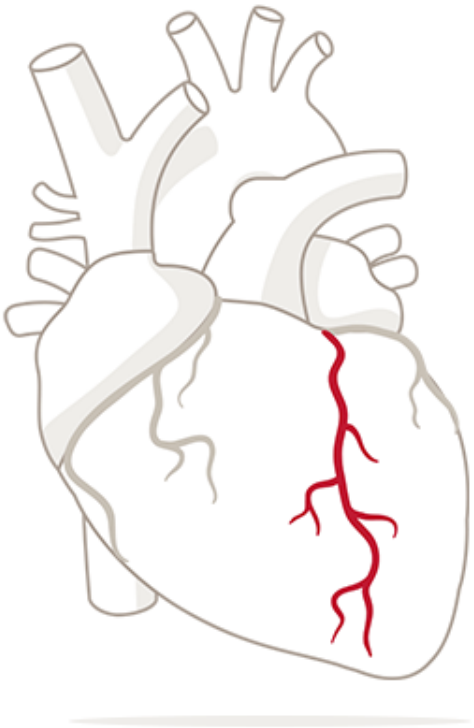
CVS

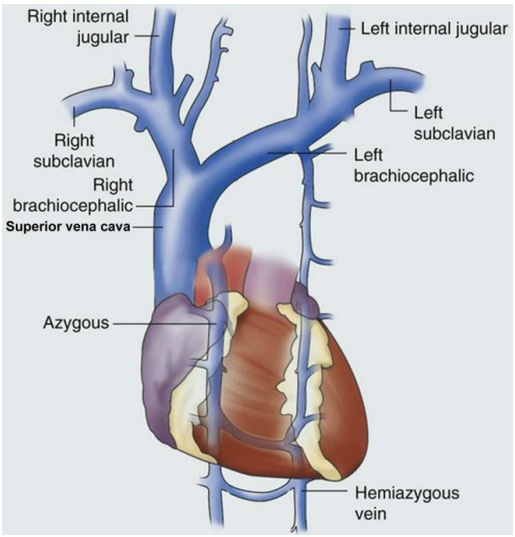


USMLE PULSE

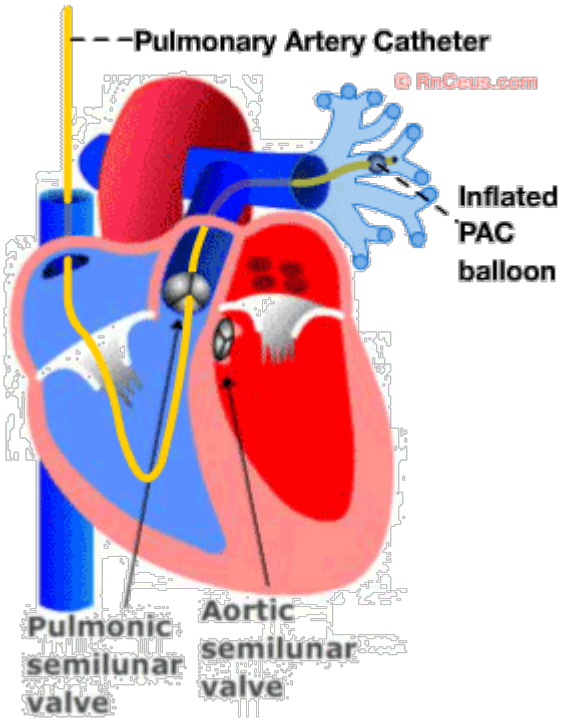
Index

1)Anatomy

1)**obstructed right brachiocephalic (innominate) vein.** The right external jugular vein drains into the right subclavian vein, so obstruction of the right brachiocephalic vein will also cause venous congestion of structures drained by the external jugular vein. It is important to note that the right brachiocephalic vein also drains the right lymphatic duct, which drains lymph from the right upper extremity, the right face and neck, the right hemithorax, and the right upper quadrant of the abdomen.



2.**Pulmonary artery catheters** used to diagnose pulmonary hypertension and occasionally for management of critically ill patients. During pulmonary artery catheterization, the balloon at the distal tip of the catheter is inflated, and the catheter is advanced forward through the right atrium, right ventricle, and pulmonary artery and finally into a branch of the pulmonary artery. Once lodged in a pulmonary artery branch, the inflated balloon obstructs forward blood flow, creating a continuous static column of blood between the catheter tip and **left atrium**.

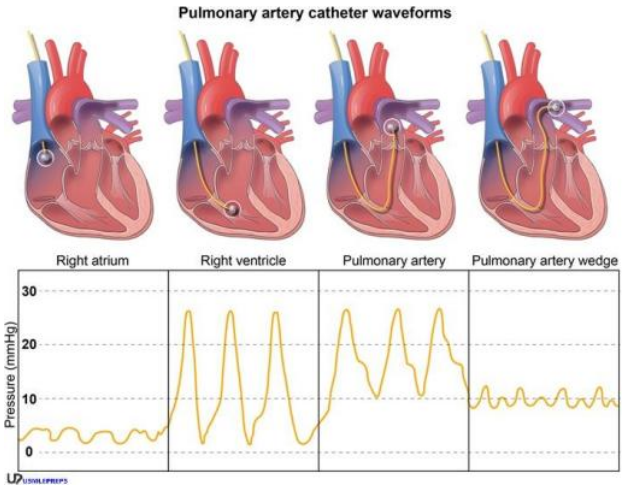


No more pulsations from the RV reach the catheter tip because the column of blood in front of it is now isolated from RV pressure changes. Pressure here transmits *backward* from the **left atrium**, not forward from the right ventricle.

Why not the right ventricle?

The balloon acts like a plug — RV pressure waves cannot get past it. Everything between the **tip of the catheter and the left atrium** is filled with stationary blood, so the tip now measures a pressure that reflects **left atrial pressure** (pulmonary capillary wedge pressure, PCWP).

The pressure measured at the catheter tip at this time is called the **pulmonary artery occlusion pressure** (PAOP; or pulmonary capillary wedge pressure [PCWP]) and closely reflects **left atrial and left ventricular end-diastolic pressures.**



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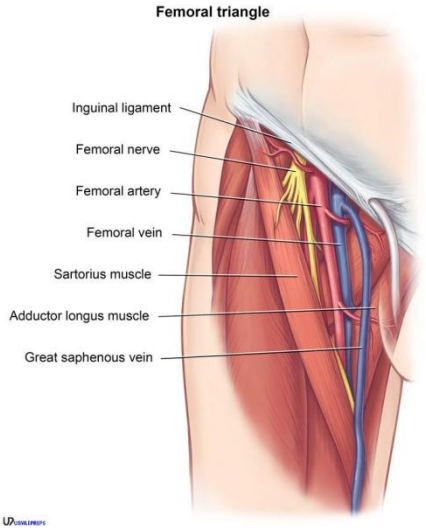
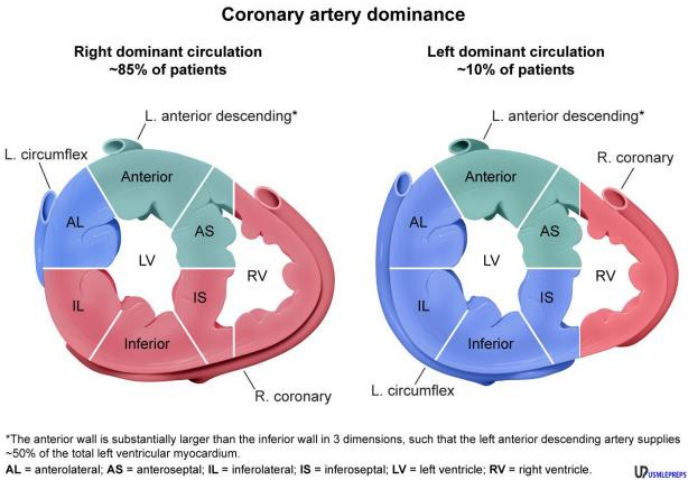
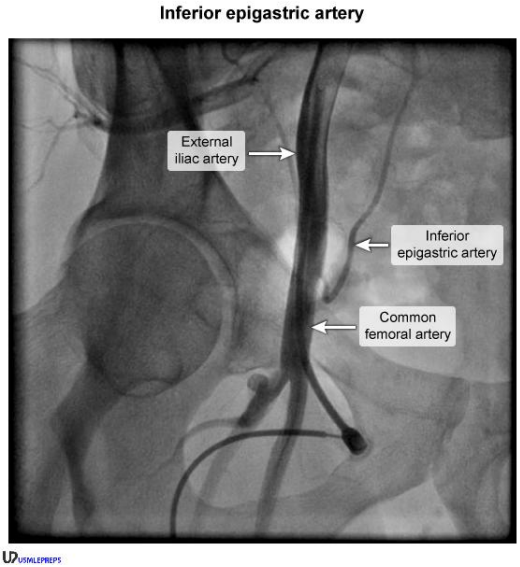
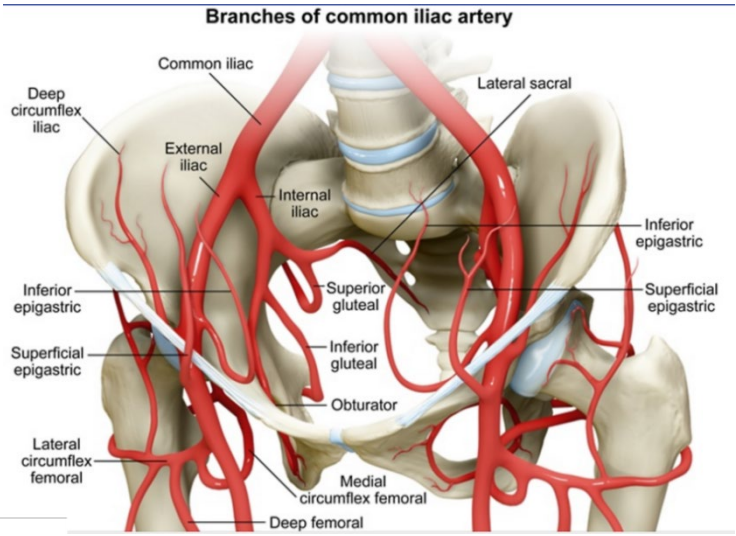
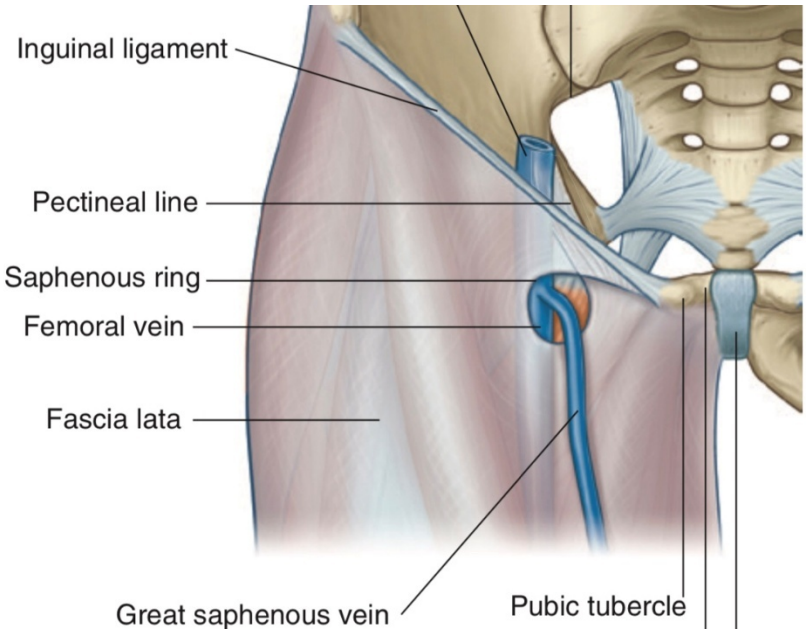




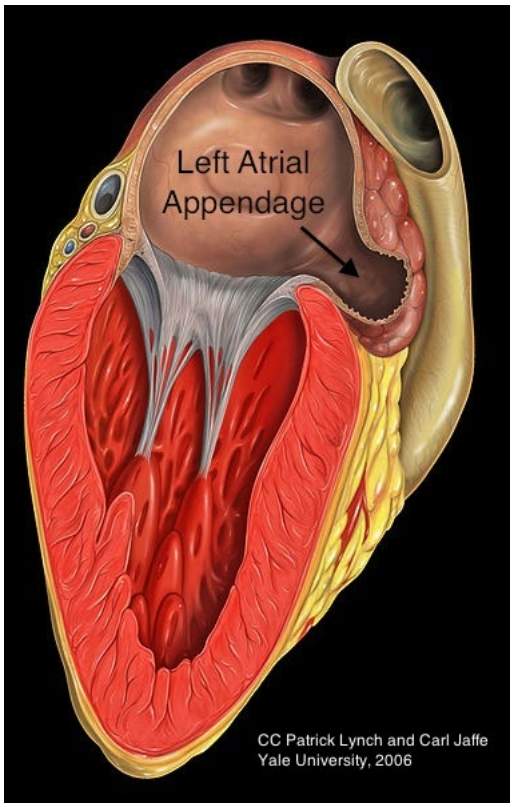




5)**saphenous vein** can be accessed Just inferolateral to the pubic tubercle



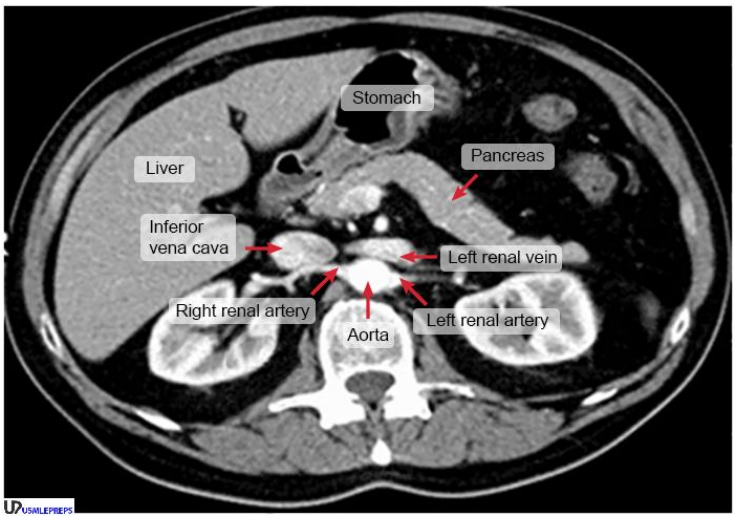
6)The left atrial appendage is a small saclike structure in the left atrium that is particularly susceptible to thrombus formation. Approximately 90% of left atrial thrombi are found within the left atrial appendage in patients with nonvalvular atrial fibrillation. These clots can then systemically embolize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



- A left ventricular (LV) apical thrombus poses risk of systemic embolization and stroke, but it typically only develops in patients with LV aneurysm or severe LV systolic dysfunction. It is **not associated with atrial fibrillation.**
- **Prosthetic valve** thrombosis can occur with bioprosthetic or mechanical mitral valves in patients without adequate anticoagulation. Thrombus formation on a native mitral valve is extremely rare, especially when valve function is normal or near normal.
- **Thrombosis of the pulmonary veins or sinus of Valsalva** (aortic sinus) is rare and not associated with atrial fibrillation.
- Thrombus formation can occur in the right atrial appendage with atrial fibrillation, though less frequently than in the left atrial appendage. A

right atrial thrombus poses risk of embolization to the pulmonary (rather than systemic) circulation, resulting in pulmonary embolism.

