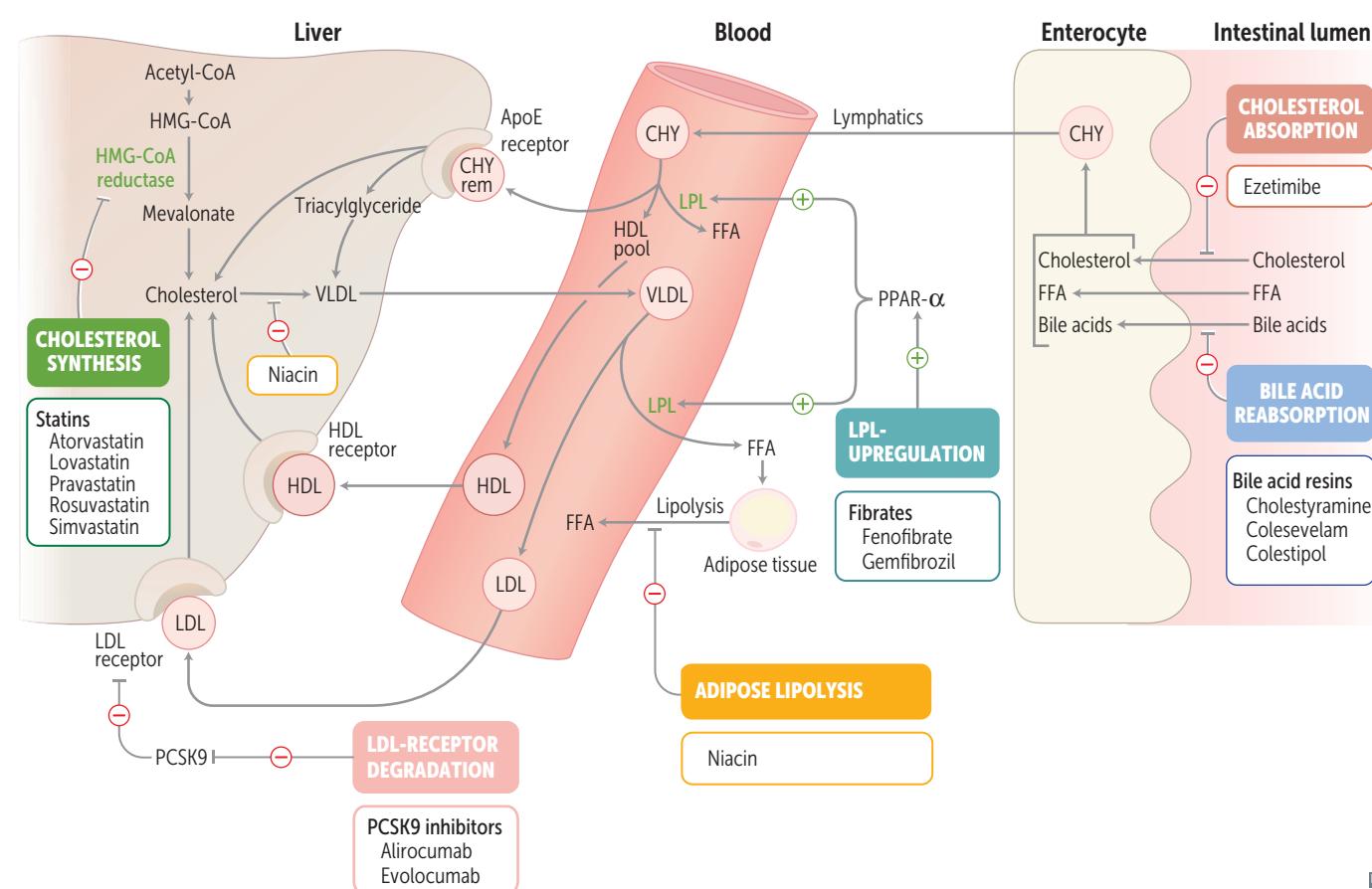
MECHANISM	A neprilysin inhibitor; prevents degradation of bradykinin, natriuretic peptides, angiotensin II, and substance P → ↑ vasodilation, ↓ ECF volume.
CLINICAL USE	Used in combination with valsartan (an ARB) to treat HFrEF.
ADVERSE EFFECTS	Hypotension, hyperkalemia (due to ARB component of HFrEF therapy), cough, dizziness; contraindicated with ACE inhibitors due to angioedema (both drugs ↑ bradykinin).

