Thromboembolism

Objectives:

(1) Understand the basic pathology of thrombogenesis and the risk factors for development of deep vein thrombosis.

(2) Know the types of embolus than can occur and the pathology of pulmonary embolism.

Editing file

Black: original content.
Red: Important.
Light Purple:From Robbin's.
Blue:only found in boys slides.

Green: Boy's doctor notes .
Dark orange: Girl's Doctor notes.
Grey: Explanation.
Pink: Only found in girls slides.

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MED438 KING SAUD UNIVERSITY

Pathology Teamwork 438

Thrombosis

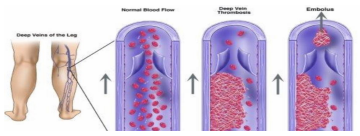
Definition

Definition: It is a process by which a thrombus is formed.

- It represents hemostasis in the intact vascular system.
- It is considered as an **intravascular** coagulation of blood that often causes significant interruption to blood flow.

What is a thrombus? A thrombus is a solid mass (blood clot) made up of blood constituents which develops in an artery or vein.

A thrombus results from interaction of platelets, damaged endothelial cells and the coagulation cascade.



Components of the hemostatic process

1

Platelets

They maintain the integrity of the vascular endothelium and participate in endothelial repair. They form platelet plugs and promote the coagulation cascade.

2

Endothelial cells

They are resistant to the thrombogenic influence of platelets and coagulation proteins. Intact endothelial cells are thromboresistant.

3

Coagulation Cascade[1]

It is a major contributor to thrombosis. It is a series of enzymatic conversions, that end in the formation of thrombin. Thrombin then converts the soluble plasma protein fibrinogen into the insoluble protein fibrin. And fibrin is a constituent of the thrombus.

Three primary influences called as Virchow triad predispose to thrombus formation [2]

- endothelial injury
- stasis or turbulence of blood flow (abnormal blood flow)
- blood hypercoagulability

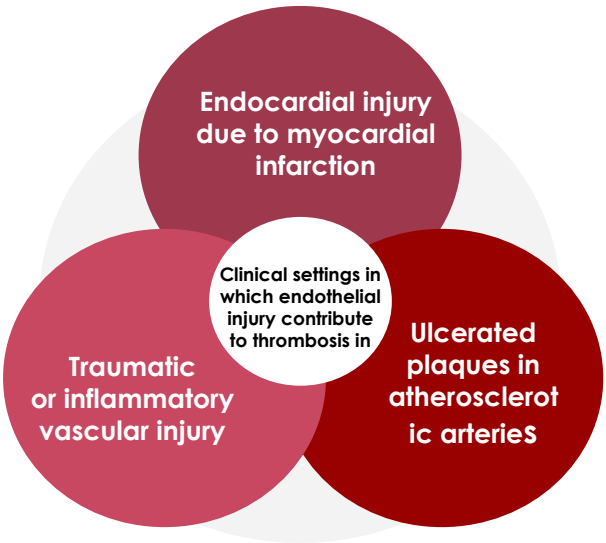
(1)under normal conditions, fibrinolytic cascade is activated once coagulation cascade is, in order to balance one another.
(2) We don't need all factors to exist, one is enough.

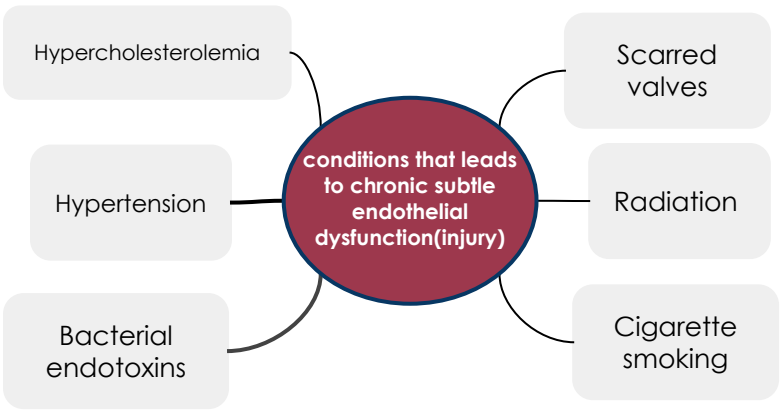
Thrombosis

A- Endothelial injury

It is a major cause of thrombosis in the heart or arteries. It may lead to:

- Exposure of subendothelial ECM (the basement membrane)
- Adhesion of platelets
- Release of tissue factor and ultimately thrombosis

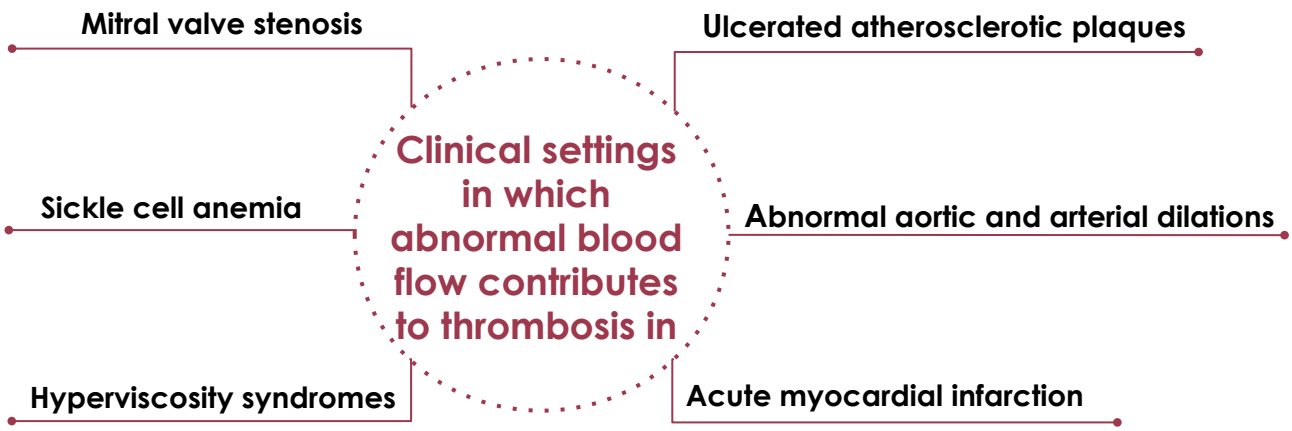




B- Abnormal Blood Flow

Disruption of laminar blood flow can bring platelets into contact with the endothelium and promote endothelial cell activation.

1. **Stasis** plays a major role in the development of **venous** thrombi(A thrombus within a vein).
2. **Turbulence** contributes to **arterial** and cardiac thrombosis by causing endothelial injury or dysfunction.



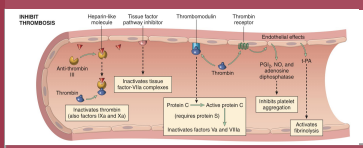
Thrombosis

C- Hypercoagulable States

Refers to an abnormally high tendency of the blood to clot, and is typically caused by alterations in coagulation factors.

Types

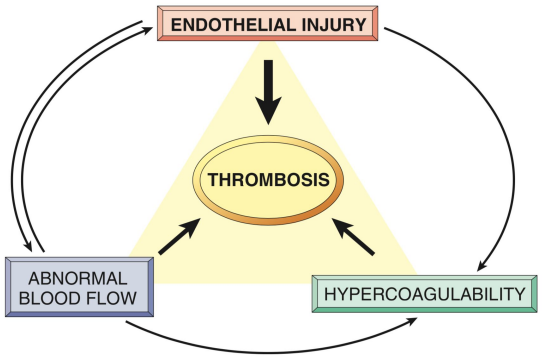
A- Primary/Genetic/inherited:



- Mutation in factor V or Prothrombin gene (common)
- Antithrombin III, Proteins C or S deficiencies(1)(Rare)
- Fibrinolysis defects (Very rare)

