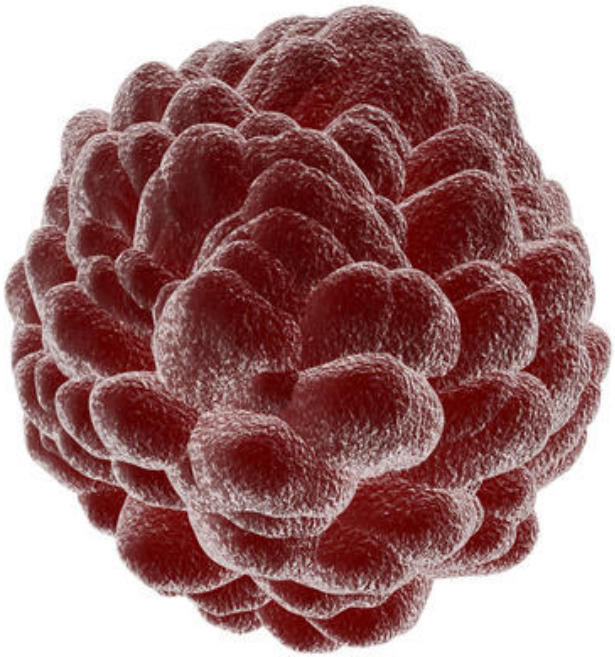
THROMBOEMBOLISM

Robbins page 86



Objectives:

- Understand the basic pathology of thrombogenesis and the risk factors for development of deep vein thrombosis.
- Know the types of embolus than can occur and the pathology of pulmonary embolism.
- Pathological aspects of thrombogenesis: vessel wall abnormality, vascular stasis or turbulent flow and increased blood coagulability.
- Causes of embolism formation.
- Predisposing factors for deep vein thrombosis.
- Pathology of pulmonary thrombo-embolism.
- Brief description of other forms of emboli like: fat embolism, air embolism, atherosclerotic plaque embolism, amniotic fluid embolism, nitrogen embolism and infective endocarditis.

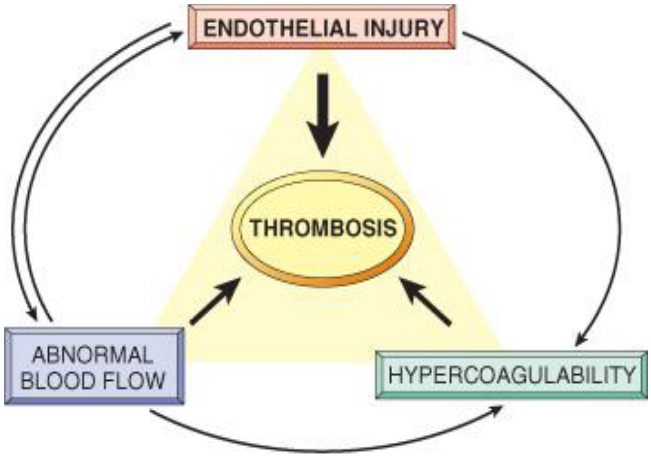
Important note: During the previous blocks, we noticed some mistakes just before the exam and we didn't have the time to edit the files. To make sure that all students are aware of any changes, please check out this link before viewing the file to know if there are any additions or changes. The same link will be used for all of our work: Pathology Edit

Introduction.

Thrombosis: It is a process by which a thrombus is formed. It represents pathologic hemostasis in the intact vascular system. Think about it as a pathological clot.

- A thrombus is a solid mass of blood constituents which develops in an artery or vein.
- It is intravascular coagulation of blood and it often causes significant interruption to blood flow.

Pathogenesis.



Three primary influences called as **Virchow triad** predispose to thrombus formation:

(1) Endothelial injury (by toxin , hypertension ,inflammation)

(2) Stasis or turbulence of blood flow(due aneurysms . atherosclerotic plaque)

(3) Blood hypercoagulability

The factors that influence blood coagulability are: platelet factors, endothelial factors, & coagulation cascade factors.

Just to make this statement clear, if a patient has decreased platelet count, there is an increased risk of bleeding

If a patient has a deficiency in one of the factors of the coagulation cascade → bleeding

Finally, if a patient had a damaged endothelium, there is an increased probability of blood clotting.