**Lipid-lowering agents**

DRUG	LDL	HDL	TRIGLYCERIDES	MECHANISM	ADVERSE EFFECTS
Statins Atorvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin	↓↓	↑	↓	Inhibit HMG-CoA reductase → ↓ cholesterol synthesis; → ↓ intrahepatic cholesterol → ↑ LDL receptor recycling → ↑ LDL catabolism ↓ in mortality in patients with CAD	Hepatotoxicity (↑ LFTs), myopathy (especially when used with fibrates or niacin)
Bile acid resins Cholestyramine, colesevelam, colestipol	↓↓	↑ slightly	↑ slightly	Disrupt enterohepatic bile acid circulation → compensatory ↑ conversion of cholesterol to bile → ↓ intrahepatic cholesterol → ↑ LDL receptor recycling	GI upset, ↓ absorption of other drugs and fat-soluble vitamins
Ezetimibe	↓↓	↑/-	↓/-	Prevents cholesterol absorption at small intestine brush border	Rare ↑ LFTs, diarrhea

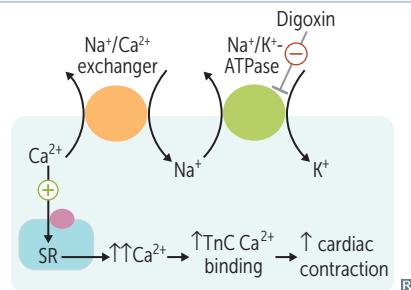
Lipid-lowering agents (continued)

DRUG	LDL	HDL	TRIGLYCERIDES	MECHANISM	ADVERSE EFFECTS
Fibrates Fenofibrate, gemfibrozil	↓	↑	↓↓	Activate PPAR- α → upregulate LPL → ↑ TG clearance Activate PPAR- α → induce HDL synthesis	Myopathy (↑ risk with statins), cholesterol gallstones (via inhibition of cholesterol 7 α -hydroxylase)
Niacin	↓↓	↑↑	↓	Inhibits lipolysis (hormone- sensitive lipase) in adipose tissue; reduces hepatic VLDL synthesis	Flushed face (prostaglandin mediated; ↓ by NSAIDs or long- term use) Hyperglycemia Hyperuricemia
PCSK9 inhibitors Alirocumab, evolocumab	↓↓	↑	↓	Inactivation of LDL-receptor degradation → ↑ removal of LDL from bloodstream	Myalgias, delirium, dementia, other neurocognitive effects
Fish oil and marine omega-3 fatty acids	↑ slightly	↑ slightly	↓ at high doses	Believed to ↓ FFA delivery to liver, ↓ activity of TG- synthesizing enzymes, ↓ VLDL production, and inhibit synthesis of ApoB	Nausea, fishlike taste



Digoxin**MECHANISM**

Direct inhibition of Na^+/K^+ -ATPase.
 → indirect inhibition of $\text{Na}^+/\text{Ca}^{2+}$ exchanger.
 $\uparrow [\text{Ca}^{2+}]_i \rightarrow$ positive inotropy. Stimulates vagus nerve → $\downarrow \text{HR}$.

**CLINICAL USE**

HF (\uparrow contractility); atrial fibrillation (\downarrow conduction at AV node and depression of SA node).

ADVERSE EFFECTS

Cholinergic effects (nausea, vomiting, diarrhea), blurry yellow vision (“van Glow”), arrhythmias, atrial tachycardia with AV block.
 Can lead to hyperkalemia, which indicates poor prognosis.
 Factors predisposing to toxicity: renal failure (\downarrow excretion), hypokalemia (permissive for digoxin binding at K^+ -binding site on Na^+/K^+ -ATPase), drugs that displace digoxin from tissue-binding sites, and \downarrow clearance (eg, verapamil, amiodarone, quinidine).