7)



2)Physiology

A. General Cardio Physiology

1)The driving force behind maternal hemodynamic changes in pregnant woman is a

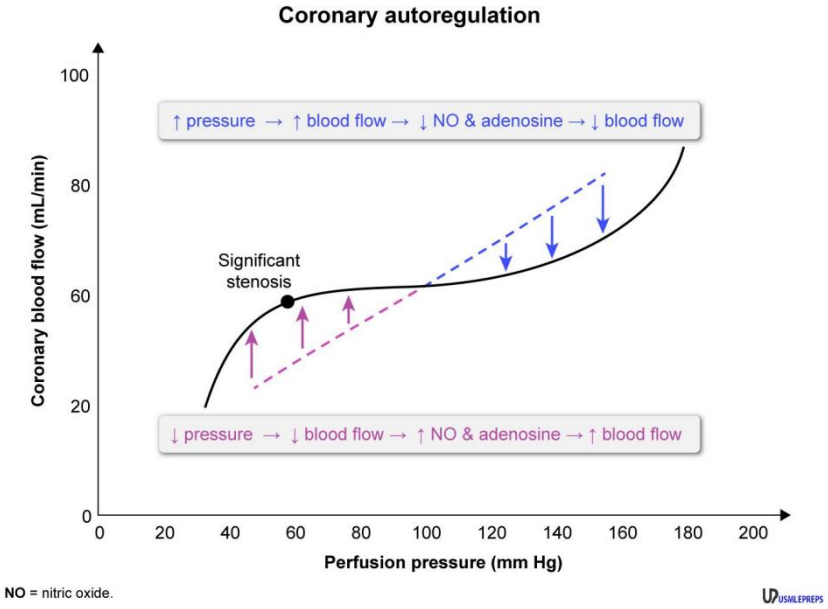
- **significant decrease in systemic vascular resistance** (SVR) due to both increased release of peripheral vasodilators (eg, nitric oxide, prostacyclin) and formation of a high-flow, low-resistance uteroplacental circuit (increases blood flow to the placenta and fetus)

- **There is also significantly increased blood volume.** These changes have the following effects on cardiac preload and afterload:

- Both increased blood volume and decreased SVR (which allows blood to return to the heart more quickly and easily) contribute to increased cardiac venous return (ie, increased preload).
- The marked reduction in SVR leads to decreased blood pressure (ie, reduced afterload).

Both **the increased preload and decreased afterload** facilitate an increase in stroke volume, which is the primary cause of increased cardiac output (ie, stroke volume x heart rate) in early pregnancy. As the pregnancy progresses, the stroke volume decreases but maternal heart rate gradually increases, contributing to an **overall increase in cardiac output of up** to 30%-50% during pregnancy.

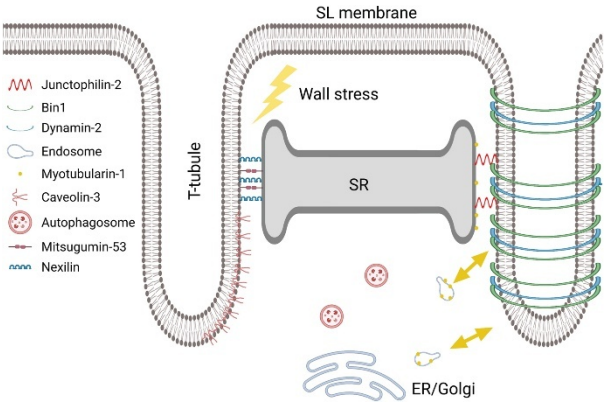
2)Coronary autoregulation helps maintain relatively constant coronary blood flow despite changes in perfusion pressure. A significant stenosis (eg, >50%) causes reduced distal perfusion pressure, resulting in an initial decrease in distal blood flow with corresponding myocardial ischemia. In response, the ischemic myocardium triggers the release of vasodilators (eg, nitric oxide, adenosine), to facilitate arteriolar vasodilation and reduce downstream vascular resistance. The reduced vascular resistance allows for a corrective increase in blood flow at the new, reduced perfusion pressure (blood flow = perfusion pressure / vascular resistance), keeping blood flow nearly unchanged.
The effects of coronary autoregulation are limited in the setting of extreme changes in perfusion pressure. Once arterioles reach the point of maximal vasodilation, vascular resistance cannot be further reduced, and a further decrease in perfusion pressure results in a precipitous drop in blood flow (as seen on the far-left side of the coronary autoregulation curve)

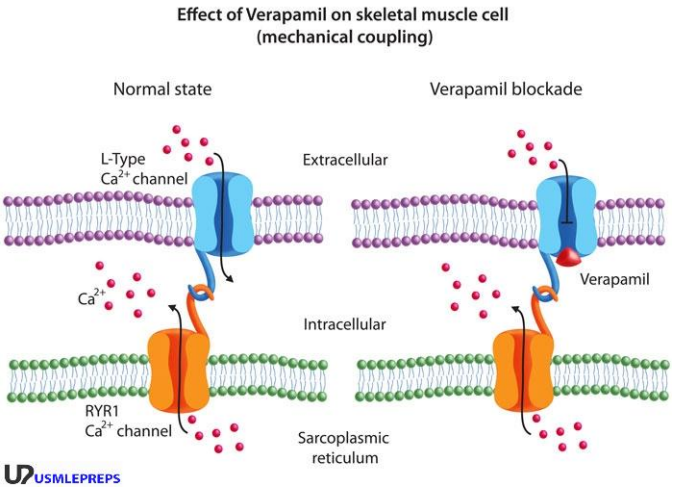


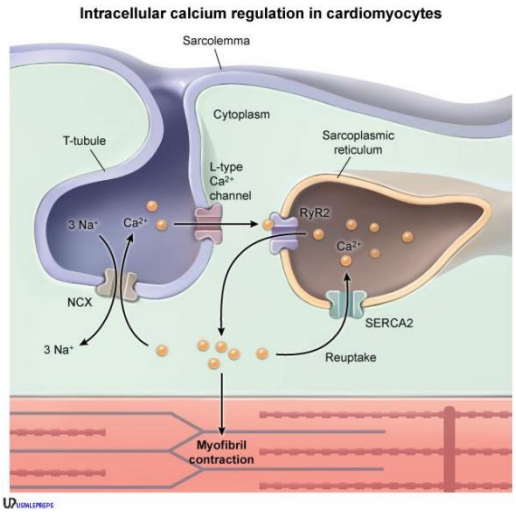
3) The calcium released from the sarcoplasmic reticulum diffuses through the myofilament network and binds to troponin C. Tropomyosin is then moved out of the way so that actin and myosin can interact, leading to muscle contraction.
The final stage of excitation-contraction coupling is myocyte relaxation, which occurs subsequent **to calcium efflux from the cytoplasm**. Intracellular calcium is removed primarily via an Na+/Ca2+ exchange pump (NCX) and sarcoplasmic reticulum Ca2+-ATPase pump (SERCA). NCX uses the large extracellular Na+ concentration gradient to help pump Ca2+ out of the cell and, in the process, removes one intracellular Ca2+ in exchange for 3 extracellular Na+ ions. In contrast, SERCA is a Ca2+-ATPase pump that actively transfers Ca2+ from the cytosol to the lumen of sarcoplasmic reticulum at the expense of ATP hydrolysis.

4.The released calcium binds to troponin (cardiac muscle) or calmodulin (smooth muscle), allowing actin and myosin to interact and cause muscle contraction.
In contrast, the L-type calcium channels in skeletal muscle directly interact with RyR calcium channels to release calcium from the sarcoplasmic reticulum. This mechanical coupling between the receptors allows sarcoplasmic calcium release to occur without significant influx of calcium across the plasma membrane. Because skeletal muscle is not dependent on extracellular calcium influx, calcium channel blockers do not affect skeletal muscle contractility.

- Troponin (but not calmodulin) is responsible for contraction of both cardiac and skeletal muscle.
- A rise in intracellular calcium concentration results in a structural change in the troponin complex that allows actin and myosin to interact and cause skeletal muscle contraction. **Calcium channel blockers do not affect troponin's affinity to intracellular calcium.**
- An elaborate T tubule system is present in skeletal and cardiac muscle but not in smooth muscle. T tubules are a communication of the extracellular space that allows the depolarization impulse to reach deep into the cell, nearer to the myofilaments. They are in close proximity to the sarcoplasmic reticulum and therefore facilitate rapid release of intracellular calcium stores.







4)

Cardiovascular effects of hyperthyroidism	
Increased rate	Tachycardia/palpitations Atrial fibrillation
Increased contractility	↑ Ejection fraction & cardiac output ↑ Myocardial oxygen demand & angina ↑ **Pulmonary artery pressure**
Peripheral vasodilation	↓ Systemic vascular resistance

Additional effects	↓ Diastolic pressure ↑ Systolic pressure ↑ Pulse pressure High-output heart failure

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5.During systole, pressures in the right ventricle are much lower than in the left ventricle (only ~25 mm Hg compared to ~120 mm Hg). As a result, coronary perfusion pressure is able to overcome right ventricular wall pressure throughout the cardiac cycle, leading to relatively constant blood flow to the right ventricular myocardium

6)Pulmonary artery systolic pressure typically rises during exercise; however, similar to systemic circulation, the rise in pulmonary pressure is much smaller than the increase in blood flow across the pulmonary circulation due to a fall in pulmonary vascular resistance

7)This patient's history of vomiting and diarrhea and physical examination findings of tachycardia, dry mucous membranes, and decreased skin turgor are consistent with moderate to severe hypovolemia. Vomiting and diarrhea cause gastrointestinal losses of both sodium and water from the extracellular space with a consequent decrease in plasma volume. Because red blood cells and proteins such as albumin are relatively large and trapped intravascularly, these blood components become concentrated, leading to **increased hematocrit and increased serum albumin**. **Such hemoconcentration can be a clue to hypovolemia caused by salt and/or water depletion; however, it does not occur with hypovolemia due to acute blood loss because red blood cells and albumin are also depleted**. In the setting of hypovolemia, the kidneys respond by increasing sodium reabsorption to increase circulating blood volume. This increased sodium reabsorption occurs in both the distal renal tubule via increased **aldosterone activity** and the proximal renal tubule through poorly understood mechanisms**. Uric acid absorption is closely tied and directly related to sodium absorption in the proximal renal tubule**; therefore, there is typically increased serum uric acid in the setting of hypovolemia. Although uric acid levels are not typically collected in the management of hypovolemia, the relationship between hypovolemia and serum uric acid level has clinical application in that hypovolemia increases the risk of acute gout flares.

8)permissiveness a hormone has no direct effect on a physiologic process but allows another hormone to exert its maximal effect on that process. **Cortisol** exerts its potentiating effect on vasoconstriction in part through upregulation of **alpha-1 adrenergic receptors** on vascular smooth muscle cells., cortisol's influence on vascular responsiveness is best described as permissive rather than synergistic because cortisol has no intrinsic vasoconstrictive effect

9)This patient's bilateral hippocampal necrosis is characteristic of the effects of **global cerebral ischemia due to systemic hypotension**. The hippocampus is particularly vulnerable during shock because of the high metabolic demand of its **CA1 pyramidal neurons**.
Watershed areas located between the distal terminal branches of 2 different vascular territories (border zones) are also susceptible to ischemia because they have a low baseline perfusion pressure and poorly tolerate sustained decreases in systemic blood pressure.

10)

Collagen subtypes		
Type	**Locations**	**Associated diseases**
I	Skin, bone, tendons, ligaments, dentin, cornea, blood vessels & scar tissue	Osteogenesis imperfecta
II	Cartilage, vitreous humor & nucleus pulposus	Skeletal dysplasias
III	Skin, lungs, intestines, blood vessels, bone marrow, lymphatics & granulation tissue	Vascular Ehlers-Danlos syndrome (Type IV)
IV	Basement membrane	Alport syndrome

B) Valve pathology

1.Aortic stenosis

A)Why does angina occur with AS?

Increased left ventricular mass due to concentric hypertrophy further increases myocardial oxygen demand and contributes to anginal symptoms

B) The most common cause of aortic stenosis (AS) in elderly patients (age >70) is **degenerative calcification of the aortic valve leaflets**. Calcific AS is caused by **chronic hemodynamic stress or atherosclerotic inflammation** that eventually leads to progressive aortic valve leaflet thickening, calcification, and stenosis. **A longer and late-peaking murmur usually indicates severe AS, whereas a brief and early-peaking murmur indicates less severe stenosis.** However, **the intensity of the murmur does not correlate with the severity of stenosis.** The intensity of the murmur of AS is directly related to the magnitude of the left ventricle to aorta pressure gradient.

c) The early pathogenesis of AS is analogous to that of arterial atherosclerosis. The endothelium lining the aortic side of the aortic valve cusps is exposed to the same high pressure and turbulent blood flow as the aortic vascular endothelium. As occurs with atheroma development in the vascular endothelium, these mechanical forces (along with smoking, hyperglycemia, and hyperlipidemia) over time cause damage to the aortic valve cusp endothelium, triggering endothelial dysfunction and the onset of a similar atherosclerotic process. There is subendothelial lipid deposition and infiltration of inflammatory cells (ie, macrophages, T lymphocytes) followed by the release of inflammatory mediators (eg, interleukin-1-beta, transforming growth factor beta-1).
Subsequently, there is increased production of proteins involved in tissue calcification (eg, osteopontin). Fibroblasts differentiate into osteoblast-like cells, leading to aberrant bone matrix deposition with progressive valvular calcification and stenosis.

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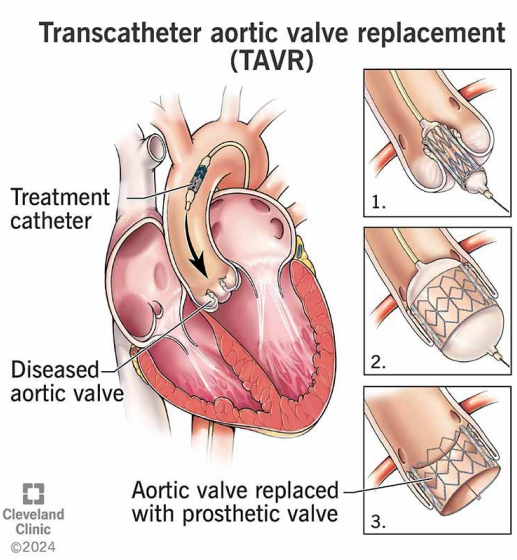
D)Rheumatic heart disease is the most common cause of AS in the developing world (Latin America, Africa, or Asia) and is invariably accompanied by rheumatic mitral valve disease (mitral stenosis and/or regurgitation). **It is an uncommon cause of AS in developed nations**.

E)Bicuspid aortic valves (right and left aortic cusp fusion) occur in approximately 1%-2% of live births, making it one of the **most common congenital heart defects**. The abnormally shaped valve experiences increased hemodynamic stress, which accelerates the normal aging process and causes premature atherosclerosis and calcification of the aortic valve. These deposits begin accumulating as early as **adolescence** and lead to aortic stenosis in >50% of affected patients. Symptomatic aortic stenosis develops on average around age 50 (10 years earlier than the average onset of senile calcific aortic stenosis in patients with normal aortic valves)

F)Second heart sound (S2) is diminished in intensity due to reduced mobility of the aortic leaflets, and a fourth heart sound (S4) may be heard due to decreased compliance of the hypertrophic myocardium.

G)Many elderly patients with severe AS have multiple other comorbidities, making them poor candidates for open surgical valve replacement due to unacceptably high operative risk. Transcatheter aortic valve implantation (TAVI) provides an alternative option for such patients; the catheter is advanced through the aorta to the aortic valve where a bioprosthetic valve is placed over the native aortic valve leaflets. This patient's intraoperative pressure readings of **decreased diastolic blood pressure and increased LVEDP (left ventricular end-diastolic pressure) are consistent with aortic regurgitation**, a common complication of TAVI that results from improper sealing of the prosthetic valve to the native valve annulus, leading to paravalvular leak (blood leakage around the valve). Inappropriate valve size or improper valve positioning is often responsible. Other intraoperative complications of **TAVI include stroke** (due to embolization of native valve calcification) and myocardial infarction (due to obstruction of coronary artery ostia by the implanted valve).



2)Aortic regurgitation (AR)

A)the characteristic decrescendo diastolic murmur is best heard with the patient leaning forward.