B- Secondary/acquired

High risk for thrombosis	Lower risk for thrombosis
• Prolonged bed rest or immobilization • Myocardial infarction • Atrial fibrillation • Tissue damage (surgery, fracture, burns) • Cancer (Release of procoagulant tumor products) • Prosthetic cardiac valves • Disseminated intravascular coagulation (Thrombin generation) • Heparin-induced thrombocytopenia • Antiphospholipid antibody syndrome (lupus anticoagulant syndrome) (Autoantibodies)	• Cardiomyopathy • Nephrotic syndrome • Hyperestrogenic states (pregnancy and postpartum) • Oral contraceptive use • Sickle cell anemia • Smoking



Virchow triad in thrombosis.

Endothelial integrity is the single most important factor. Note that injury to endothelial cells can affect local blood flow and/or coagulability; abnormal blood flow (stasis or turbulence) can, in turn, cause endothelial injury. The elements of the triad may act independently or may combine to cause thrombus formation

Fibrinolysis (thrombus dissolution)

Activation of the clotting cascade induces coagulation. It also triggers the fibrinolytic cascade that limits the size of the final clot. It runs concurrently with thrombogenesis.

Fibrinolytic cascade helps dissolve the thrombus and therefore restores blood flow in vessels occluded by the thrombus. The thrombus is dissolved by plasmin.

In the fibrinolytic cascade the inactive proenzyme plasminogen is converted to active plasmin. Plasmin then splits the fibrin in the thrombus.

(1) Antithrombin 3: inhibits coagulation by neutralizing the enzymatic activity of thrombin.
Protein C: inactivate coagulation factors Va and VIIIa.
Protein S: enhances the catalytic activity of Protein C.

Thrombotic disorders

Thrombotic disorders

Anti-Thrombotic (Hemorrhagic)

leading to pathologic bleeding states such as

- Hemophilia.
- Christmas disease
- Von Willebrand disease.

Prothrombotic

Hypercoagulability with pathologic thrombosis, for example:

1-Hereditary Thrombophilia

- Is a prothrombotic familial syndrome.
- Characterized by recurrent venous thrombosis and thromboembolism
- Can be caused by deficiency of antithrombotic proteins e,g. antithrombin III, protein C, and protein S.
- **Factor V Leiden** thrombophilia is a genetically inherited prothrombotic disorder of blood. Factor V Leiden is a mutated form of human factor V that causes an increase in blood clotting (hypercoagulability).

2- Antiphospholipid antibody syndrome

(previously called the lupus anti-coagulant syndrome)

- Is a prothrombotic hypercoagulable autoimmune multisystemic disorder caused by the presence of a type of antiphospholipid antibodies.
- Is characterized by recurrent thrombosis and embolism and fetal loss in pregnancy.
- Patients have prolonged partial thromboplastin time (PTT)
- It is sometimes associated Systemic Lupus Erythematosus and so this antibody is also known as lupus anticoagulant.

Disseminated intravascular coagulation

Is both prothrombotic and antithrombotic disorder characterized by widespread thrombosis and hemorrhage resulting from the consumption of platelets and coagulation factors.

Clinical effects of thrombosis

Thrombi are significant because:

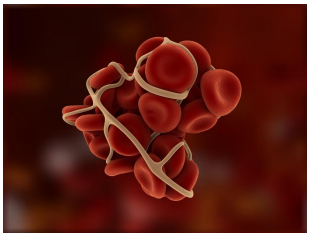
- They cause obstruction of arteries and veins.
- They are potential sources of emboli.

It depends on the site of thrombosis

Venous thrombi have capacity to embolize to the lungs and can cause death.

Arterial thrombi can cause vascular obstruction at critical sites and cause serious consequence e.g. ischemia and necrosis.