This is just to give examples on the factors affecting blood coagulability.

Components of the hemostatic process.

1. Platelets maintain the integrity of the vascular endothelium and participate in endothelial repair through the contribution of PDGF (Platelet Derived Growth Factor). They form platelet plugs and promote the coagulation cascade through the platelet phospholipid complex.
2. Endothelial cells are resistant to the thrombogenic influence of platelets and coagulation proteins. Intact endothelial cells oppose coagulation after injury. Intact endothelial cells are resistant to thrombus formation.

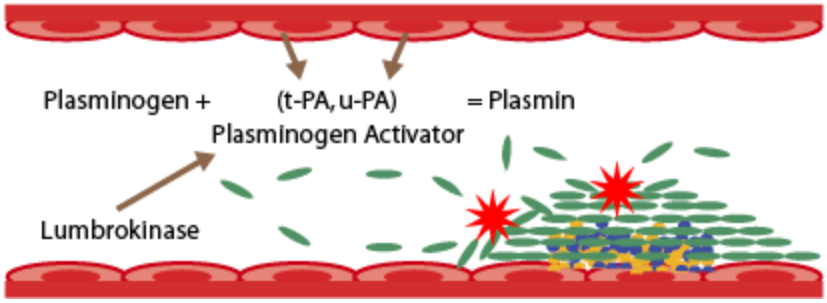
(Extra info.): If you remember the lectures on inflammation back in the foundation block, we learned about the arachidonic acid cascade. To put what we are talking about here into context: platelets produce thrombxane A2 (TXA2) which are potent platelet aggregators (favor clotting). On the other hand, intact endothelial cells produce prostacyclin (PGI2) which inhibit platelet aggregation & cause vasodilation.

3. Coagulation cascade is a major contributor to thrombosis. It is a series of enzymatic conversions, turning inactive proenzymes into activated enzymes and culminating [1]in **-the formation of thrombin. Thrombin then converts the soluble plasma protein fibrinogen precursor into the insoluble fibrous protein fibrin. And fibrin is a constituent of the thrombus.**

[1] ending in the formation of thrombin

Fibrinolysis (thrombus dissolution):

- Besides inducing coagulation, activation of the coagulation cascade also *sets into motion*[2] a *fibrinolytic cascade* that limits the size of the final clot. It runs concurrently [3]with thrombogenesis[4].
  The idea here is that there must be a mechanism to control thrombogenesis or else, clots formed would end up occluding the whole artery. This mechanism is explained here.
- Restores blood flow in vessels occluded by a thrombus and facilitates healing after inflammation and injury.
- This is accomplished by the generation of *plasmin..*
  The circulating proenzyme **plasminogen** (inactive) → **Plasmin** (active) by *proteolysis*. Plasmin then splits fibrin.



Hypercoagulability: any alteration of the coagulation pathway that predisposes to thrombosis.

Hypercoagulable States: (People with hypercoagulable states are more likely to develop clots and thrombosis), it can be:

1. **Primary**/Genetic:
   A. Common: mutation in factor V gene or prothrombin gene.
   B. Rare: anti-thrombin III deficiency, protein C or S deficiencies.
   C. Very rare: fibrinolysis defects).

2. **Secondary**/acquired states:
   A. High risk for thrombosis:
   - Prolonged bed rest or immobilization
   - Myocardial infarction, Atrial fibrillation
   - Tissue damage (e.g. surgery, fracture or burns)
   - Cancer
   - Prosthetic cardiac valves
   - Disseminated intravascular coagulation
   - Heparin-induced thrombocytopenia
   - Antiphospholipid antibody syndrome (lupus anticoagulant syndrome)

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[2] starts
[3] at the same time
[4]the formation of thrombus.

B. Lower risk for thrombosis:

Cardiomyopathy, nephrotic syndrome, hyperestrogenic states (pregnancy), oral contraceptives use, sickle cell anemia, smoking.

Thrombotic disorders.

Can be anti-thrombotic (hemorrhagic), leading to pathologic bleeding states such as hemophilia, Christmas disease and von Willebrand disease. Can also be prothrombotic, leading to hypercoagulability with pathologic thrombosis e.g. hereditary thrombophilia and antiphospholipid antibody syndrome.