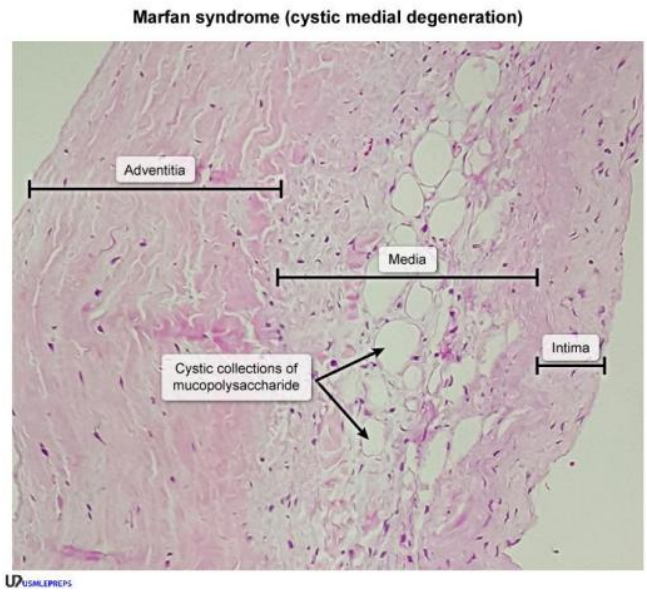
B)In developed countries, aortic root dilation is one of the most common causes of chronic aortic regurgitation. This individual with an ascending aortic aneurysm likely had aortic root dilation with consequent chronic aortic regurgitation, leading to LV volume overload and eccentric hypertrophy

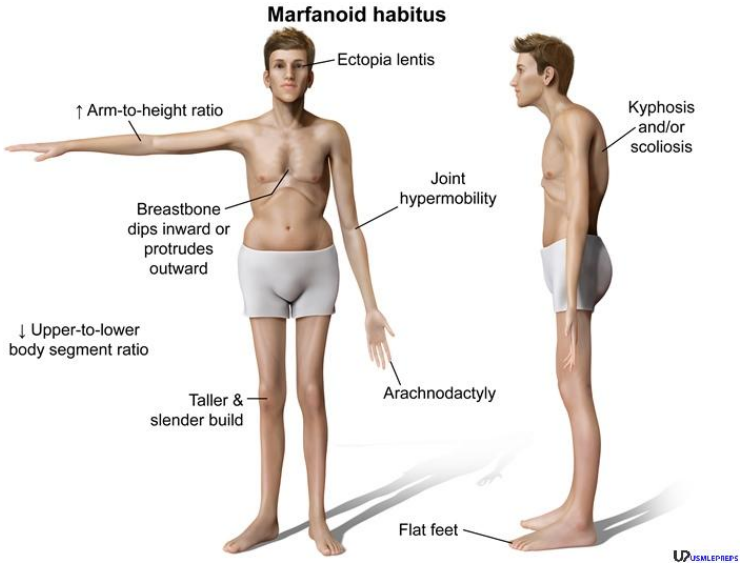
C)Forceful pulsations in the intracranial arteries can cause head bobbing with each heart beat (de **Musset sign**), and patients may experience palpitations due to forceful left ventricular contraction. In addition, physical examination can show abrupt distension and collapse of the carotid arteries **(Corrigan sign)** and peripheral arteries **("water-hammer" pulse)**, and reveal "pistol-shot" femoral pulses **(Traube sign)** on auscultation.

D)**Ankylosing spondylitis** is a chronic inflammatory disease of the axial skeleton characterized by progressive pain and stiffness of the spine, sacroiliitis, and increased risk of **aortic regurgitation**

E) This patient has clinical features of **Marfan syndrome**, an autosomal dominant disorder caused by mutations in the **FBN1 gene encoding fibrillin-1**, a main component of extracellular matrix microfibrils. Fibrillin-1 provides support to elastic fibers and helps **maintain connective tissue integrity**. It also regulates extracellular matrix remodelling by binding to and sequestering transforming growth factor-beta (TGF-beta). In Marfan syndrome, defective fibrillin-1 is unable to bind TGF-beta. The resulting overexpression of **free, active TGF**-beta leads to increased production **of matrix metalloproteinases**, which cleave elastic fibers and other components of the extracellular matrix, reducing tissue integrity. Within the mitral valve, this process results in fragmentation of elastic fibers and decreased collagen density with pooling of glycosaminoglycans (myxomatous mitral degeneration).

The most common histologic findings in Marfan-related aortic root disease include **fragmentation and loss of the elastic lamellae with fibrosis and cystic medial degeneration** (replacement of collagen, elastin, and smooth muscle by a basophilic mucoid extracellular matrix with irregular fiber cross-linkages and cystic collections of mucopolysaccharide). Cystic medial degeneration also occurs with normal aging, but is accelerated in Marfan syndrome.





3) Mitral stenosis

A)Rumbling diastolic sound ,the audible snap observed with mitral stenosis is created by the stenotic and calcified valve snapping open (ie, opening snap) and is heard during mitral valve opening, and s1 sound.

B)Fibrous thickening and fusion of the valve leaflets in chronic rheumatic heart disease following acute rheumatic fever is the **most common cause of MS, accounting for up to 99% of cases.**
There is often a latency period of 10-20 years between the initial episode of rheumatic fever and symptomatic MS, with most patients manifesting during the fourth or fifth decade of life.

4)Mitral regurgation

Hemodynamic changes in mitral regurgitation			
	Acute MR	**Compensated chronic MR**	**Decompensated chronic MR**
Preload	↑↑	↑	↑
Afterload	↓	No change	↑
Contractile function	No change	No change	↓
Ejection fraction	↑↑	↑	↓
Forward stroke volume	↓	No change	↓
MR = mitral regurgitation.			

1.Acute MR

This patient has acute mitral regurgitation (MR) due to a spontaneous chordae tendineae rupture. In acute MR, the left atrium (LA) is of normal size and compliance and is suddenly exposed to a large volume of regurgitant blood from the left ventricle (LV). This leads to very high LA pressures and subsequent pulmonary edema.

Meanwhile, the incompetent mitral valve forms a low-resistance regurgitant pathway for blood to flow into the LA during ventricular systole, decreasing LV afterload. The decreased afterload leads to increased LV ejection fraction (via increased stroke volume); however, much of the stroke volume is lost to regurgitation into the LA, resulting in overall decreased forward stroke volume and reduced cardiac output (manifesting as hypotension and cardiogenic shock).

Chronic MR

In chronic MR, compensatory LA enlargement allows the LA to receive the regurgitant volume at lower filling pressures, preventing pulmonary edema from developing. Chronic volume overload also causes the LV to undergo substantial enlargement due to eccentric hypertrophy. Early on, the larger ventricular volume helps maintain forward stroke volume even in the setting of substantial regurgitant flow. However, with prolonged hemodynamic overload, progressive eccentric remodeling of the LV becomes maladaptive, resulting in an overwhelming increase in wall stress with eventual contractile dysfunction. The impaired contractility culminates in decompensation of chronic MR with reduced forward stroke volume (decreased cardiac output) and increased left-sided filling pressures (pulmonary edema). Due to LV disfunction less blood is pumped in aorta leading to reflex sympathetic increase in afterload

B)an audible S3 gallop occurs when the left ventricle is unable to accommodate the excess blood flow**. An S3 is generated by the sudden cessation of blood flow into the left ventricle during the passive filling phase of diastole**. A higher volume of blood flow or a more dilated left ventricle is more likely to produce an S3 In patients with MR, an S3 is the best indicator of severe MR with left-sided volume overload**; the absence of an S3 can be used to exclude severe chronic MR**

C)**Whereas primary MR** is caused by an intrinsic defect of the mitral valve apparatus (eg, cleft in a valve cusp, myxomatous degeneration of the chordae tendineae), **secondary MR** occurs due to other factors. Decompensated heart failure is a common cause of secondary MR because it leads to an increase in left ventricular end-diastolic volume

(LVEDV), or preload, with dilation of the mitral valve annulus (the tissue on which the mitral valve cusps are mounted) and taut stretching of the chordae tendineae. The dilated annulus and restricted movement of the chordae tendineae can cause insufficient closure of an intrinsically normal mitral valve, resulting in MR. Systemic hypertension can also contribute to secondary MR by **favoring relatively lower-resistance regurgitant flow**. Treatment with diuretics to reduce LVEDV and vasodilators to reduce blood pressure can lead to resolution of heart failure-induced MR

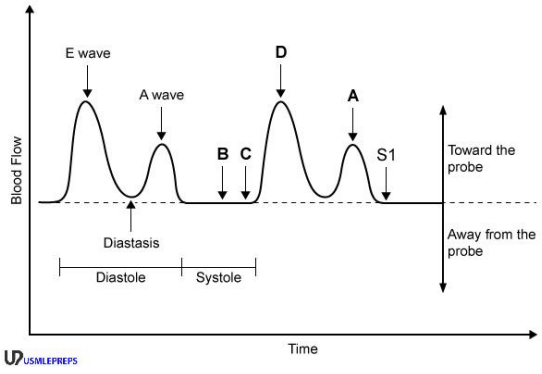
D) Pharmacologic vasodilators (eg, nitroprusside) help to increase forward cardiac output and reduce pulmonary congestion in patients with MR by reducing amount of backflow SV and increasing amount of forward SV.

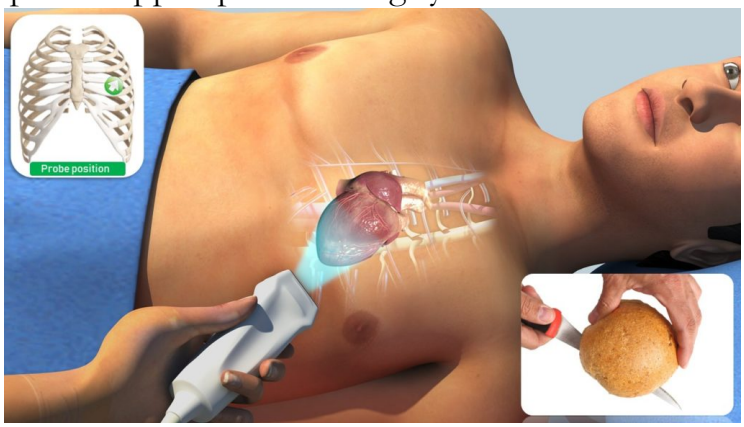
E) **apical Doppler probe**

The graph shows the normal pattern of blood flow across the mitral valve from the left atrium to left ventricle during diastole.

1) There is an initial phase of rapid transmitral blood flow after the mitral valve opens, which represents early passive ventricular filling (E wave).
2) This is followed by a period of minimal blood flow (diastasis), which occurs due to equalization in pressure between the left atrium and ventricle.
3) Finally, there is a second peak corresponding to increased transmitral blood flow due to atrial contraction (A wave). The A wave ends with the first heart sound (S1) caused by mitral (and tricuspid) valve closure.

- In patients with mitral valve prolapse and mitral regurgitation, there will be blood flow away from an apical Doppler probe during systole.





5)Tricuspid regurgitation

A)Carcinoid

Endocardial thickening and fibrosis of tricuspid and pulmonary valves - are characteristic of carcinoid heart disease.

- Carcinoids are well-differentiated neuroendocrine tumors found most commonly in the distal small intestine and proximal colon, with a strong propensity for metastasis to the liver.
- These tumors secrete several products (including histamine, serotonin, and vasoactive intestinal peptide) that are metabolized in the liver. In patients with liver metastasis, these hormones are released directly into the systemic circulation, leading to carcinoid syndrome.
- Carcinoid heart disease is caused by excessive secretion of serotonin, which stimulates **fibroblast growth and fibrogenesis**. Pathognomonic plaque-like deposits of fibrous tissue occur most commonly on the endocardium, leading to tricuspid regurgitation, pulmonic valvulopathy, and right-sided heart failure (eg, ascites, peripheral edema). Endocardial fibrosis and thickening are generally limited to the **right heart as vasoactive products are inactivated distally by pulmonary vascular endothelial monoamine oxidase**.
- 5-hydroxyindoleacetic acid (5-HIAA) is an end product of serotonin metabolism, and elevated 24-hour urinary 5-HIAA levels are helpful in diagnosing suspected carcinoid syndrome.

B)This patient likely has tricuspid valve regurgitation (TR) due to an adverse effect of her permanent pacemaker. The right ventricular lead of an implantable pacemaker or cardioverter-defibrillator passes through the superior vena cava into the right atrium and then through the tricuspid valve orifice to terminate on the endocardium of the right ventricle. Damage to the tricuspid valve leaflets or inadequate leaflet coaptation can sometimes occur, leading to severe TR in some patients.

Pathology

1)Congenital:

1)**Postnatal right-to-left shunting through the ductus arteriosus** occurs only with an abnormality that causes pulmonary arterial pressure to be greater than systemic arterial pressure as PPHN.
With most right-to-left shunts, **the pressure gradient across the shunt is low**; therefore, the shunt itself rarely creates a murmur (in contrast to the continuous murmur heard with left-to-right shunting through a PDA). The **classic murmur of PPHN is a murmur of tricuspid regurgitation** resulting from the elevated pulmonary pressure causing tricuspid valve insufficiency. This patient's strong femoral pulses are also consistent with PPHN (other causes of right-to-left shunting through the ductus arteriosus [eg, critical aortic coarctation] are associated with diminished femoral pulses)

2)In testing for a PFO (patent foramen ovale) , normal saline bubbles are injected intravenously, and echocardiography is performed to observe whether the bubbles pass from the right into the left atrium. The release phase of the Valsalva maneuver increases venous return to the right atrium and consequently increases right atrial pressure to facilitate right-to-left shunting of saline bubbles. In contrast, the strain phase of Valsalva maneuver decreases venous return to the right atrium and discourages shunting through a PFO

3)tetralogy of fallot due to pulmonary stenosis the pulmonary blood pressure will be lowered not increased

4)When the PDA shunt is ablated during surgery, there is an immediate reduction in pulmonary venous return to the left atrium (ie, decreased LV preload) and increased diastolic blood pressure in the aorta (ie, increased LV afterload). The combination of these two immediate changes can result in an acute decrease in LV stroke volume and cardiac output

5)VSD associated murmur may not be audible immediately after birth due to high pulmonary vascular resistance (PVR) that limits left-to-right shunting through the VSD; it typically develops over the ensuing days as PVR declines (as in this case).

2)Aorta

1.Blunt deceleration during chest trauma can cause tearing of the aorta (ie, aortic rupture). However, **aortic rupture** usually causes massive internal hemorrhage with rapidly developing hypovolemic shock (eg, flat jugular veins). Most affected patients do not survive transport to the hospital

- **Blunt chest trauma** could cause a massive hemothorax with hypotension and tachycardia (ie, hypovolemic shock) as well as tachypnea due to the mass effect on the lung. However, flat jugular veins and absent basilar breath sounds are expected.
- **Tension pneumothorax** can result from blunt chest trauma that injures the visceral pleura or tracheobronchial tree. It can cause tachypnea and obstructive shock (eg, hypotension, tachycardia, jugular venous distension); however, unilaterally absent breath sounds are expected, and tracheal deviation is often present.

2) **Coarctation of the aorta**

Coarctation of the aorta is a congenital cardiac defect associated with secondary hypertension and is a risk factor for cerebral aneurysm development.

Aortic aneurysms usually develop near the site of coarctation due to embryologic vessel wall abnormalities and may lead to dissection or fatal rupture

Patients with severe COA may **develop cardiogenic shock** in the neonatal period due to critical aortic obstruction. In contrast, those with milder COA typically present in childhood or adulthood as enough blood is able to pass through the defect to prevent development of heart failure.

Over time, a compensatory network of collateral vessels that bypasses the coarctation can develop. For instance, distal branches of the ascending aorta (eg, internal thoracic artery) can supply the intercostal arteries below the obstruction; the relatively low pressure distally allows retrograde flow through the intercostal arteries into the descending aorta. This flow through collateral blood vessels frequently causes a **continuous murmur that can be heard over the back in the interscapular area**; patients may also have a **systolic murmur caused by flow through the coarctation itself. Concentric left ventricular hypertrophy can also develop due to pressure overload, creating an S4.**

3)Aortic Aneurism :

1.The most common symptomatic presentation of TAA is pain, which is typically localized to the chest and back. If the TAA impinges upon the esophagus, it can also cause dysphagia. Similarly, compression of the left recurrent laryngeal nerve or left vagus nerve results in **hoarseness,** whereas compression of the phrenic nerve can cause **hemidiaphragmatic paralysis**. Respiratory manifestations, including wheeze, cough, hemoptysis, and dyspnea may occur due to **tracheobronchial obstruction**. Other complications include heart failure due to **aortic valve regurgitation** and superior vena cava syndrome from **venous compression and occlusion**. Chest x-ray may suggest the diagnosis of TAA, demonstrating a widened mediastinum, enlarged aortic knob, and tracheal deviation

2.This patient's pulsating, central abdominal mass most likely represents an abdominal aortic aneurysm (AAA), which is a focal dilation of the abdominal aorta that typically occurs below the renal arteries.
AAA is associated with several risk factors (eg, age >60, smoking, hypertension, male sex, family history) that lead to **oxidative stress, vascular smooth muscle apoptosis, and chronic transmural inflammation of the aorta**. Inflammatory cells (particularly macrophages) release matrix metalloproteinases and elastases that degrade extracellular matrix components (eg, elastin, collagen), leading to weakening and progressive expansion of the aortic wall. Furthermore, ischemia of the tunica media may play a role as the infrarenal abdominal aorta has a tenuous vasa vasorum, and atherosclerotic thickening of the intimal layer increases the diffusion distance for oxygen.