Thrombosis

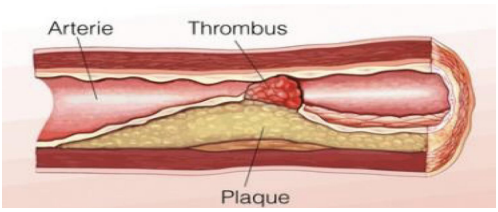
Characteristics Of Thrombus	• Thrombi may develop anywhere in the cardiovascular system, the cardiac chambers, valve cusps, arteries, veins, or capillaries. They vary in size and shape, depending on the site of origin. • The propagating tail of either thrombi may not be well attached (particularly in veins) is prone to fragmentation, creating an embolus.
Components Of Thrombus	A thrombus is made up of: • Fibrin • platelets • Red blood cell • Few inflammatory cells. 

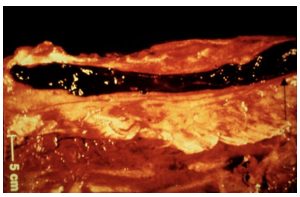
Arterial Thrombi

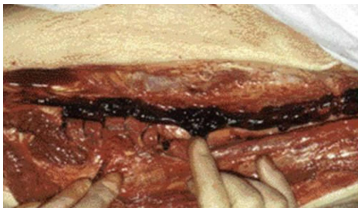
- Arterial or cardiac thrombi usually begin at a site of endothelial injury (e.g., atherosclerotic plaque) or turbulence (vessel bifurcation).
- They grow in a retrograde direction from the point of attachment (i.e. toward the heart).
- Are usually **occlusive.**
- Most common sites in descending order are: **coronary**, then **cerebral**, then **femoral** arteries.
- It is usually superimposed on an atherosclerotic plaque and are firmly adherent to the injured arterial wall.
- Arterial thrombi are gray-white and friable.

Venous Thrombi

- Characteristically occur in sites of stasis. Thus, they contain more enmeshed erythrocytes and are therefore known as **red**, or **stasis thrombi**.
- Venous thrombi extend in the direction of blood flow (i.e. toward the heart).
- Also called **phlebothrombosis**, is almost invariably occlusive
- the thrombus often takes the shape of the vein.
- Phlebothrombosis most commonly affects the veins of the lower extremities (90% of cases).
- Venous thrombi also can occur in the upper extremities, periprostatic plexus, or ovarian and periuterine veins, and under special circumstances they may be found in the dural sinuses, portal vein, or hepatic vein.







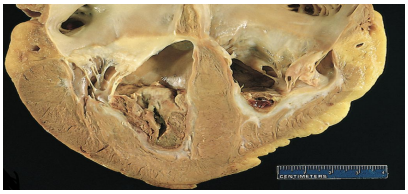
Thrombosis

Lines Of Zahn

When a thrombus is formed in the heart or aorta, thrombi may have grossly (and microscopically) apparent laminations, called lines of Zahn; these are produced by alternating pale layers of platelets admixed with some fibrin and darker layers containing more red cells.

Mural Thrombi

When arterial thrombi arise in heart chambers or in the aortic lumen they are termed mural thrombi. Abnormal myocardial contraction or endomyocardial injury promotes cardiac mural thrombi.



Deep Vein Thrombosis & Thrombophlebitis

- Venous thrombosis often arises in the deep veins of the legs and then it is called deep vein thrombosis (DVT). (commonly cause deep pain in the calf muscles).
- They occur with stasis or in hypercoagulable states.
- Often associated with inflammation and then it is termed thrombophlebitis
- DVT may embolize to the lungs giving rise to pulmonary embolism with resultant pulmonary infarct.(DVT → Right atrium →Right ventricle→lungs→ Pulmonary embolism)
- Common in deep the larger leg veins— at or above the knee (e.g., popliteal, femoral, and iliac veins)
- can cause local pain and edema.
- DVTs are asymptomatic in approximately 50% of affected individuals and are recognized only in retrospect after embolization

Common predisposing factors for DVT
(are included in the hypercoagulable status table)

- **Pregnancy**
  - The potential for amniotic fluid infusion into the circulation at the time of delivery can cause thrombogenesis.
  - Late pregnancy and the postpartum period are also associated with systemic hypercoagulability.
- **Trauma, surgery, and burns**
- **Tumors**
- **Congestive heart failure** (a cause of impaired venous return)
- **Advanced age**
- **Bed rest and immobilization**