1. Hereditary Thrombophilia.

Is a **prothrombotic** familial syndrome. Characterized by recurrent venous thrombosis and thromboembolism. Can be caused by deficiency of antithrombotic proteins including antithrombin 3, protein C, and protein S.

2. Antiphospholipid antibody syndrome

Is a **prothrombotic** disorder characterized by **autoantibodies** attacking some protein antigens that form complexes with phospholipids. It might be associated with SLE , so this antibody is also known as **lupus anticoagulant**.
Clinically, the findings include:

- recurrent thromboses
- repeated miscarriages
- cardiac valve vegetations
- Thrombocytopenia

It is most often diagnosed because of an incidental finding of prolonged PTT.
The partial thromboplastin time : medical test that characterizes blood coagulation

3. Disseminated Intravascular Coagulation (DIC)

Is **both prothrombotic and antithrombotic** disorder characterized by widespread thrombosis , which can cause diffuse circulatory insufficiency in the brain, lungs, heart, and kidneys. and hemorrhage resulting from the consumption of platelets and coagulation factors.
How is it prothrombotic and antithrombotic at the same time? At the beginning, it is prothrombotic and there is DIC. After a while, the coagulation factors would be used up & there wouldn't be enough to form anymore blood clots → then it becomes antithrombotic.
It is not a primary disease but rather a potential complication of any condition associated with widespread activation of thrombin .

Morphology 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.

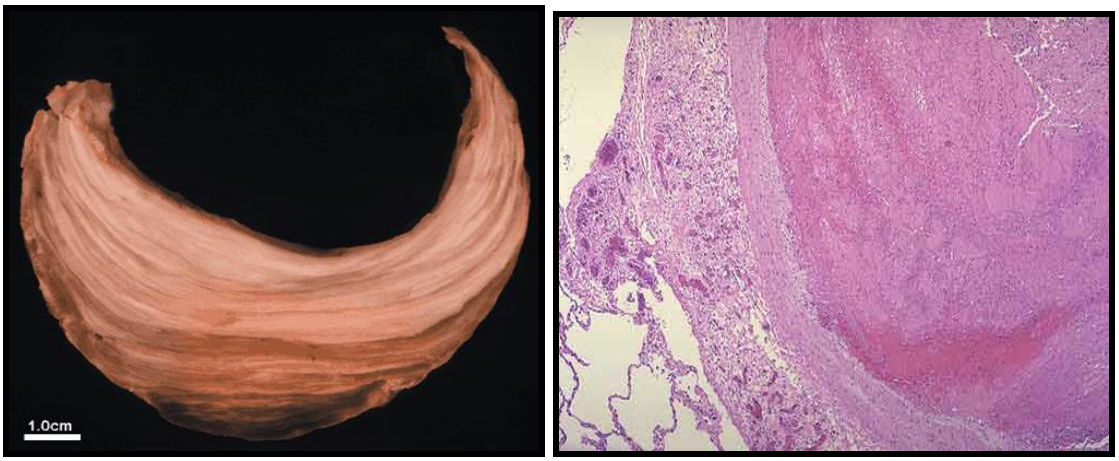
- Arterial thrombi → close to the heart
- Venous thrombi → sited of stasis (deep veins of the legs after a long flight)

Portions of a thrombus might fragment and form an embolus

- Lines of Zahn: microscopic alternating lines of platelets and fibrin. They are important because they are only found in blood clots that were formed before death (important for autopsy people)
- Mural thrombi: thrombi occurring in the heart chambers or in aortic lumen.

Cardiac mural thrombi can occur due to abnormal myocardial contraction (arrhythmia, dilated cardiomyopathy or myocardial infarction) or endomyocardial injury (myocarditis, catheter trauma)

While aortic thrombi occur due to ulcerated atherosclerotic plaque and aneurysmal dilatation.



Lines of Zahn

Arterial thrombi

- Order from most common to least common: coronary >> cerebral> femoral

Usually affects a damaged artery (for example, an artery with atherosclerosis)

- Arterial thrombi are typically relatively rich in **platelets**, as the processes underlying their development (e.g., endothelial injury) leads to platelet activation.
- Usually occurs on a ruptured ***atherosclerotic plaque***
- It can be caused by other **vascular injuries** (vasculitis, trauma).
- Arterial thrombi are gray-white and friable.