4)Aortic dissection

1.This patient's presentation is most consistent with aortic dissection, which is characterized by severe retrosternal chest pain radiating to the mid-to-upper back that can move downward as the dissection progresses. It is initiated by a tear in the aortic intima that typically extends for about 1-5 cm in a **transverse or oblique direction**. The dissection can progress both proximally and distally as blood is forced through the tear, bisecting through the aortic media. As the dissecting intramural hematoma spreads along the aortic wall, it can compress major arterial branches. This patient's brachial blood pressure discrepancy suggests compromise of the brachiocephalic trunk servicing his right arm.
Hypertension is the primary risk factor for aortic dissection. In many patients with longstanding hypertension, there is medial hypertrophy of the **aortic vasa vasorum** and, consequently, reduced blood flow to the aortic media. This can cause medial degeneration with a loss of smooth muscle cells, leading to aortic enlargement and increased wall stiffness. Both of

these changes exacerbate aortic wall stress, which is already increased due to the hypertension itself. This synergistic increase in aortic wall stress greatly increases the risk of intimal tearing and subsequent development of aortic dissection.

3)Atherosclerosis

A)The pathogenesis of atherosclerosis

1) **Endothelial cell injury**
2) Endothelial cell dysfunction results in **monocyte and lymphocyte adhesion and migration** into the intima while exposure of subendothelial collagen promotes **platelet adhesion**
3) Growth factors produced by monocytes(transform into macrophages and engulf lipid particles to become foam cells) and platelets stimulate **medial smooth muscle cell (SMC) migration into the intima**
4) At the same time, increased vascular permeability allows **LDL cholesterol into the intima**, where it is phagocytosed by the accumulating macrophages and SMCs to produce **lipid-laden foam cells** (fatty streak).The continued release of cytokines and growth factors results in a chronic inflammatory state within the underlying intima
5) This promotes further deposition of LDL cholesterol within the intima and stimulates SMC proliferation with increased production of collagen and proteoglycans. **Necrosis of foam cells results in release of toxic oxidized LDL into the extracellular matrix, perpetuating a cycle of injury**. The lesion eventually organizes into a core of lipid debris surrounded by monocytes and lymphocytes covered by a fibrous cap with intermixed SMCs (fibrofatty atheroma).

B)**Fibroblasts and mast cells** do not contribute significantly to atheroma formation. The fibrous tissue, including the fibrous cap, of atheromas is synthesized by SMCs that have migrated to the intimal layer in which the plaque forms

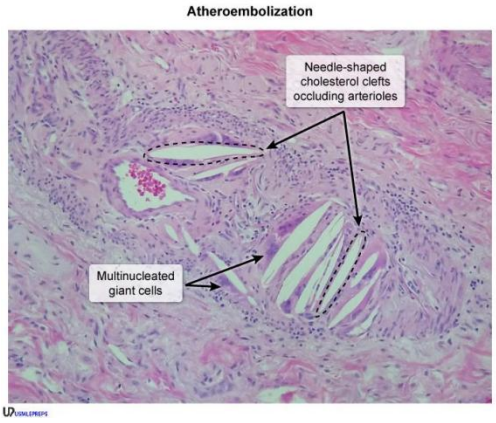
C)**Pericytes** are pluripotent cells that surround the smallest blood vessels (especially postcapillary venules). Because atherosclerosis affects the large elastic arteries and large- and medium-sized muscular arteries, these cells do not play a significant role.

2)Plaque stability largely depends on the **mechanical strength of the fibrous cap**: Thin-cap fibroatheromas are generally unstable and more vulnerable to rupture.
During the **chronic inflammatory progression of an atheroma**, the fibrous cap is continually being remodeled. The balance of collagen synthesis and degradation determines the mechanical strength of the cap. Thin-cap fibroatheromas are characterized by a large necrotic core covered by a thin fibrous cap. **Activated macrophages infiltrating the atheroma contribute to the breakdown of extracellular matrix proteins (eg, collagen) by secreting metalloproteinases.** Ongoing intimal

inflammation can destabilize the mechanical integrity of the plaque through release of **these metalloproteinases**, resulting in plaque rupture and consequent acute coronary syndrome.

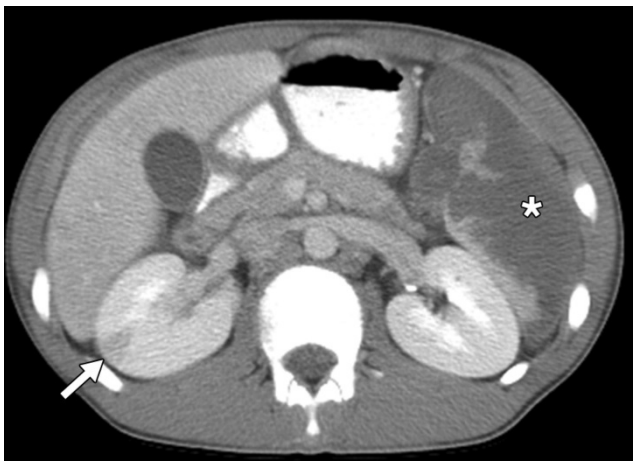
3) **Growth factors**, namely platelet-derived growth factor (PDGF), are released from platelets, activated macrophages, and endothelial cells. This triggers smooth muscle cell (SMC) recruitment from the media and proliferation in the intima

4)This patient developed acute abdominal pain after recent coronary angiography. Small bowel histology demonstrate**s needle-shaped intravascular cholesterol clefts**, a characteristic finding in **atheroembolic disease (ie, cholesterol crystal embolism).** Cholesterol is dissolved during tissue processing, leaving empty clefts on histologic evaluation.
Clinical manifestations depend on the location of the embolic scatter.



5.**Lipoprotein lipase deficiency** can cause **familial hypertriglyceridemia** (heterozygous deficiency) and **chylomicronemia** (homozygous deficiency) syndromes. These conditions present with elevated serum triglyceride levels but do not cause elevation in LDL level.

6. This patient with flank pain, hematuria, and a wedge-shaped kidney lesion on CT scan likely has a renal infarction, which results from interruption of the normal blood supply to the kidney. The lack of collaterals between segmental renal arteries ("end-organ" blood supply) means that any interruption of blood flow can lead to coagulative infarcts.



Common laboratory findings include

1. **elevated lactate dehydrogenase** (reflecting cell necrosis)
2. **mild leukocytosis**
3. **hematuria**
4. **Serum creatinine is usually normal due to compensation by the unaffected kidney**. Macroscopically, renal infarcts appear as pale wedges, with the base (widest part) at the renal cortex and the apex pointing to the medulla.

The most common cause of renal infarction is systemic thromboembolism from the left atrium or ventricle. Thromboembolism is a common complication of atrial fibrillation because the irregular contractions lead to sluggish, uneven flow in the left atrium and facilitate clot formation. Emboli from atrial fibrillation, which can be paroxysmal (thereby going undiagnosed), may have also caused this patient's recent stroke. **The brain and kidneys are more likely than other organs to suffer embolic infarctions because they are perfused at a higher rate.**

4) Blood pressure and hypertension

1)**Hypertensive emergency**: Severe hypertension can cause damage to the vascular endothelium, leading to increased vascular permeability to coagulation factors (eg, fibrinogen), platelet activation, and endothelial cell death.

- In the kidney, this manifests as **malignant nephrosclerosis**, which is characterized by 2 distinct histopathologic patterns:

- **Fibrinoid necrosis:** Cell death and excessive fibrin deposition within the arteriolar walls is visible as circumferential, amorphous, pink material with smudged, necrotic endothelial cells that lack cytologic detail.

- **Hyperplastic arteriolosclerosis:** Over time, activated platelets and injured endothelial cells release growth factors, which induce concentric hyperplasia and layering of smooth muscle cells and collagen, resulting in intimal thickening and an "onion-skin" appearance.

These changes result in narrowing and/or obliteration of the arteriolar lumen; the resultant erythrocyte fragmentation and platelet consumption can cause a **microangiopathic hemolytic anemia that is histologically indistinguishable from hemolytic uremic syndrome**. Laboratory abnormalities reflect **renal injury** (eg, elevated creatinine and blood urea nitrogen) and **hemolytic anemia** (eg, schistocytes [fragmented red blood cells] on peripheral smear, elevated lactate dehydrogenase and indirect bilirubin).

- **Hypertensive nephrosclerosis** (ie, long-term essential hypertension) is characterized by interstitial fibrosis, tubular atrophy, and varying degrees of glomerulosclerosis (eg, focal or global).
- **Hyaline arteriolosclerosis** is characterized by deposition of hyaline (glassy, homogenous) material in the intima and media of small arteries and arterioles. These changes may be seen in chronic hypertension,

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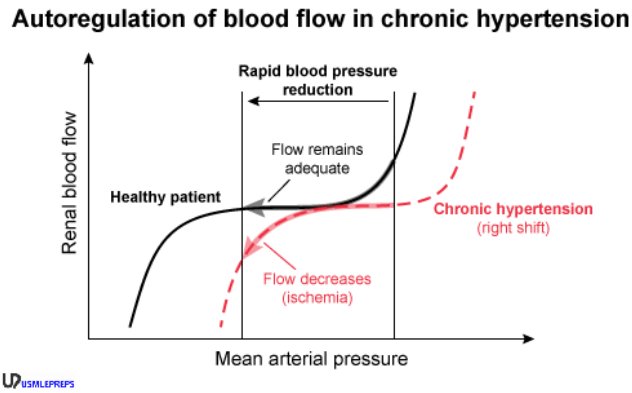
2)A Patient with chronic hypertension has hypertensive urgency. He received hydralazine, a fast-acting antihypertensive agent. After abrupt normalization of blood pressure (BP), he developed acute tubular necrosis (ATN) (granular casts). This sequence of events is consistent with normotensive ischemia (ie, inadequate renal perfusion despite a normal BP).



Blood flow autoregulation allows organs to receive the same perfusion (flow) across a wide range of pressure.

The autoregulation response protects organs from dangerous, persistent BP elevations. In chronic hypertension, there is baseline constriction of afferent glomerular arterioles. This causes the entire renal autoregulation curve to be shifted to the right: a hypertensive patient's kidneys receive less blood flow at any given BP relative to those of a healthy patient without hypertension. Quickly lowering the BP to normal (eg, 145/95 mm Hg) causes a steep drop in blood flow, leading to ischemic ATN; as a result, BP should be lowered gently, targeting above-normal values (eg, 25% reduction over several hours).

3)

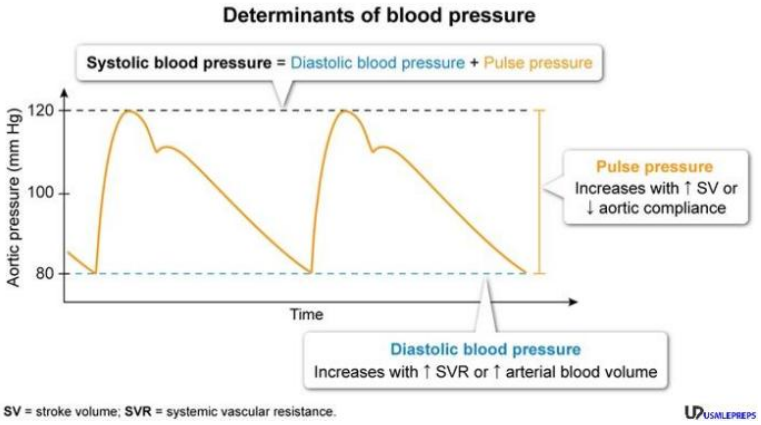
Renal artery stenosis	
Etiology	Atherosclerotic narrowing of the renal artery (>90% of cases) Fibromuscular dysplasia (younger women)
Risk factors	Other atherosclerotic disease (eg, CAD, carotid stenosis) Smoking, diabetes, hypertension
Presentation	Refractory hypertension Recurrent flash pulmonary edema Abdominal bruits Acute kidney injury after initiation of ACE inhibitor
Pathology	Gross: Shrunken, atrophic kidney Microscopic: Crowded glomeruli, tubular atrophy, interstitial fibrosis, focal inflammatory infiltrates

The most common cause of renal artery stenosis is obstruction by atheromatous plaque at the origin of the renal artery, leading to **unilateral renal ischemia**. The ischemic kidney secretes high levels of renin, which activates the renin-angiotensin-aldosterone system and results in systemic hypertension that is often difficult to control despite aggressive antihypertensive therapy. Eventually, the stenosis may also cause renal atrophy due to oxygen and nutrient deprivation.
Unilateral RAS causes morphologic changes that markedly differ in the stenotic (right) kidney and the nonstenotic (left) kidney.

- **Narrowing of the renal artery in the stenotic (right) kidney** leads to hypoperfusion and renal parenchymal ischemia, which manifests as **diffuse cortical thinning, tubular atrophy, interstitial fibrosis, and small crowded glomeruli**. **Juxtaglomerular apparatus enlargement can also occur due to chronic stimulation and increased renin release.**

- **Nonstenotic (left) kidney** is exposed to high blood pressure and therefore demonstrates typical signs of hypertensive nephrosclerosis, which is characterized by arteriolar wall thickening due to hyaline arteriolosclerosis (hyalinization of the arterioles due to extravasation of plasma proteins) and hyperplastic arteriolosclerosis (concentric smooth muscle cell proliferation in response to pressure ["onion-skinning"]).

3)Diastolic blood pressure (DBP) is the baseline hydrostatic pressure in the arterial system and is directly related to systemic vascular resistance (SVR) and arterial blood volume. Pulse pressure (PP) is the amount that arterial pressure increases above DBP during left ventricular contraction; it is **directly related to stroke volume and inversely related to aortic compliance** (which is generally constant but decreases with advancing age). Systolic blood pressure (SBP) is the summation of DBP and PP. During aerobic exercise, there is vasoconstriction of splanchnic arterioles and a larger degree of vasodilation of skeletal muscle arterioles, which shunts blood to exercising muscle and leads **to overall reduced SVR**. In addition, venoconstriction of capacitance veins mobilizes stored blood to increase venous return (ie, increased preload), and myocardial contractility is also increased. Both the increased preload and increased myocardial contractility increase stroke volume, which in combination with increased heart rate, markedly increases cardiac output.



The reduced SVR during aerobic exercise facilitates decreased DBP but it is somewhat offset by mobilization of a higher percentage of blood volume from the venous to the arterial circulation (due to venoconstriction and increased heart rate), resulting in slightly decreased or unchanged DBP. The increased stroke volume leads to increased PP, and consequently increased SBP

5)Myocardial infarction

1.**signs of reversible myocyte injury**

1. **Simple mitochondrial swelling** may be associated with reversible cellular injury. The **appearance of vacuoles and phospholipid-containing amorphous densities within mitochondria** generally signifies irreversible injury, and implies a permanent inability to generate further ATP via oxidative phosphorylation.
2. **Myofibril relaxation** is an early sign of **reversible injury** in cardiac myocytes, which occurs within the first 30 minutes of severe ischemia. Myofibril relaxation corresponds with intracellular ATP depletion and lactate accumulation due to anaerobic glycolysis during this period.
3. **Disaggregation of polysomes** denotes the dissociation of rRNA from mRNA in reversible ischemic/hypoxic injury. Depletion of intracellular ATP is thought to promote the dissolution of polysomes into monosomes as well as the detachment of ribosomes from the rough endoplasmic reticulum. Disaggregation of polysomes results in impaired protein synthesis.
4. **Disaggregation of granular and fibrillar elements of the nucleus** is associated with reversible cell injury. Another common nuclear change associated with reversible cell injury is clumping of nuclear chromatin, perhaps secondary to a decrease in intracellular pH.
5. **Triglyceride droplet accumulation** is characteristic of reversible cell injury, **especially in hepatocytes, and also in striated muscle cells and renal cells.** This fatty change may result from the decreased synthesis of intracellular proteins that occurs with cell injury. In the hepatocyte, decreased production of lipid acceptor proteins prevents the normal incorporation of triglycerides into lipoproteins. Since triglycerides cannot be rapidly exported from the cell in the form of lipoproteins, they accumulate intracellularly.
6. **Glycogen loss** is another early and reversible cellular response to injury. As a result of lowered mitochondrial ATP production, ATP must be supplied to the cell via anaerobic glycolysis of glucose derived from the cell's glycogen stores. Myocardial glycogen stores may be completely depleted within 30 minutes of the onset of severe ischemia

2.

- **Proliferation:** Days to weeks post-MI, transforming growth factor-beta (TGF-β) and other anti-inflammatory cytokines **downregulate the inflammatory** response **and stimulate fibroblast migration and proliferation, causing extensive type I and III collagen deposition**.
- **Remodeling**: Weeks to months post-MI, TGF-β also stimulates production of matrix metalloproteinases (MMPs) that facilitate collagen remodeling (ie, fiber rearrangement) and crosslinking to form dense scar tissue.