Thrombosis

★Thrombi on Heart Valves

- Thrombi on Heart Valves are called **vegetations**, and are divided into:

Infective Vegetations	Sterile Vegetations
Bacterial or fungal bloodborne infections may result in the development of large thrombotic masses on heart valves, called as vegetations **(infective endocarditis).**	**nonbacterial thrombotic endocarditis** develop on non-infected valves in patients with: • Hypercoagulable state • Subtle endothelial abnormality • Some patients with malignancy and other debilitating disease.

- Less commonly, noninfective, verrucous (Libman-Sacks) endocarditis attributable to elevated levels of circulating immune complexes may occur in patients with systemic lupus erythematosus

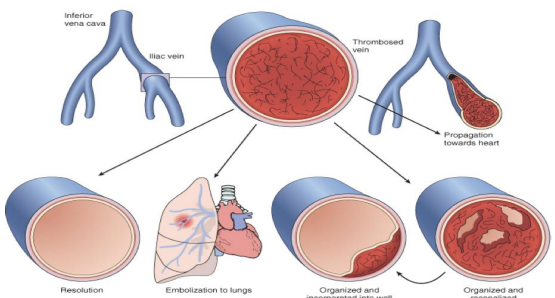
Postmortem(1) clots:

At autopsy, postmortem clots may be confused for venous thrombi.

Postmortem Clots	*Venous (Red) thrombi*
Gelatinous & Rubbery	Firm & homogenous in color
They have a dark red dependent portion where red cells have settled by gravity and a yellow fat supernatant resembling melted and clotted chicken fat.(Dark red in one side and yellow in the other).	On transection reveal vague strands of pale gray fibrin. (Rich admixture of RBCs that appears red).
They are not attached to the underlying wall(Vessel wall).	Almost always have a point of attachment (Attached to vessel wall).

Fate of Thrombus:

- **Resolution**
- **Propagation**
- **Embolism**
- **organization and recanalization**
- **organization and incorporation into the wall**



(1): Postmortem: occurring after death.
Antemortem: occurring before death (ex: thrombus)

Embolism

Definition

An embolus (plural: emboli): is a detached intravascular solid, liquid, or gaseous mass that is carried by the blood to a site distant from its point of origin.

The majority of the emboli represent some part of a dislodged thrombus, hence the commonly used term **thromboembolism**.

An embolus detach → The emboli get lodged in a vessel is too small to permit further passage → Resulting in partial or complete vascular occlusion leading to ischemic necrosis of distal tissue, (infarction). → depending on site of the blockage it can be **A- pulmonary** **B- systemic**

Types of embolism

- Air embolism
- Pulmonary thromboembolism
- Systemic thromboembolism
- Amniotic fluid embolism
- Fat embolism

1- PULMONARY THROMBOEMBOLISM

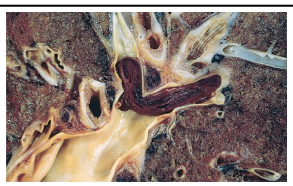
Definition

- An embolus that gets lodged in the pulmonary vasculature.
- In more than 95% of cases, venous emboli originate from deep leg vein thrombi above the level of the knee

Location

It depends upon the size of the embolus.

1. Main pulmonary artery
2. Across the bifurcation (saddle embolus)
3. Branching arterioles it may lead to infarction



Rarely, emboli may pass through an **interatrial or interventricular septal defect** to gain access to the systemic circulation. (paradoxical embolism).

Clinical complications

- Most pulmonary emboli (60% to 80%) are clinically silent because they are small.
- Sudden death, right heart failure (cor pulmonale) occurs when 60% or more of the pulmonary circulation is obstructed with emboli.
- Embolic obstruction of small end-arteriolar pulmonary branches may result in infarction.