Venous thrombosis (phlebothrombosis).

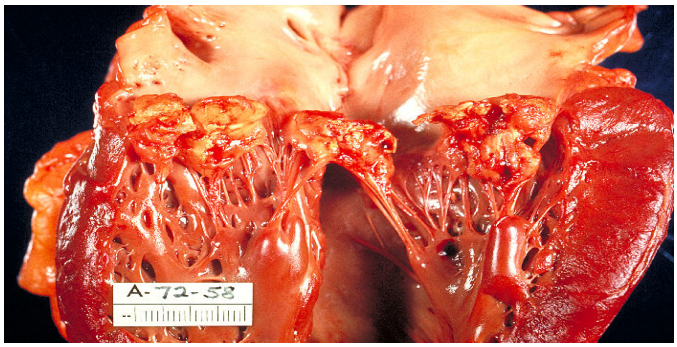
- Venous thrombosis is mostly occlusive and often takes the shape of the vein(fills the lumen).
- Because these thrombi formed in a relatively static environment, they contain more **erythrocytes** and are therefore known as **red**, or **stasis thrombi**.
- An **increase in the activity of coagulation factors** is involved in the formation of most venous thrombosis. (it is a more important cause than platelets)
- Phlebothrombosis most commonly affects the veins of the **lower extremities** (90% of cases).

Thrombi on Heart Valves.

Thrombi on Heart Valves are called **vegetations**.

Vegetations are infective or sterile:

1) Bacteremia → development of large thrombotic masses on heart valves, called as vegetations (infective endocarditis). "Most common cause"
2) Sterile vegetations can also develop on non-infected valves in patients with hypercoagulable states, so-called nonbacterial thrombotic endocarditis.