3.**Myocardial stunning:**
When ischemia lasts less than 30 minutes, loss of contractile function is reversible. However, on restoration of blood flow, full myocardial contractility is not immediately restored. Instead, there is prolonged dysfunction of the myocardium (myocardial stunning), with contractility gradually returning to normal over the next several hours to days. Increasing durations of ischemia prolong the time that the myocardium remains stunned.

4.Under hypoxic conditions, ATP within cardiomyocytes is degraded to ADP, AMP, and eventually adenosine. Adenosine is able to cross the cell membrane and function as a vasodilator when coronary blood flow is insufficient to meet myocardial demand. However, persistent ischemia can lead to depletion of massive amounts of adenosine. After 30 minutes of total myocardial ischemia, about half of the cellular adenine stores are lost. At this point, failure of cellular homeostasis is inevitable and ischemic injury becomes irreversible

5) Without ATP, the membrane Na+/K+-ATPases and the sarcoplasmic reticulum Ca2+-ATPases fail, leading to increased intracellular Na+ and Ca2+ and increased intramitochondrial Ca2+ concentrations(NET SOLUTE GAIN). These increased concentrations attract free water, causing cellular and mitochondrial swelling. Failure of the sarcoplasmic reticulum to resequester Ca2+ leads to **cessation of contraction** within ischemic zones of myocardium. **Cellular HCO3- is not elevated in cardiac ischemia**. Anaerobic metabolism leads to lactic acid production and a decrease in pH. Tissue CO2, the conjugate acid of HCO3-, is thus elevated in ischemic myocardium.

$H+HCO3 \rightarrow H2CO3 \rightarrow CO2+H2O$

The H ions are from the lactic acid combine with HCO3 and produce co2 thus co2 levels increase with low hco3 levels.

6)The **atrioventricular (AV) nodal artery** most often arises from the dominant coronary artery. This patient has left-dominant coronary circulation; therefore, his atherosclerotic lesion is most likely in the left circumflex artery. Involvement of the AV nodal artery during myocardial infarction can cause varying degrees of AV block. The diagonal arteries arise from the left anterior descending artery and supply the anterolateral wall of the left ventricle.

7)Ventricular fibrillation is the most common mechanism of sudden cardiac death due to acute **myocardial infarction**. It results from arrhythmogenic foci triggered by electrical instability in the ischemic myocardium.

8) Reperfusion injury

If the flow of blood to the ischemic tissue is restored in a timely manner, those cells that were reversibly injured will typically recover. Sometimes, however, the cells within the damaged tissue will paradoxically die at an accelerated pace through apoptosis or necrosis after resumption of blood flow. This process is termed reperfusion injury, and is thought to occur secondary to one or more of the following mechanisms:

1) **Oxygen free radical generation** by parenchymal cells, endothelial cells, and leukocytes:

1. Ischemia messes up the cell's metabolism

- During ischemia, mitochondria can't complete the electron transport chain (ETC) because there's no oxygen as the final electron acceptor.
- Electron carriers (like NADH, $FADH_2$) **pile up in a reduced state**, and enzymes (e.g., xanthine dehydrogenase) get converted to **xanthine oxidase**.

2. Oxygen rushes in during reperfusion

- Suddenly, the ETC gets a burst of oxygen.
- But damaged mitochondria can't pass electrons down the chain efficiently → electrons "leak" to oxygen prematurely.
- This incomplete reduction of O_2 forms **ROS** like **superoxide ($O_2^{\bullet -}$)**.

2)severe, irreversible mitochondrial damage described as "**mitochondrial permeability transition**":

- Ischemia damages mitochondria so they lose **membrane potential control**.
- On reperfusion, the sudden influx of calcium and ROS triggers the **mitochondrial permeability transition pore (mPTP)** to open.
- Once mPTP opens:

Mitochondria **swell** and rupture.
Oxidative phosphorylation is **irreversibly lost**.

3**) Inflammation**, which attracts circulating neutrophils that cause additional injury
4) **activation of the complement pathway**, causing cell injury and further inflammation.
When the cells within heart, brain, or skeletal muscle are injured, the enzyme creatine kinase leaks across the damaged cell membrane and into circulation (as seen in this patient).

9. Emergency reperfusion by percutaneous coronary intervention (PCI) or fibrinolysis in STEMI patients can reduce mortality and salvage ischemic myocardium. PCI is preferred due to lower rates of hemorrhage and recurrent MI; however, it may not be available at all institutions. In such cases, early treatment with fibrinolytics improves clinical outcomes.
Intracerebral hemorrhage (ICH) is the most devastating adverse effect of fibrinolytic therapy; contraindications include prior stroke (especially hemorrhagic), intracranial neoplasm/vascular malformation, recent head trauma, and severe uncontrolled hypertension. A sudden change in neurologic status following treatment with fibrinolytics should raise suspicion for ICH.

10.If a patient had an ST-elevation myocardial infarction (STEMI) and, following medical treatment, experienced symptomatic improvement and reperfusion-related arrhythmia; this is most likely the result of fibrinolytic (thrombolytic) therapy. Fibrinolytic agents (eg, alteplase) are indicated in patients with acute STEMI who cannot receive percutaneous coronary intervention in a timely manner. Administration of these agents leads to breakdown of fibrin clot and often restoration of myocardial perfusion; **some patients develop a self-limiting reperfusion-related arrhythmia** (most commonly an accelerated idioventricular rhythm).
In the fibrinolytic pathway, tissue plasminogen activator (tPA) is released by the endothelium and cleaves plasminogen to form plasmin. Plasmin then acts to both degrade individual fibrinogen molecules and break down fibrin clot that has already formed. The breakdown of fibrin clot leads to elevated levels of fibrin split products (eg, d-dimer) in the blood.
Pharmacologic fibrinolytic agents that are used clinically include streptokinase and recombinant forms of tPA (eg, alteplase, tenecteplase). All of these agents inherently increase bleeding risk and are contraindicated in patients with increased risk of bleeding complications (eg, recent hemorrhagic stroke).

6)ECG

A) narrow complex tachycardia

1.paroxysmal supraventricular tachycardia

The most common type of PSVT is **AV nodal reentrant tachycardia (AVNRT)**, which usually affects young patients (eg, age <40) with an otherwise normal heart.

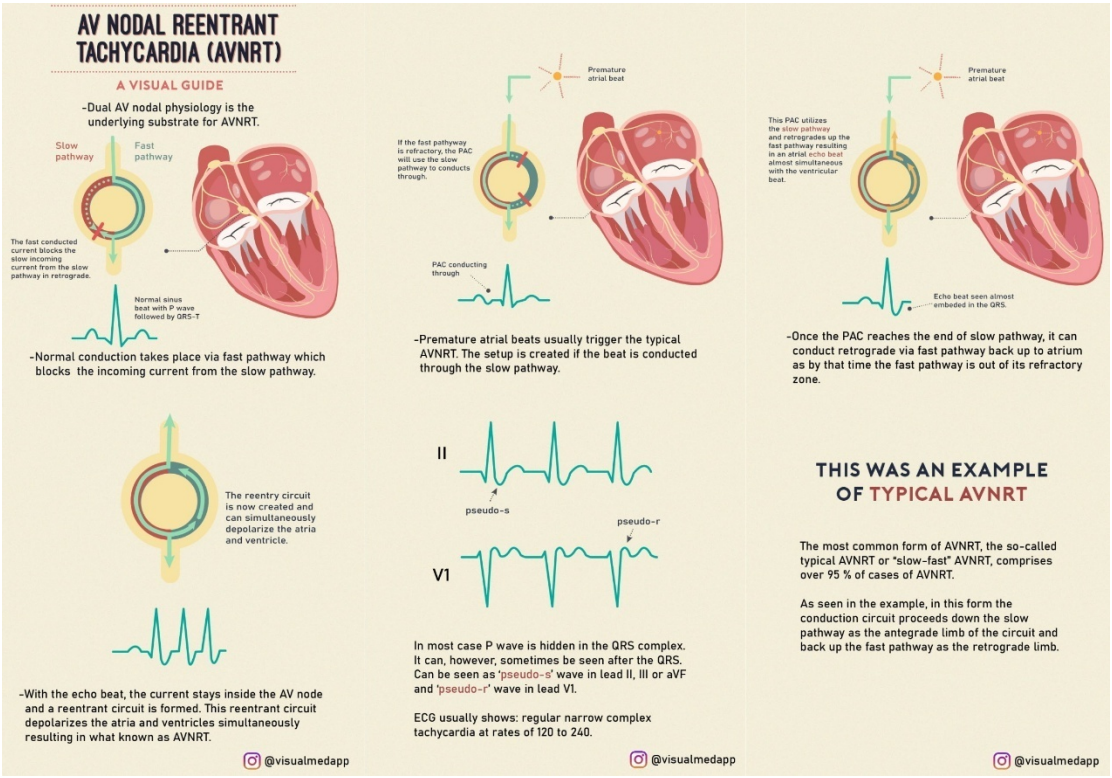
Patients with AVNRT have 2 distinct AV nodal conduction pathways:

- fast pathway with a long refractory period
- slow pathway with a short refractory period.

During normal conduction, an impulse from the atria travels down both the fast and slow pathways, and the impulse from the slow pathway is blocked by the long refractory period of the fast pathway, **allowing organized conduction of one impulse to the ventricles.**

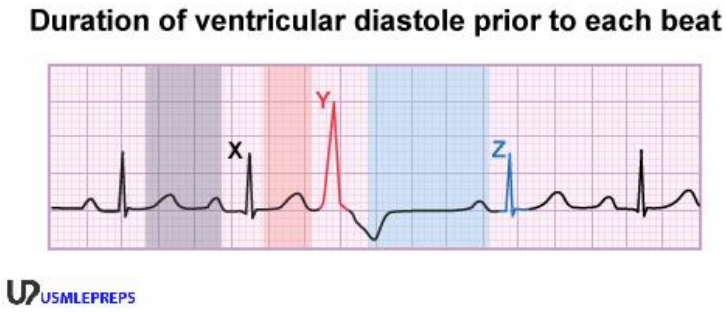
On occasion, an impulse from the atria (eg, premature atrial contraction) occurs while the fast pathway is still refractory, traveling down only the slow pathway(short refractory period). If the fast pathway is no longer refractory by the time the impulse reaches the bottom of the slow pathway, the impulse may travel back up the fast pathway, creating a reentrant circuit with rapid conduction of impulses to the ventricles.

On ECG, retrograde conduction up the fast pathway creates a retrograde P wave; however, because this conduction is usually simultaneous with anterograde conduction to the ventricles, the P wave is often buried within



B)Premature beats

1.When a PVC (Premature ventricular contractions) occurs, it interrupts diastolic filling of the left ventricle, resulting in decreased end-diastolic volume (EDV) compared to the previous normal beat (beat X > Y). The sinus pause that occurs after a PVC allows for longer-than-normal filling time before the next ventricular contraction (ie, prolonged ventricular diastole), which creates increased EDV at the time of the post-PVC beat (beat Z > X). The greater-than-normal EDV causes a large-stroke volume ventricular ejection, which may be responsible for the palpitations that some patients experience with PVCs



C)sick sinus syndrome

1.most commonly results from age-related degeneration of the sinoatrial node, which is located on the right atrial wall and is responsible for initiating normal cardiac conduction. Impaired signaling from the sinoatrial node can markedly slow the rate of ventricular contraction, leading to reduced cardiac output and symptoms of dyspnea, fatigue, lightheadedness, presyncope, and syncope.

7)Cardiomyopathy

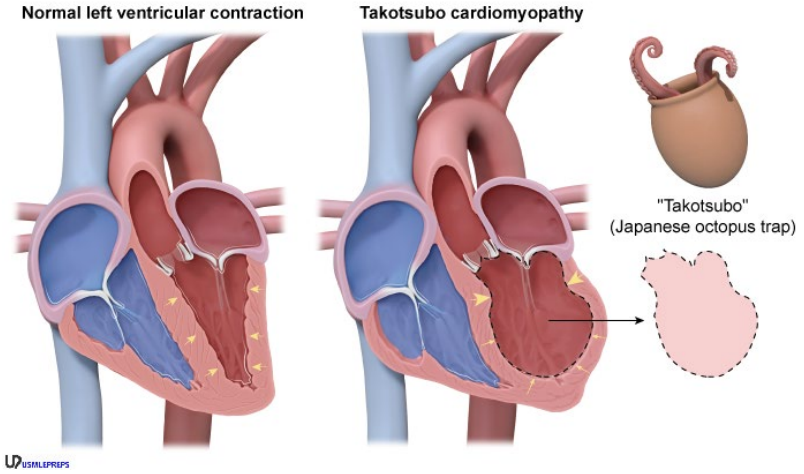
1)Dilated cardio myopathy

A) Peripartum cardiomyopathy is relatively uncommon and manifests as a dilated cardiomyopathy that occurs during the **last month of pregnancy or within 5 months after delivery**.

Pathogenesis:

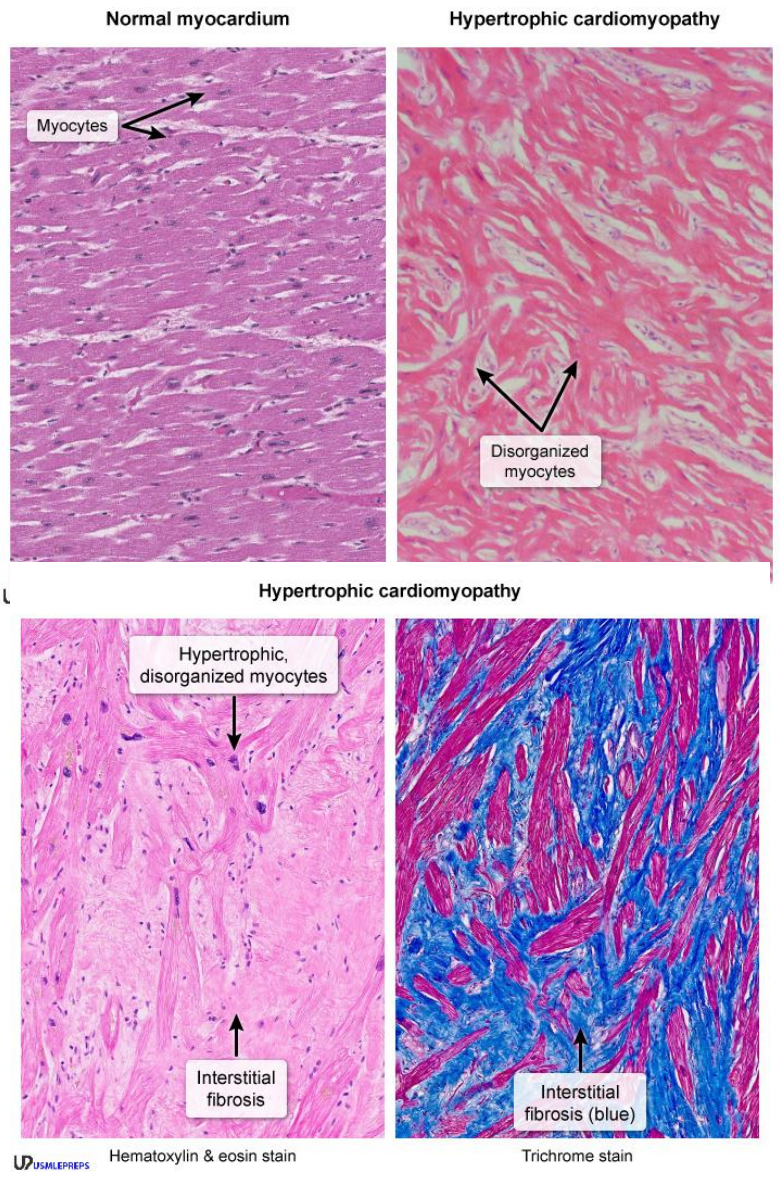
- Poorly understood, but it may be related to **impaired function of angiogenic growth factors (eg, vascular endothelial growth factor)** during the peripartum period.
- In addition, certain individuals may have genetic **mutations affecting cardiac structural proteins** that predispose to the development of peripartum cardiomyopathy.

B) **Stress-induced (takotsubo) cardiomyopathy** is characterized by hypokinesis of the mid and apical segments and hyperkinesis of the basal segments of the left ventricle (LV), leading to **systolic dysfunction and reduced ejection fractio**n. The condition is likely caused by a catecholamine surge in the setting of physical or emotional stress (eg, death of a loved one). **Catecholamines may cause microvascular spasm** leading to ischemia and myocardial stunning or they may cause direct myocardial dysfunction. The resulting segmental LV dysfunction creates a characteristic balloon shape on echocardiogram that mimics that of an octopus trap (takotsubo means "octopus trap" in Japanese).
Stress-induced cardiomyopathy most commonly affects **postmenopausal women.** Patients typically have chest pain that can mimic a myocardial infarction and may also have symptoms of heart failure (eg, dyspnea, lower extremity swelling). ECG often shows evidence of ischemia (eg, ST elevation, T-wave inversion) in the anterior precordial leads; however, coronary angiography typically reveals an absence of obstructive coronary artery disease. The condition usually resolves within several weeks with supportive treatment only.