Embolism

2- SYSTEMIC THROMBOEMBOLISM

Definition	It is an embolus traveling within the arterial circulation.
Origin	Most (80%) arise from **intracardiac mural thrombi.** (the ventricular chamber).
Location	The major sites for arterial embolization are the lower extremities (75%) and the brain (10%).
Complications	The consequences of systemic emboli depend on the extent of collateral vascular supply in the affected tissue, the tissue's vulnerability to ischemia, and the caliber of the vessel occluded; in general, arterial emboli cause infarction of tissues supplied by the artery.

3- FAT EMBOLISM

Definition	Microscopic fat globules that are found in the circulation.
Origin	**Fractures of long bones** (which have fatty marrow) or, rarely, in soft and adipose tissue **trauma** and **burns** which will release fat into the circulation through rupture of the blood vessels and act as an embolus.
Fat embolism syndrome	It is characterized by pulmonary insufficiency, neurologic symptoms, anemia, and thrombocytopenia.
Fact	Less than 10% of patients with fat emboli have any clinical findings.

4- AMNIOTIC FLUID EMBOLISM

Definition	A grave and **uncommon complication of labor** and the immediate postpartum period caused by infusion of amniotic fluid or fetal tissue into the maternal circulation via a tear in the placental membranes or rupture of uterine veins
characteristics	• Patient will suffer from sudden severe dyspnea, cyanosis, and hypotensive shock, followed by seizures and coma. • If the patient survives the initial crisis, pulmonary edema develops, along with disseminated intravascular coagulation, owing to release of thrombogenic substances from amniotic.
Microscopy	• Presence in the pulmonary microcirculation of squamous cells shed from fetal skin, fetal hair, fetal fat etc. • Marked pulmonary edema and diffuse alveolar damage. • Systemic fibrin thrombi indicative of DIC can also be seen.

Embolism

5- AIR EMBOLISM

Definition		Gas bubbles within the circulation that can obstruct vascular flow (and cause distal ischemic injury) acting as thrombotic masses. **Bubbles may coalesce to form frothy masses sufficiently large to occlude major vessels.**
When does it happens?		Air may enter the circulation during obstetric procedures or as a consequence of chest wall injury. **An excess of 100 cubic centimetres of air is required to have a clinical effect.**
Air embolism: decompression sickness	**Definition** (and to whom it happens)	Occurs when individuals are exposed to sudden changes in atmospheric pressure. such as: • SCUBA and deep sea divers • underwater construction workers • individuals in unpressurized aircraft in rapid ascent.
	Pathogenesis	Air is breathed at high pressure (e.g. during a deep sea dive) → increased amount of gasses (especially nitrogen) in blood and tissues → diver ascend (depressurizes) too rapidly → nitrogen expands in the tissues & bubbles out of solution in the blood → gas emboli.
	symptoms	• ***'Grecian Bends'*** I.e. joint/muscle pain • ***'chokes'*** i.e. respiratory distress
	Treatment	placing the individuals in a compression chamber where the barometric pressure may be raised, thus forcing the gas bubbles back into solution followed by subsequent slow decompression.
	Caisson disease	More **chronic form of decompression sickness**, in which, persistence of gas emboli in the skeletal system leads to multiple foci of ischemic necrosis; the more common sites are heads of: • femurs • tibia • humeri.

Summary

Thrombosis

Composed of	• Fibrin • Platelets • RBCs • Some inflammatory cells	
Pathogenesis	Virchow Triade: • Endothelial cell injury • Stasis or turbulence of blood flow • Blood hypercoagulability	
Morphology	**Arterial**	**Venous (Phlebothrombosis)**
	Endothelial injury or turbulence	Stasis
	Coronary, Cerebral and Femoral arteries	Popliteal, Femoral and Iliac veins (Deep Vein Thrombosis)
	Occlusive can cause ischemia and necrosis	Prone to fragmentation can cause pulmonary embolism
Fibrinolysis	Thrombus is dissolved by plasmin • Fibrinolytic cascade: Plasminogen → Plasmin	