ANTIDOTE

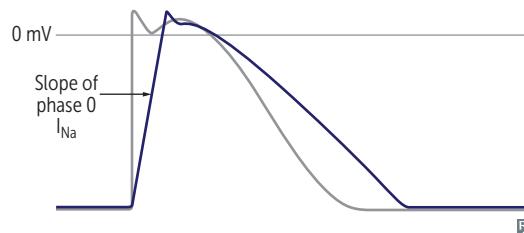
Slowly normalize K^+ , cardiac pacer, anti-digoxin Fab fragments, Mg^{2+} .

Antiarrhythmics—sodium channel blockers (class I)

Slow or block conduction (especially in depolarized cells). \downarrow slope of phase 0 depolarization.
 \uparrow action at faster HR. State dependent \uparrow HR → shorter diastole, Na^+ channels spend less time in resting state (drugs dissociate during this state) → less time for drug to dissociate from receptor.
 Effect most pronounced in IC>IA>IB due to relative binding strength. **Fast taxi CAB.**

Class IA

Quinidine, procainamide, disopyramide.
 “The queen proclaims **Diso’s pyramid**.”

**MECHANISM**

Moderate Na^+ channel blockade.
 \uparrow AP duration, \uparrow effective refractory period (ERP) in ventricular action potential, \uparrow QT interval, some K^+ channel blocking effects.

CLINICAL USE

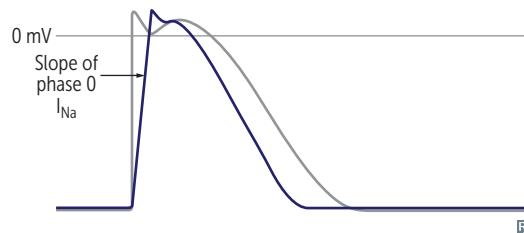
Both atrial and ventricular arrhythmias, especially reentrant and ectopic SVT and VT.

ADVERSE EFFECTS

Cinchonism (headache, tinnitus with quinidine), reversible SLE-like syndrome (procainamide), HF (disopyramide), thrombocytopenia, torsades de pointes due to \uparrow QT interval.

Class IB

Lidocaine, mexiletine.
 “I’d Buy Liddy’s Mexican tacos.”

**MECHANISM**

Weak Na^+ channel blockade.
 \downarrow AP duration. Preferentially affect ischemic or depolarized Purkinje and ventricular tissue.

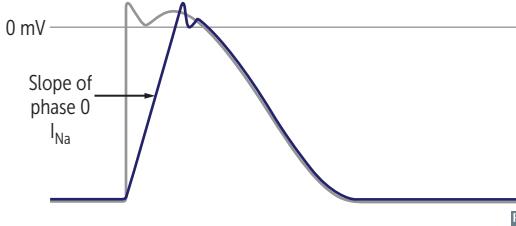
CLINICAL USE

Acute ventricular arrhythmias (especially post-MI), digitalis-induced arrhythmias.
IB is Best post-MI.

ADVERSE EFFECTS

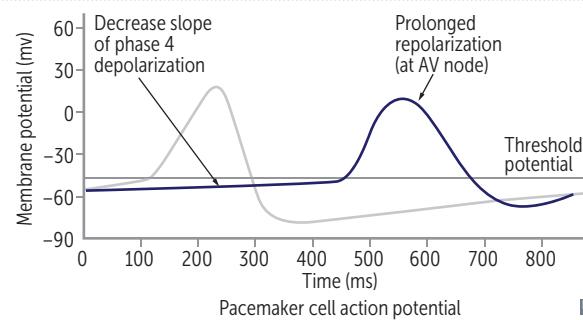
CNS stimulation/depression, cardiovascular depression.

Antiarrhythmics—sodium channel blockers (class I) (continued)

Class IC	Flecainide, propafenone. “Can I have fries, please?”	
MECHANISM	Strong Na^+ channel blockade. Significantly prolongs ERP in AV node and accessory bypass tracts. No effect on ERP in Purkinje and ventricular tissue. Minimal effect on AP duration.	
CLINICAL USE	SVTs, including atrial fibrillation. Only as a last resort in refractory VT.	
ADVERSE EFFECTS	Poarrhythmic, especially post-MI (contraindicated). IC is Contraindicated in structural and ischemic heart disease.	