2)Hypertrophic cardiomyopathy

A)Histologic examination for hypertrophic cardiomyopathy (HCM) is characterized by cardiomyocyte hypertrophy with haphazard cellular arrangement and prominent interstitial spacing with fibrosis.
It is believed that cardiomyocyte disarray and fibrosis alter the spatial relationship of intercalated discs (the primary mediators of organized cardiac conduction), increasing susceptibility to ventricular arrhythmia. Chronic myocardial ischemia, which can occur due to microvascular dysfunction and insufficient blood supply to hypertrophied myocardium, also contributes to interstitial fibrosis and the risk of arrhythmia



B) Despite the autosomal dominant inheritance, affected patients may not always have an identifiable first-degree relative who is similarly affected because not all mutations responsible for HCM have been identified and many known mutations have variable penetrance. The most common mutations are single-point missense mutations affecting myosin-binding protein C and beta-myosin heavy chain

Effect of maneuvers on hypertrophic cardiomyopathy			
	Physiologic effect	**Left ventricular blood volume**	**Murmur intensity**
Valsalva (strain phase)	↓ Preload	↓	↑
Abrupt standing			

Nitroglycerin administration			
Sustained hand grip	↑ Afterload	↑	↓
Squatting	↑ Afterload & preload		
Passive leg raise	↑ Preload		

1. LV filling drops → LV chamber **shrinks**.
2. Septum and leaflet are **closer**.
3. **More obstruction** → louder murmur.

C.) Chronic hypertension leads to increased local expression of the vasoconstrictors angiotensin II and endothelin in the heart; these 2 mediators likely have a prominent role in the development of LVH.

D) HCM is characterized by asymmetric ventricular septal hypertrophy, which often causes left ventricular outflow tract (LVOT) obstruction. Systolic anterior motion of the mitral valve toward the interventricular septum can exacerbate the obstruction, with the anterior leaflet of the mitral valve physically blocking the LVOT.
Many patients with HCM are asymptomatic and may be diagnosed via an abnormal ECG or murmur during routine evaluation. However, patients can also experience exertional dyspnea, chest pain, fatigue, palpitations, lightheadedness, syncope, or sudden cardiac death (due to ventricular arrhythmias). Examination often reveals a harsh crescendo-decrescendo systolic murmur at the apex and left lower sternal border; the murmur is caused by blood flow through the narrowed LVOT. Because the degree of LVOT obstruction is dynamic and changes with left ventricular blood volume, the murmur varies in intensity with physiologic maneuvers.

E) Sudden cardiac death (SCD) most often precipitated by cardiac arrhythmia (eg, ventricular tachycardia/fibrillation) that leads to markedly decreased cardiac output and impaired coronary artery perfusion. In older adults (eg, age ≥35), myocardial ischemia due to atherosclerotic coronary artery disease (Choice A) is the most common cause of SCD. However, young adults who experience SCD usually have underlying structural heart disease; hypertrophic cardiomyopathy (HCM) is one of the most common precipitating diseases. Most patients with HCM

are asymptomatic, but some may experience exertional dyspnea, fatigue, chest pain, or syncope.
It is characterized by cardiomyocyte hypertrophy (predominantly affecting the septum) and myofiber disarray consisting of an irregular arrangement of abnormally shaped cardiomyocytes and increased interstitial fibrosis. This structural disarray leads to conduction abnormalities that predispose to ventricular arrhythmia and SCD.

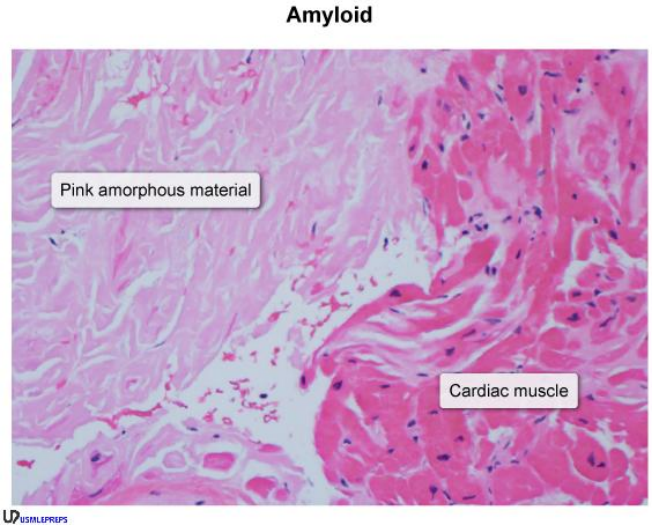
F)Hypertrophic cardiomyopathy is associated with

1) Normal or increased LV ejection fraction
2) Left atrial enlargement (secondary to increased LV end-diastolic pressure)
3) poorly developed coronary capillary network in hypertrophied regions with evidence of chronic ischemia (ie, fibrosis, scarring).

3.restrictive cardiomyopathy

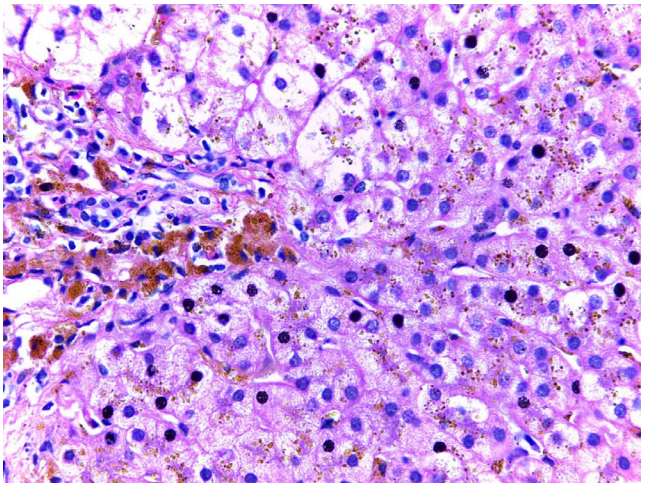
A) Restrictive cardiomyopathy have preserved ejection fraction

B)The 2 types of **amyloidosis** that most commonly affect the heart are **amyloid transthyretin (ATTR) and amyloid light chain (AL).** Cardiac amyloid deposition typically causes a restrictive cardiomyopathy with uniformly thickened ventricular walls that are stiff and have impaired diastolic relaxation (normal wall thickness can be seen with other, noninfiltrative etiologies of restrictive cardiomyopathy). Left ventricular (LV) cavity size is normal or decreased, and the impaired diastolic relaxation both increases LV filling pressure and reduces cardiac output (leading to dyspnea). The elevated LV pressure is transmitted backward, leading to left atrial dilation, increased pulmonary arterial pressure, and progressive right-sided heart failure (eg, jugular venous distension, peripheral edema). LV contractility is intact with infiltrative restrictive cardiomyopathy (especially early in the disease process), but it can decrease as the disease progresses, eventually leading to LV cavity dilation and a picture consistent with dilated cardiomyopathy.



C) Cardiac hemochromatosis

Cardiac hemochromatosis	
Pathophysiology	Excess intestinal iron absorption Deposition of iron (ferritin, hemosiderin, free iron) in myocardium Oxidative injury to myocytes
Cardiomyopathy	Early: diastolic left ventricular dysfunction (restrictive pattern) Later: cardiac remodeling & dilated cardiomyopathy
Conduction system disease	Sinus node dysfunction (sick sinus syndrome) Atrial & ventricular arrhythmias Sudden cardiac death



This patient has syncope associated with diastolic dysfunction, hepatomegaly, and skin hyperpigmentation. This presentation is suggestive of hereditary hemochromatosis (HH**), an autosomal recessive** disorder characterized by excessive intestinal iron absorption with accumulation of the excess iron in parenchymal tissues. Cardiac manifestations of HH include heart failure and conduction system disease. In early stages, myocardial iron overload is expressed as diastolic left ventricular (LV) dysfunction with a restrictive filling pattern. As the disease advances, progressive ventricular remodeling leads to dilated cardiomyopathy and reduced LV ejection fraction. Iron deposition can also affect the cardiac conduction system. Sinus node dysfunction (ie, sick sinus syndrome) can lead to presyncope or syncope; malignant arrhythmias with sudden cardiac death occasionally occur.

On light microscopy, cardiac hemochromatosis is visible as brown, granular deposits in myocytes that stain strongly with Prussian blue. Cardiomyopathy can be the first presenting manifestation of HH, although careful assessment can usually find evidence of iron deposition elsewhere (eg, elevated hepatic transaminases, hepatomegaly). Treatment includes therapeutic phlebotomy to remove excess iron stores, which can lead to regression of cardiomyopathy in some patients.

8)Heart failure

1) **Prussian blue stain detects** ferric iron stores (eg, ferritin and hemosiderin). In the Prussian blue reaction, colorless potassium ferrocyanide is converted by iron to blue-black ferric ferrocyanide. Macrophages containing golden-brown cytoplasmic granules that turn blue with Prussian blue staining represent hemosiderin-laden macrophages (siderophages). These cells may be found in any tissue where macrophages encounter extravasated red blood cells; in the alveolar parenchyma, they are often called "heart failure cells

2) pulmonary embolism (PE).

- Up to 30% of cases may present with no apparent risk factors (eg, hypercoagulability).
- Massive PE can lead to hypotension and obstructive shock. There is a rapid increase in pulmonary arterial resistance that leads to an increase in pulmonary arterial and right ventricular (RV) pressure. The rapid pressure increase causes RV cavity enlargement due to increased RV wall tension and cardiac muscle stretching. RV myocardial oxygen demand increases and coronary artery perfusion decreases, leading to a supply/demand mismatch and RV ischemia. Consequent RV dysfunction then leads to an inability to pump blood through the pulmonary circulation, resulting in decreased left-sided preload and decreased cardiac output. Such RV failure caused by an increase in pulmonary vascular resistance is sometimes called cor pulmonale.
- In acute PE, the LV cavity is either normal or somewhat reduced in size due to reduced blood flow coming from the right side of the heart
- RV wall thickening is seen with the concentric hypertrophy that occurs in patients with chronic pulmonary hypertension. In acute PE, there is no time for compensatory wall thickening to occur in response to the increased pressure load; **the rapid increase in pressure causes RV dilation that may be accompanied by RV failure.**

3) Syncope

vasovagal syncope, a type of reflex syncope. Patients with vasovagal syncope typically have a trigger (eg, prolonged standing) and experience a prodrome (eg, warmth, light-headedness) that immediately precedes loss of consciousness. The episodes usually have a short duration (eg, 1-2 min) and typically involve a rapid recovery. When vasovagal syncope is repeatedly triggered by a certain activity (eg, coughing, micturition), it is referred to as situational syncope.

Reflex syncope is the result of inappropriate autonomic output from the brainstem in response to signals relayed by various baroreceptors or

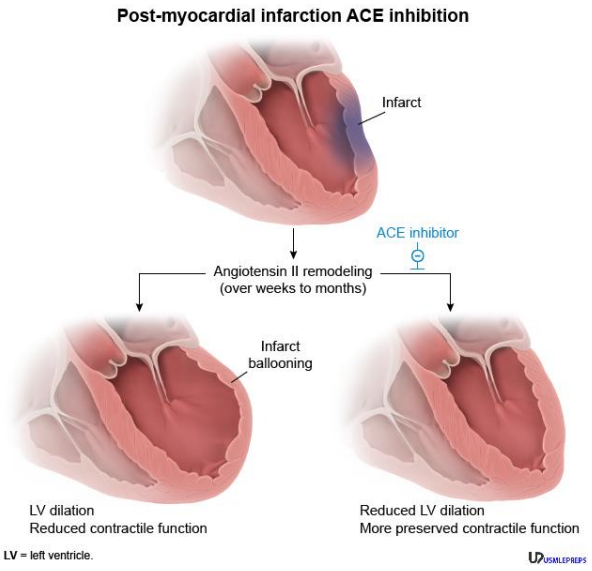
mechanoreceptors. Vasovagal syncope is often triggered by cortical emotions that increase sensitivity to afferent signals, but it can also be triggered situationally by increased afferent transmission from pulmonary, gastrointestinal, or genitourinary mechanoreceptors. Once these afferent signals are received by the brainstem cardioregulatory center, some combination of the following effector responses occurs:

- **Cardioinhibitory response**: Increased parasympathetic stimulation to the sinoatrial and atrioventricular (AV) nodes slows the heart rate. In addition, decreased sympathetic output to the myocardium decreases myocardial contractility.

- **Vasodepressor response**: Decreased sympathetic output to vascular smooth muscle causes vasodilation of venous capacitance veins (ie, decreased cardiac preload) and systemic arterioles (ie, decreased perfusion pressure)

The result of these responses is a brief but profound decrease in cardiac output that leads to hypotension, decreased cerebral perfusion, and syncope

4.



5.

Medication-induced orthostasis	
Mechanism	Examples
α1 blockade–mediated vasodilation	Terazosin, prazosin, doxazosin Antipsychotics (eg, risperidone) Antihistamines, TCAs
Other vasodilation	ACE inhibitors & ARBs Dihydropyridine CCBs Hydralazine, nitrates Phosphodiesterase inhibitors
Volume depletion	Diuretics SGLT-2 inhibitors
Sympathetic blockade	Beta blockers Clonidine

This patient's syncopal episodes are due to bradycardia and decreased peripheral vascular resistance caused by clonidine. Clonidine is used in the treatment of **severe or refractory hypertension.** It exerts its effects on both heart rate and blood pressure by stimulating presynaptic alpha-2 adrenergic receptors in the rostral ventrolateral medulla (area responsible for basal and reflex control of sympathetic activity). This effect results in a subsequent decrease in presynaptic release of norepinephrine and decreased sympathetic outflow causing both bradycardia and a decrease in peripheral vascular resistance.

Normally, to maintain cerebral perfusion while standing, a baroreceptor-mediated increase in sympathetic drive causes vasoconstriction to increase peripheral resistance and increased heart rate and contractility to aid cardiac output. These changes facilitate a corrective increase in blood pressure to prevent a drop in cerebral perfusion. However, when an orthostatic stress is applied (eg, upright posture) to this patient with attenuated sympathetic outflow due to clonidine, she is unable to maintain cerebral perfusion and syncope results.

Lisinopril and amlodipine can also contribute to orthostatic syncope by impairing peripheral vasoconstriction, but their effects are not as profound as those of clonidine because they do not affect heart rate; in fact, they may result in reflex tachycardia.

6.

Differential diagnosis & features of chest pain	
Coronary artery disease	Substernal Precipitated by exertion Relieved by rest or nitroglycerin
Pulmonary/pleuritic (pleurisy, pneumonia, pericarditis, PE)	Sharp/stabbing pain Worse with inspiration Pericarditis: worse when lying flat
Aortic (dissection, intramural hematoma)	Abrupt (maximal at onset), severe "tearing" pain May radiate to back Hypertension and/or inherited aortopathy
Esophageal	Substernal, may refer to neck Associated with regurgitation Provoked by recumbent position Nonexertional, relieved by antacids
Chest wall/ musculoskeletal	Persistent pain Worse with movement or change in position Often follows repetitive activity
PE = pulmonary embolism.	

This patient's chest pain is most likely due to costosternal syndrome (also known as costochondritis or anterior chest wall syndrome) involving the regional chest wall. It usually occurs after repetitive activity and involves the upper costal cartilage at the costochondral or costosternal junctions. The pain is typically reproduced with palpation and worsened with movement or changes in position (eg, horizontal arm flexion). Patients typically do not have palpable warmth, swelling, or erythema.

7.This patient's histopathologic findings of engorged alveolar capillaries (reflecting increased pulmonary venous pressure) and pink, acellular material within the alveoli (transuded plasma across the alveolar-capillary membrane) are most consistent with acute pulmonary edema. Given the patient's history of chronic alcohol use, he likely had underlying dilated cardiomyopathy. Subsequent decompensation then led to increased alveolar capillary hydrostatic pressure, causing pulmonary congestion and acute respiratory failure.