Embolism

Types	**Pulmonary Thromboembolism**	**Systemic Thromboembolism**	**Fat Embolism**	**Air Embolism**	**Amniotic Fluid Embolism**
Arise from	DVT	Intracardiac Mural Thrombi	Release of fat from bone marrow after long bone fracture	Entry of air due to chest wall injury or obstetric procedure	Infusion of amniotic fluid due to a tear in the placental membranes or rupture of uterine veins
Site	Pulmonary artery	Lower extremities and brain	Circulation	Circulation	Circulation
Leads to	Sudden death Cor pulmonale	Infarction	Fat embolism syndrome	Decompression sickness	Pulmonary edema

Quiz

Answer key: Answers Explanation File

1) A 67-year-old man presents with sudden left leg pain, absence of pulses, and a cold limb. His past medical history is significant for coronary artery disease and a small aortic aneurysm. Which of the following is most likely responsible for development of a cold limb in this patient?

A) Acute myocardial infarction.
B) Arterial thromboembolism.
C) Cardiogenic shock.
D) Deep venous thrombosis.
E) Ruptured aortic aneurysm.

2) A 60-year-old man with a history of emphysema returns home from the hospital after suffering a myocardial infarction involving the apex of the left ventricle. Six months later, an echocardiogram reveals the development of a ventricular bulge that does not contract during systole. The patient subsequently suffers a massive stroke and suddenly expires. Which of the following is an expected pathologic findings at autopsy?

A) Calcific aortic stenosis
B) Dilated cardiomyopathy
C) Mitral valve prolapse
D) Mural thrombus.
E) Ventricular rupture

3) A 60-year-old man who is recovering from surgery to correct an abdominal aneurysm suddenly develops acute chest pain and dies. A thromboembolism at the bifurcation of the left and right pulmonary arteries is noted at autopsy (shown in the image). Which of the following is the most likely cause of this patient's pulmonary embolism?

A) Bacterial endocarditis.
B) Complicated atherosclerotic plaque.
C) Deep venous thrombosis.
D) Paradoxical embolization.
E) Right ventricular mural thrombus.

4) A 69-year-old retired man is brought to the emergency department because he experienced sudden onset of left-sided chest pain, which is exacerbated upon inspiration. He is taking no medications and has been in good health. Physical examination reveals dyspnea and hemoptysis. Temperature is 38°C (101°F), pulse rate is 98 per minute, respirations are 35 per minute, and blood pressure is 158/100 mm Hg. A pleural friction rub is present on auscultation. The left leg is markedly edematous, with a positive Homans' sign. An ECG shows a normal sinus rhythm. A chest X-ray reveals a left pleural effusion. What is the most likely cause of this patient's pulmonary condition?

A) Congestive heart failure.
B) Cor pulmonale.
C) Mitral stenosis.
D) Subacute endocarditis.
E) Thromboembolism.

5) A 68-year-old obese woman (BMI = 32 kg/m2) presents with substernal chest pain and a history of recurrent angina pectoris and intermittent claudication. The following day, she develops a fever of 38°C (101°F). Results of laboratory studies include an elevated WBC count (13,000/µL), CK-MB of 6.6 ng/mL, and troponin-I of 2.5 ng/mL. ECG confirms a myocardial infarction of the left ventricular wall. Which of the follow-
ing mechanisms is most likely responsible for the myocardial infarction in this patient?

A) Coronary artery thrombosis
B) Coronary artery vasospasm
C) Decreased collateral blood flow
D) Deep venous thrombosis
E) Paradoxical embolism

6) A 30-year-old woman presents with a heart murmur. There is a history of recurrent episodes of arthritis, skin rash, and glomerulonephritis. Blood cultures are negative. Laboratory tests for antinuclear antibodies (ANA) and anti–double-stranded DNA are positive. Which of the following is the most likely cause of heart murmur in this patient?

A) Libman-Sacks endocarditis
B) Mitral valve regurgitation
C) Myocardial infarct
D) Mitral valve prolapse
E) Rheumatic fever

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THANK YOU