Antiarrhythmics— β -blockers (class II)

	Metoprolol, propranolol, esmolol, atenolol, timolol, carvedilol.
MECHANISM	Decrease SA and AV nodal activity by \downarrow cAMP, $\downarrow \text{Ca}^{2+}$ currents. Suppress abnormal pacemakers by \downarrow slope of phase 4. AV node particularly sensitive— \uparrow PR interval. Esmolol very short acting.
CLINICAL USE	SVT, ventricular rate control for atrial fibrillation and atrial flutter, prevent ventricular arrhythmia post-MI.
ADVERSE EFFECTS	Impotence, exacerbation of COPD and asthma, cardiovascular effects (bradycardia, AV block, HF), CNS effects (sedation, sleep alterations). May mask the signs of hypoglycemia. Metoprolol can cause dyslipidemia. Propranolol can exacerbate vasospasm in vasospastic angina. β -blockers (except the nonselective α - and β -antagonists carvedilol and labetalol) cause unopposed α_1 -agonism if given alone for pheochromocytoma or for cocaine toxicity (unsubstantiated). Treat β -blocker overdose with Glucagon, Atropine, Saline (GAS).

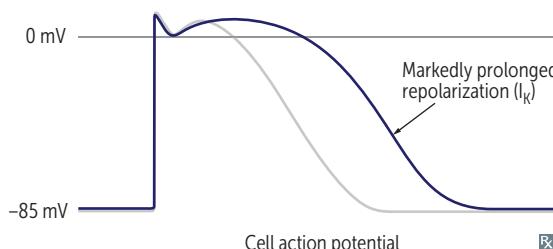


Antiarrhythmics—potassium channel blockers (class III)

Amiodarone, Ibutilide, Dofetilide, Sotalol.

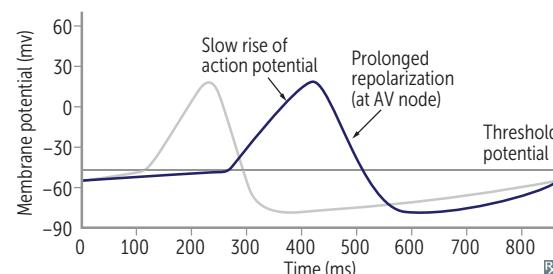
AIDS.

MECHANISM	↑ AP duration, ↑ ERP, ↑ QT interval.	
CLINICAL USE	Atrial fibrillation, atrial flutter; ventricular tachycardia (amiodarone, sotalol).	
ADVERSE EFFECTS	Sotalol—torsades de pointes, excessive β blockade. Ibutilide—torsades de pointes. Amiodarone—pulmonary fibrosis, hepatotoxicity, hypothyroidism or hyperthyroidism (amiodarone is 40% iodine by weight), acts as hapten (corneal deposits, blue/gray skin deposits resulting in photodermatitis), neurologic effects, constipation, cardiovascular effects (bradycardia, heart block, HF).	Remember to check PFTs, LFTs, and TFTs when using amiodarone. Amiodarone is lipophilic and has class I, II, III, and IV effects.

**Antiarrhythmics—calcium channel blockers (class IV)**

Diltiazem, verapamil.

MECHANISM	Decrease conduction velocity, ↑ ERP, ↑ PR interval.
CLINICAL USE	Rate control in atrial fibrillation/flutter, prevention of nodal arrhythmias.
ADVERSE EFFECTS	Constipation, gingival hyperplasia, flushing, edema, cardiovascular effects (HF, AV block, sinus node depression).

**Other antiarrhythmics**

Adenosine	↑ K ⁺ out of cells → hyperpolarizing the cell and ↓ I _{Ca} , decreasing AV node conduction. Drug of choice in diagnosing/terminating certain forms of SVT. Very short acting (~ 15 sec). Effects blunted by theophylline and caffeine (both are adenosine receptor antagonists). Adverse effects include flushing, hypotension, chest pain, sense of impending doom, bronchospasm.
Magnesium	Effective in torsades de pointes and digoxin toxicity.

Ivabradine

MECHANISM	IVabradine prolongs slow depolarization (phase “IV”) by selectively inhibiting “funny” sodium channels (I _f).
CLINICAL USE	Chronic HFrEF.
ADVERSE EFFECTS	Luminous phenomena/visual brightness, hypertension, bradycardia.