8)

Chronic lymphedema	
Etiology	Physical disruption of lymphatic drainage Lymphadenectomy, radiation Malignant obstruction Chronic inflammation (eg, recurrent cellulitis) Parasitic infection (eg, filariasis) Congenital (eg, Turner syndrome) Obesity is often a strong contributing factor.
Clinical presentation	Swelling, heaviness, discomfort in one or more extremities. Early: soft skin, pitting edema Late: firm, dry & thickened skin; nonpitting edema
Treatment	Weight loss, limb elevation Compression bandages & physiotherapy **Diuretics contraindicated**

This patient with chronic swelling and thickened skin of the right leg most likely has **chronic lymphedema**. Lymphedema can be congenital, but it most commonly results from an acquired disruption of lymphatic drainage that allows for accumulation of lymphatic fluid in the interstitial tissue.

In early disease, the edema is pitting and the skin remains soft. However, over time there is progressive deposition of **subcutaneous collagen and adipose tissue,** which leads to firm, dry, and thickened skin and nonpitting edema. Treatment is difficult and typically involves conservative management to increase lymphatic drainage via compression bandages or physiotherapy (ie, manual lymphatic drainage).

Diuretics reduce intravascular volume and are useful in treating lower extremity edema that results from elevated venous hydrostatic pressure in true volume overloaded states (eg, heart failure, cirrhosis). However, they are ineffective and contraindicated for lymphedema because lymphedematous fluid cannot be easily mobilized from the interstitial space into the vasculature. When used for lymphedema, diuretics are likely to cause intravascular volume depletion and consequent acute kidney injury.

9)Patients with chronic respiratory disorders (eg, emphysema, obstructive sleep apnea) often have baseline pulmonary hypertension due to hypoxia-induced pulmonary vasoconstriction and associated vascular remodelling, which increases the pressure that the right ventricle (RV) must work against to maintain forward flow. These patients are predisposed to RHF, which can develop subacutely from progressive pulmonary hypertension or acutely in the setting of a PE (due to abrupt obstruction of an already compromised pulmonary capillary bed).

Ascites due to RHF is associated with the following findings:

- Increased hydrostatic pressure: RV dysfunction results in the backup of blood within the venous circulation, leading to increased central venous pressure, which is transmitted to the portal capillaries (ie, hepatic sinusoids).
- Normal oncotic pressure: Although passive congestion from prolonged RHF eventually causes sinusoidal injury, leading to cirrhosis and hepatic synthetic dysfunction (ie hypoalbuminemia), this alteration occurs after a prolonged period (weeks). Albumin has a half-life of approximately 21 days; therefore, early in the disease process, oncotic pressure remains normal (Choice B).
- Normal capillary permeability: Hepatic congestion is characterized by sinusoidal engorgement, but sinusoidal permeability, which is already high at baseline due to the discontinuous sinusoidal endothelium, remains essentially unchanged.

9)Infective endocarditis and rheumatic fever

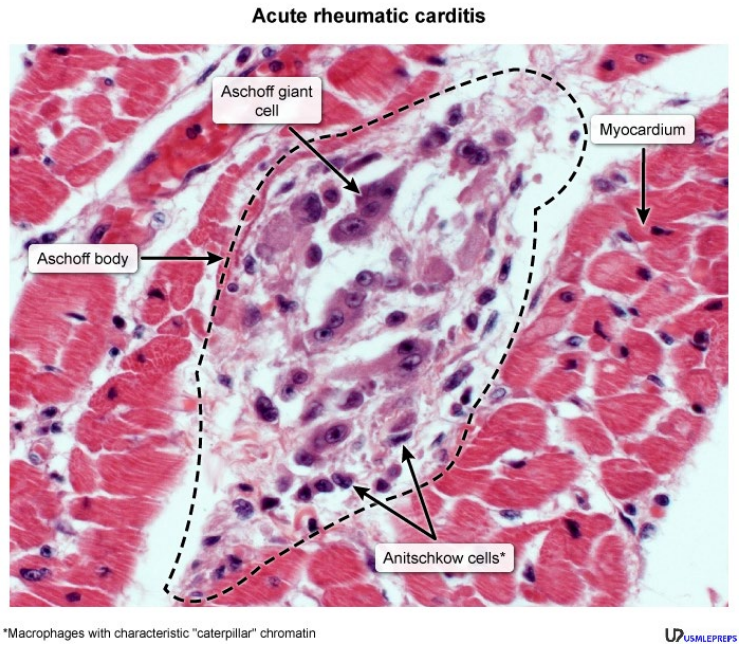
A)The initial process involved in the pathogenesis of infective endocarditis (IE) is a disruption of normal endocardial surface. This occurs most commonly at the areas of maximal turbulence to blood flow in preexisting valvular lesions, typically the **atrial surface of incompetent atrioventricular valves or the ventricular surface of incompetent semilunar valves**. This is followed by focal adherence of fibrin and platelets, forming a sterile fibrin-platelet nidus.
During bacteremia from any cause, microorganisms colonize the sterile nidus on the endothelial surface with subsequent microbial growth leading to further activation of the coagulation system. Streptococci infect the cardiac valves with preexisting endothelial lesions. In contrast, Staphylococcus aureus can adhere to damaged or normal endothelial cells. Macroscopic vegetations consist of fibrin and platelets on the surface, with red blood cell debris, leukocytes, and clusters of microorganisms embedded deep within the lesion.

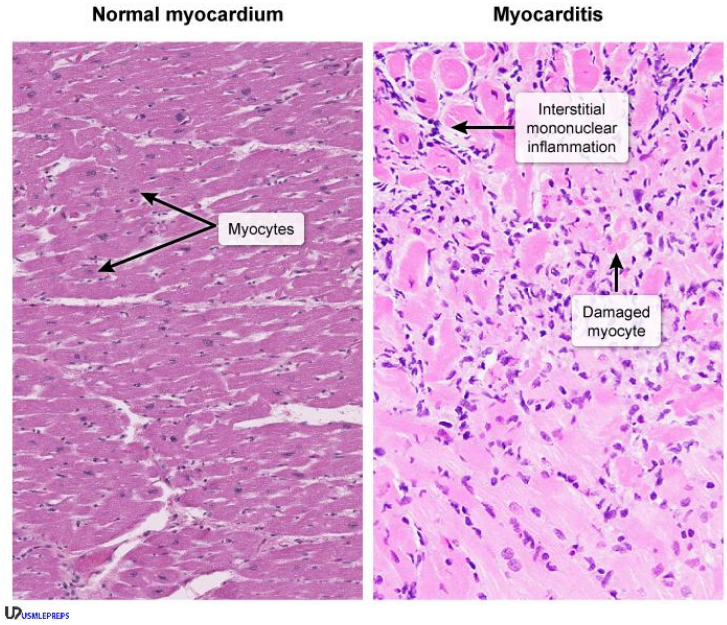
B)This patient had subacute infective endocarditis (IE) complicated by an embolic stroke. The large, friable irregular masses seen on autopsy are most likely vegetations and are the most probable source of this patient's left middle cerebral artery embolus (eg, right-sided weakness, speech difficulty).
Mitral valve prolapse (MVP) is the most common underlying valvular disease predisposing to the development of IE in developed countries, particularly when it is associated with coexistent mitral regurgitation.
In developing countries, the most common acquired heart disease leading to IE development is rheumatic heart disease (RHD). RHD was historically considered a frequent predisposing factor for IE; however, MVP, valvular sclerosis, and mechanical valves are now more common causes in **developed nations** due to the recognition and treatment of group A streptococcal pharyngitis.

C) nonbacterial thrombotic endocarditis (NBTE)
The autopsy finding of sterile platelet-rich thrombi attached to the mitral valve leaflets is characteristic of nonbacterial thrombotic endocarditis (NBTE) (marantic endocarditis). The pathogenesis of NBTE is thought to begin with valvular endothelial injury caused by circulating inflammatory cytokines, which triggers platelet deposition in the presence of an underlying hypercoagulable state. NBTE is most commonly associated with advanced malignancy (especially mucinous adenocarcinoma) and systemic lupus erythematosus (Libman-Sacks endocarditis); less commonly, it can occur with antiphospholipid syndrome, disseminated intravascular coagulation, and extensive burns.

Histologically, NBTE vegetations consist of bland thrombus with strands of fibrin, immune complexes, and mononuclear cells (white thrombus). The vegetations typically affect the left-sided heart valves (mitral or aortic) and are often asymptomatic; however, systemic embolization (eg, stroke, acute limb ischemia) can occur and is the most common presentation of NBTE.

D) This patient's myocardial biopsy shows a lesion consisting of **lymphocytes and macrophages as well as scattered multinucleated giant cells.** This interstitial myocardial granuloma, or Aschoff body, is pathognomonic for ARF-related myocarditis. Plump macrophages with abundant cytoplasm and central, slender chromatin ribbons called Anitschkow (or caterpillar) cells are also often present. Over subsequent years, Aschoff bodies are replaced by fibrous scar tissue, leading to chronic mitral valve stenosis and regurgitation.





10)Pericardium

1) Pericardial effusion

Pericardial effusion	
Etiology	Acute pericarditis Cardiac injury (eg, MI, cardiac surgery) Malignancy (eg, metastatic spread of noncardiac tumors) Renal failure with uremia
Clinical features	Dyspnea, chest discomfort, fatigue Possible cardiac tamponade* (eg, hypotension, JVD, ↓ heart sounds) ECG: ↓ QRS voltage ± electrical alternans (a beat-to-beat alternation in the amplitude or axis of the QRS complexes, and sometimes the P waves or T waves, in a regular patter) CXR: enlarged cardiac silhouette** & clear lungs
*Acute or large effusions. **With subacute & large effusions. CXR = chest x-ray; JVD = jugular venous distension; MI = myocardial infarction.	

- Subacute (vs rapid) accumulation gives the pericardium time to progressively stretch, keeping intrapericardial pressure stable; during this period, patients often have only nonspecific symptoms (eg, dyspnea, chest discomfort). However, large volumes can eventually exceed the pericardium's stretch capacity, increase intrapericardial pressure, and compromise cardiac function.
- In malignant effusion, pericardial fluid is often hemorrhagic due to inflammation associated with metastatic invasion that causes bleeding from irritated capillaries. Cytologic analysis often reveals atypical malignant cells.

Exudative & transudative pleural effusions		
	Exudate	**Transudate**
Light criteria	Pleural protein/serum protein >0.5 OR Pleural LDH/serum LDH >0.6 OR Pleural LDH greater than two-thirds upper limit of normal of serum LDH	Exudate criteria not met
Pathophysiology	Inflammatory increase in membrane permeability	Change in hydrostatic or oncotic pressure
Common causes	Infection (eg, pneumonia, TB) Malignancy Rheumatologic disease	Heart failure Cirrhosis (hepatic hydrothorax) Nephrotic syndrome
LDH = lactate dehydrogenase; TB = tuberculosis.		

2)Acute pericarditis

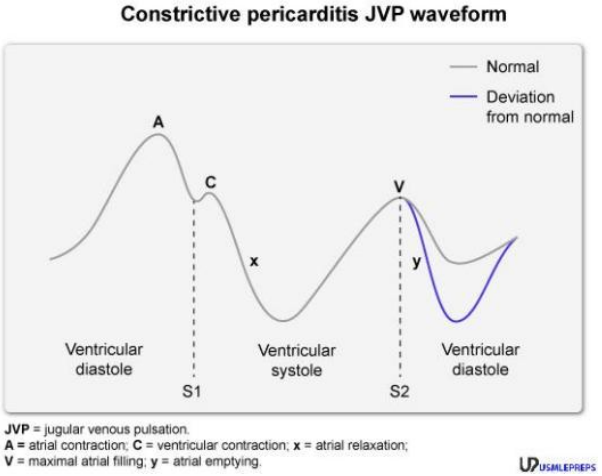
Early cause : peri-infarction pericarditis (a reaction to necrosis of the myocardium near the epicardial surface; delayed treatment presentation increases the risk of PIP (perinfarction pericarditis) due to higher levels of necrosis. Inflammation of the visceral and parietal pericardium is usually localized to the areas overlying the necrotic myocardial segment. The condition is generally short-lived and resolves with several days of supportive care; sometimes therapy with high-dose aspirin is needed.)

Late cause : Dressler syndrome (Dressler syndrome is swelling and irritation of the sac around the heart that happens after damage to the heart muscle. The damage may trigger an immune system response that causes the condition. The damage can result from a heart attack, heart surgery or a serious injury) (within weeks to months)

- Because the viral infection often cannot be confirmed, presumed viral pericarditis is sometimes referred to as idiopathic.
- Fever is common but often not present.

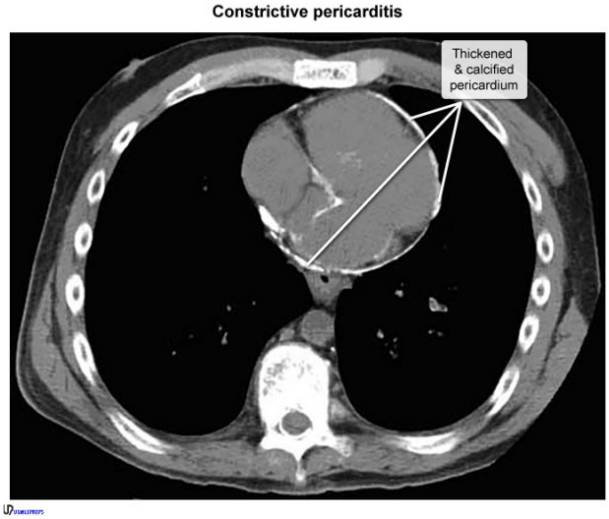
- can rarely lead to cardiac tamponade.
- ECG characteristically demonstrates diffuse ST elevation caused by inflammation of the ventricular myocardium.
- Autoimmune disease is less common than viral pericarditis and is less likely in the absence of a personal history of autoimmune disease (pericarditis is only rarely the presenting manifestation of autoimmune disease).

3) Constrictive pericarditis



- The symptomatic presentation of **constrictive pericarditis** mimics that of right-sided heart failure,
- A rapid y descent (Friedreich sign) and prominant x wave on the jugular venous pulsation waveform is a characteristic finding of constrictive pericarditis.Y descent is absent in cardiac tamponade. a pericardial knock (early diastolic sound

  that occurs before S3) can also be seen in constrictive.
- The constrictive pressure on the right atrium accentuates early filling of the right ventricle while the stiff pericardial wall restricts late diastolic filling (ينزل بسرعه و يطلع بسرعه).
- Constrictive pericarditis is potential complication of chest radiation therapy for non-Hodgkin lymphoma.



4 Fibrinous/serofibrinous pericarditis

- Most common type of pericarditis, and a pericardial friction rub (described as high pitched, leathery, and scratchy) is the most specific physical finding.
- Fibrinous pericarditis may be caused by myocardial infarction, rheumatologic disease (eg, systemic lupus erythematosus), uremia, or viral infection.
- pericardial inflammation with serous fluid and fibrin-containing exudate in the pericardial space.
- Fibrin deposition causes roughening of the visceral and parietal pericardium, often heard as a triphasic friction rub (occurring during atrial systole, ventricular systole, and early ventricular diastole) on cardiac auscultation; however, the rub can be absent if significant pericardial effusion is present. If acute fibrinous pericarditis goes

without treatment, chronic constrictive pericarditis can develop in some patients.

4) Purulent pericarditis

Purulent pericarditis	
Pathogenesis	Hematologic spread from a distant source Direct extension from a heart or lung infection Complication of penetrating injury or chest wall trauma
Common pathogens	Staphylococcus aureus (portal from skin) (end-stage renal disease who have vascular catheters) Streptococcus pneumoniae (adjacent pneumonia) Candida albicans (TPN, severe immunosuppression)
Manifestations	Fever, chills, fatigue, chest pain Examination: pericardial friction rub Echocardiogram: pericardial effusion Pericardiocentesis: high number of leukocytes/frank pus
TPN = total parenteral nutrition.	

5)Cardiac Tamponade and Pulsus Paradoxus

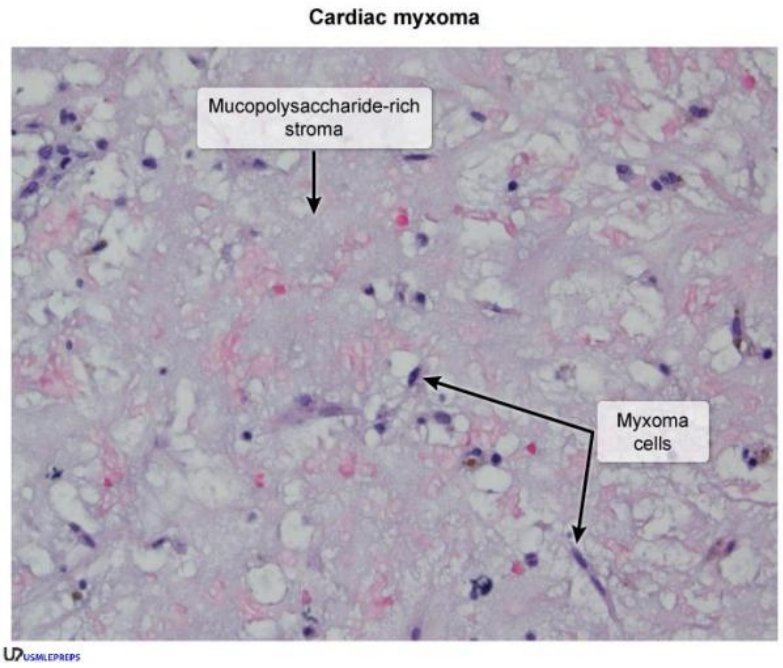
- **Pulsus Paradoxus**

It is detected by inflating a blood pressure cuff above systolic pressure and gradually deflating it.

The difference between the systolic pressure at which Korotkoff sounds first become audible during expiration and the pressure at which they are heard throughout all phases of respiration quantifies pulsus paradoxus (20 mm Hg in this patient).

Asthma and COPD exacerbation are the most frequent causes of pulsus paradoxus in the absence of significant pericardial disease (pericardial effusion or constrictive pericarditis). There is a small normal variation in intrathoracic pressure with respiration, which drops 2-5 mm Hg below the atmospheric pressure during inspiration. In patients with severe asthma or COPD exacerbation, this drop in intrathoracic pressure becomes greatly exaggerated and is transmitted to extrathoracic structures. This leads to an excessive drop in blood pressure with inspiration that is detected as pulsus paradoxus.

11)Cardiac tumors



A) This patient presented with acute limb ischemia, as evidenced by the 6 Ps:

1) Pain
2) Pallor
3) Poikilothermia (coolness to touch)
4) Paresthesia
5) Paralysis
6) Reduced or absent pulses

The ischemia resulted from systemic embolization of a gelatinous mass, with histopathology demonstrating an amorphous extracellular matrix with scattered stellate myxoma cells in mucopolysaccharide ground substance; this is consistent with tumor fragments from an atrial myxoma.

Myxomas are the most common primary cardiac neoplasm. Approximately 80% of these benign tumors originate in the left atrium
only 5% of myxomas originate on the mitral valve and even fewer originate on the aortic valve.
However, myxomas very rarely originate from the aorta.

A mural thrombus can originate in the left ventricular cavity in patients with severe left ventricular systolic dysfunction, especially with recent anterior wall myocardial infarction. Other than the left atrium, the **right atrium is the most common site for myxoma development**. It is quite rare for myxomas to originate in either ventricle.
Because of their high vascularity, these tumors often demonstrate areas of hemorrhage accompanied by brown, hemosiderin-laden macrophages

B)Because the mass is typically mobile, obstructive symptoms may be transient and influenced by position (ie, upright posture exacerbates mitral obstruction, whereas lying down alleviates it). In some patients, fragments of the mass may embolize into the systemic circulation (eg, resulting in stroke or acute limb ischemia). In addition, some myxomas can produce cytokines (eg, interleukin-6) that lead to constitutional symptoms including fever and weight loss.

C)Migratory thrombophlebitis should raise suspicion for cancer. Hypercoagulability is a very common **paraneoplastic syndrome** seen most frequently in **visceral adenocarcinomas of the pancreas, colon, and lung.** Hypercoagulability develops because

adenocarcinomas produce a thromboplastin-like substance capable of causing chronic intravascular coagulations that can disseminate and tend to migrate.
Migratory superficial thrombophlebitis, known as **Trousseau syndrome**

- Hyperthyroidism has been associated with a hypercoagulable state and is occasionally reported in cases of cerebral venous thrombosis, but there is no evidence of a significant association with venous thrombotic events.

Pharmacology:

A)calcium channel blockers

1)The vascular endothelium plays an important role in vasodilation mediated by **acetylcholine, bradykinin, serotonin, substance P, and shear forces**. These stimuli activate specific membrane receptors present on **endothelial cells, leading to an increase in cytosolic calcium levels**. This causes activation of endothelial nitric oxide synthase (eNOS). Nitric oxide then diffuses into the adjacent smooth muscle cells, where it activates guanylyl cyclase and increases formation of cyclic GMP. High levels of cyclic GMP activate protein kinase G, which causes a reduction in cytosolic calcium levels and relaxation of vascular smooth muscle cells.

The availability of arginine for synthesizing nitric oxide depends on several factors, including **exogenous food intake**, **endogenous synthesis**, **intracellular storage** and **degradation**, and the presence of **asymmetrical dimethylarginine** (an endogenous analog of arginine that works as a competitive inhibitor of eNOS)

B) Hydralazine

1.elective arteriolar vasodilators (eg, hydralazine, minoxidil) lower blood pressure by **reducing systemic vascular resistance**. However, this effect is limited by subsequent stimulation of baroreceptors with resulting reflex sympathetic activation. This leads to increased heart rate, contractility, and cardiac output. In addition, sympathetic stimulation of the renin-angiotensin-aldosterone axis results in sodium and fluid retention with peripheral edema. These effects offset much of the blood pressure lowering effect of these drugs and limit their long-term efficacy.
These agents are rarely used as monotherapy for chronic management of hypertension. However, they are useful acutely for patients with severely elevated blood pressure. They can also be given in combination with sympatholytics and diuretics to mitigate the side effects and provide synergistic blood pressure lowering in patients with resistant hypertension.

C)hypertensive emergency

A)Fenoldopam is a short-acting, selective, peripheral dopamine-1 receptor agonist with little to no effect on alpha- or beta-adrenergic receptors. Dopamine-1 receptor stimulation activates adenylyl cyclase and raises intracellular cyclic AMP, resulting in vasodilation of most arterial beds with a corresponding decrease in systemic blood pressure. Renal vasodilation is particularly prominent and leads to increased renal perfusion, increased urine output, and natriuresis (ie, sodium excretion). This makes fenoldopam especially beneficial in patients with hypertensive emergency and renal insufficiency.

D)Nitrates:

1. Pharmacologic nitrates (eg, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate) are metabolized to nitric oxide and S-nitrosothiols via mitochondrial aldehyde dehydrogenase within vascular smooth muscle cells.

2.Nitrates predominantly affect the large veins, where smooth muscle relaxation leads to venodilation and increased venous capacitance. Cardiac venous return (preload) is reduced, leading to a reduction in left ventricular end-diastolic volume and pressure and a consequent decrease in left ventricular wall stress. Decreased myocardial oxygen demand leads to relief of anginal symptoms.

3)cGMP accumulation in vascular smooth muscle cells due to both enhanced synthesis **(nitrates)** and inhibited degradation (**PDE inhibitors)** is responsible for profound hypotension due to extreme vasodilatation when these drugs are used together.

4)Nitrates are commonly used to treat stable angina. Long-acting formulations (eg, isosorbide dinitrate) are used for prevention of stable angina, and short-acting formulations (eg, sublingual nitroglycerin) are used as an abortive agent when symptoms occur.

5) Long-acting **isosorbide dinitrate** is absorbed via the gastrointestinal tract and undergoes **extensive first-pass metabolism** in the liver prior to release in the systemic circulation.

E)Milrinone

Milrinone is a selective phosphodiesterase (PDE)-3 enzyme inhibitor that can be used in patients with refractory heart failure due to left ventricular systolic dysfunction. The inhibition of cAMP degradation via milrinone has 2 positive effects on heart failure:

- In cardiomyocytes, intracellular calcium influx is increased, which increases cardiac contractility (positive inotropy) to improve stroke volume and cardiac output.
- In vascular smooth muscle, uptake of calcium by the sarcoplasmic reticulum is increased, which reduces calcium-myosin light chain kinase interaction to stimulate relaxation and vasodilation. Venous vasodilation reduces preload and arterial vasodilation reduces afterload to provide a cumulative reduction in cardiac work.

Effect of milrinone on cardiac myocytes

1. In systole:

- PKA phosphorylates L-type Ca^{2+} channels in the sarcolemma.
- This increases their open probability during the plateau phase of the action potential.
- More Ca^{2+} enters → triggers more Ca^{2+} release from the SR (via ryanodine receptors).

Result: stronger contraction.

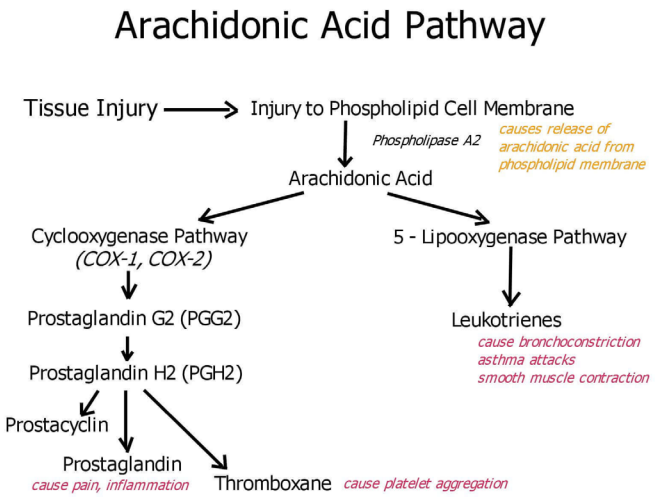
2. In diastole:

- PKA phosphorylates phospholamban (PLB).
- PLB normally inhibits SERCA (SR Ca^{2+} ATPase).
- Phosphorylated PLB releases its inhibition → SERCA works faster → SR Ca^{2+} stores refill quickly.

This doesn't decrease intracellular Ca^{2+} in the sense of reducing contractility — it just moves Ca^{2+} into the SR faster during relaxation.

On the next beat, the SR has more Ca^{2+} to release, increasing the systolic Ca^{2+} transient.

F)Arachidonic acid pathway



1.synthetic prostacyclin as **epoprostenol** can be used in the treatment of pulmonary hypertension, peripheral vascular disease, and Raynaud syndrome.

2.Aspirin impairs prostaglandin synthesis by irreversibly inhibiting cyclooxygenase (COX). Inhibition of COX-1 in platelets prevents synthesis of thromboxane A2, a potent stimulator of platelet aggregation and vasoconstriction. This helps reduce the risk of occlusive thrombus formation and subsequent myocardial infarction.

Some patients are unable to tolerate aspirin due to exacerbation of preexisting respiratory symptoms (eg, rhinitis, asthma) or development of allergic reactions (eg, urticaria, angioedema, anaphylaxis). In these patients,

alternate antiplatelet agents should be used for prevention of cardiovascular events. Clopidogrel irreversibly blocks the P2Y12 component of ADP receptors on the platelet surface and prevents platelet aggregation. Clopidogrel is as effective as aspirin for prevention of cardiovascular events and **should be used in patients with aspirin allergy**

3.Treatment of PDA includes nonsteroidal anti-inflammatory drugs (NSAIDs) (eg, indomethacin, ibuprofen), which inhibit cyclooxygenase. Because cyclooxygenase normally synthesizes prostaglandins from arachidonic acid, NSAIDs inhibit PGE2 synthesis, thereby inducing ductal smooth muscle contraction and promoting PDA closure.

4. Agents that increase intra-platelet cAMP levels decrease platelet aggregation by preventing platelet shape change and granule release.

G) Statin

1.Statins are an effective treatment for hypercholesteremia and are **now routinely prescribed for all patients with symptomatic coronary artery disease, regardless of baseline cholesterol levels**. Myopathy is the most common complication of statin use, and symptoms can range from myalgia or myopathy, with or without myonecrosis (elevated serum creatine kinase), to frank rhabdomyolysis

2.

Concurrent medications & statin myopathy	
Cytochrome P-450 (CYP3A4) inhibitors	Non–dihydropyridine CCBs (eg, verapamil, diltiazem) Protease inhibitors (eg, ritonavir, saquinavir) Erythromycin
OATP inhibitors	Cyclosporine (also a CYP3A4 inhibitor)
Additive myocyte toxicity	Corticosteroids Fibrates (eg, gemfibrozil) Colchicine (also competes with statins for CYP3A4 metabolism)
CCBs = calcium channel blockers; OATP = organic anion transport protein.	

H)Niacin

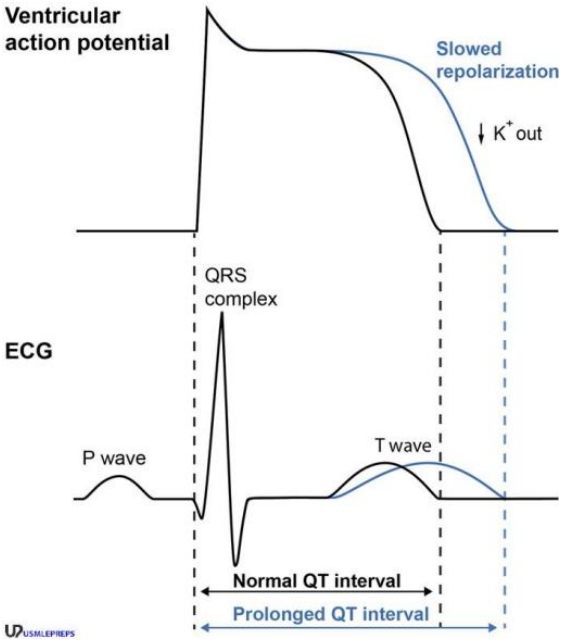
Niacin's main side effects are cutaneous flushing, warmth, and itching; these are primarily mediated by release of prostaglandins (particularly PGD2 and PGE2). Aspirin, which inhibits prostaglandin synthesis, can significantly reduce these side effects if given 30-60 minutes before niacin administration. The side effects are also reduced with slow-release preparations or if niacin is taken with meals. They are worst when niacin is first initiated and tend to fade over time due to tachyphylaxis.

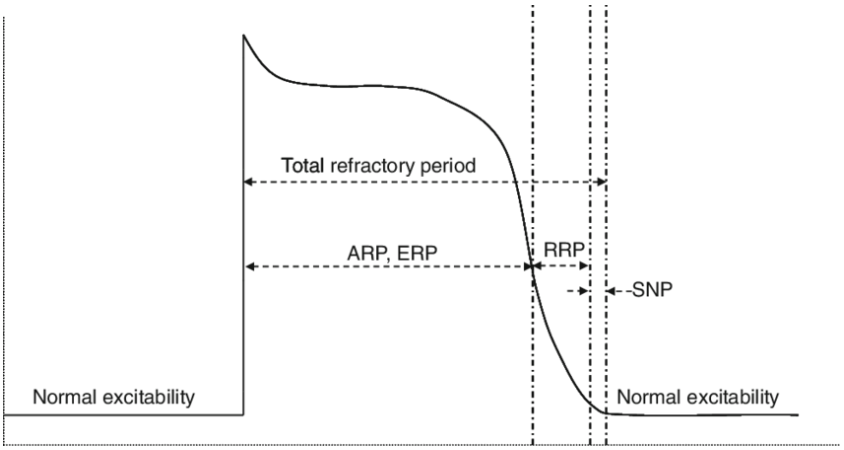
I) Antiarrthmic

Persistent atrial fibrillation is usually managed with a rate-control strategy that focuses on maintaining an acceptable ventricular contraction rate during both rest (eg, <85/min) and moderate exercise (eg, <110-120/min) **despite continued rapid and disorganized conduction of the atria.**

Pharmacologic agents that allow for rate control do so by slowing conduction through the atrioventricular (AV) node via various mechanisms:

- **Beta blockers** (eg, atenolol, metoprolol) slow AV node conduction via blockade of sympathetic tone. This mechanism allows for effective rate control both during rest and exercise. For this reason, beta blockers are often the preferred agent for rate control of atrial fibrillation.
- **Nondihydropyridine calcium channel blockers** (eg, verapamil, diltiazem) block AV nodal calcium channels to slow AV node conduction both at rest and during exercise. These drugs have similar rate control efficacy to that of beta blockers, although beta blockers are **slightly superior at controlling heart rate during exercise.**
- **Digoxin** slows AV node conduction via increased parasympathetic tone. This mechanism **is effective at rest, when sympathetic tone is low, but it poorly controls ventricular rate during exercise**, when high levels of sympathetic tone accelerate AV node conduction. For this reason**, digoxin is often used only as an adjunctive agent for rate control in atrial fibrillation.**


Ventricular action potential
Slowed repolarization
K^+ out
QRS complex
ECG
P wave
T wave
Normal QT interval
Prolonged QT interval


Total refractory period
ARP, ERP
RRP
SNP
Normal excitability
Normal excitability