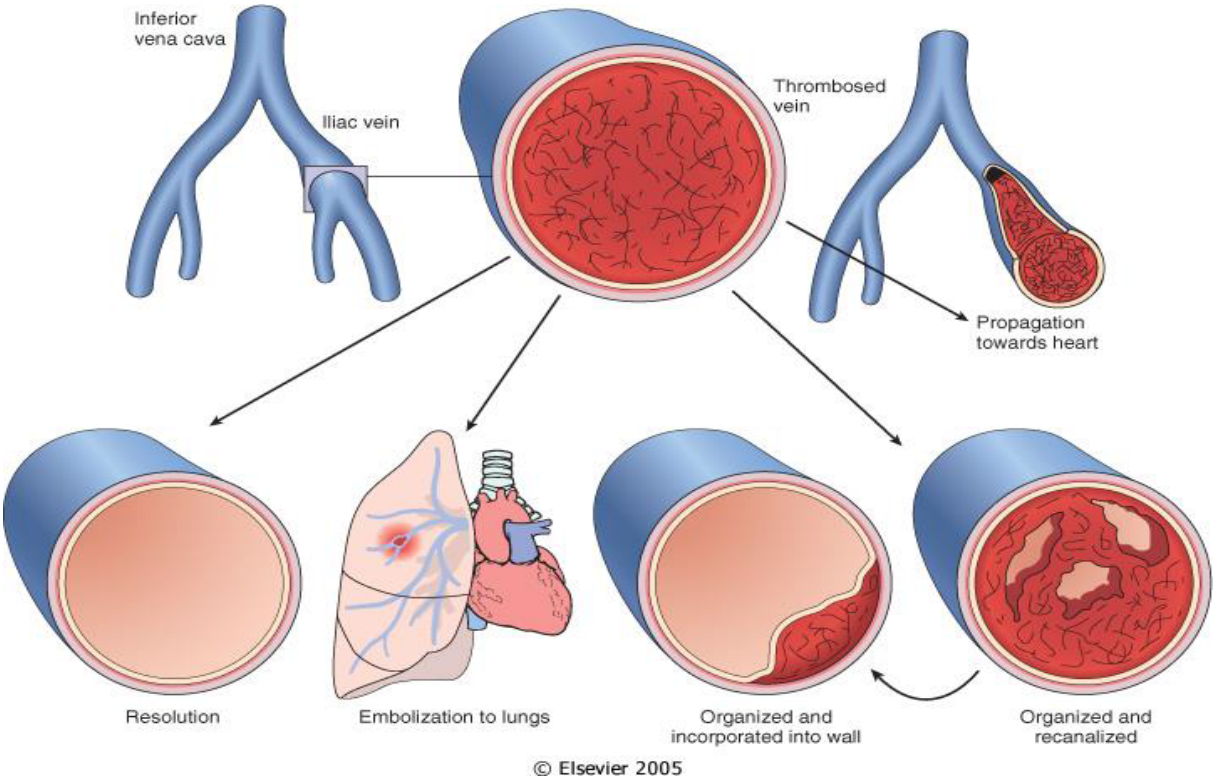


Less commonly, noninfective, verrucous (Libman-Sacks) endocarditis attributable to elevated levels of circulating immune complexes may occur in patients with systemic lupus erythematosus.

Fate of Thrombus.

One of five fates:

- Resolution.
- Propagation.
- Embolism.
- Organization and recanalization.
- Organization and incorporation into the wall.

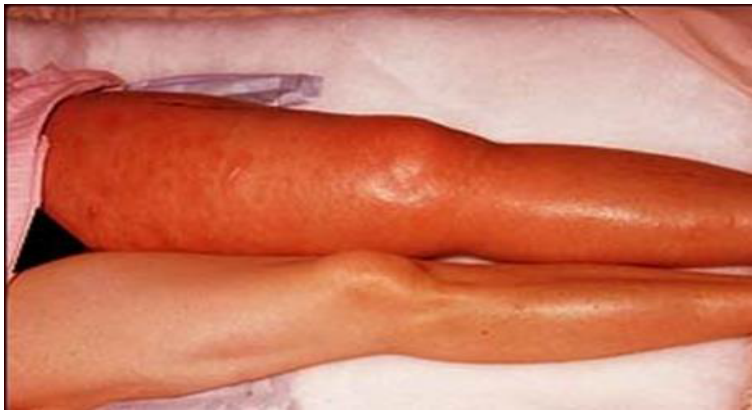


Deep vein thrombosis & Thrombophlebitis

Venous thrombosis often arises in the deep veins of the legs and then it is called deep vein thrombosis (DVT).

- DVT may give rise to pulmonary embolism with resultant pulmonary infarct.
- Often associated with inflammation and then it is termed thrombophlebitis
- Usually occur in the larger leg veins—at or above the knee (e.g., popliteal, femoral, and iliac veins)
- Such thrombi more often embolize to the lungs and give rise to pulmonary infarction
- Can cause local pain and edema.
- Deep vein thrombosis are asymptomatic in approximately 50% of affected individuals and are recognized only in retrospect [5]after embolization.

[5] We don't know they are there unless they embolize and cause other serious problems



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

1. Bed rest and immobilization.
2. Congestive heart failure (a cause of impaired venous return).
3. Trauma, surgery, and burns.
4. Pregnancy: the potential for amniotic fluid infusion into the circulation at the time of delivery can cause amniotic fluid emboli. late pregnancy and the postpartum period are also associated with systemic hypercoagulability.
5. Tumors.
6. Advanced age.

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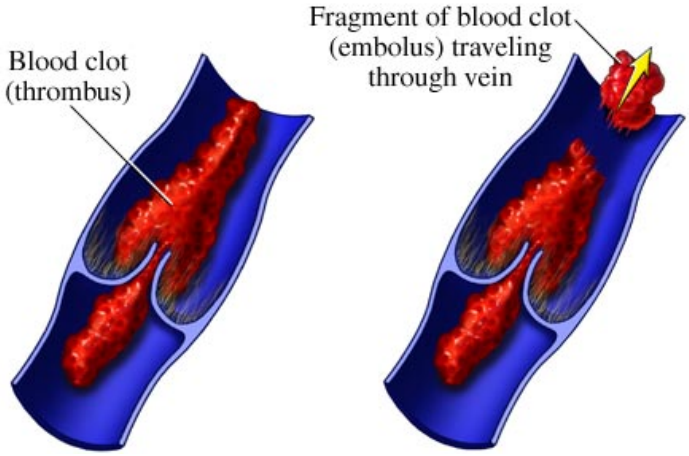
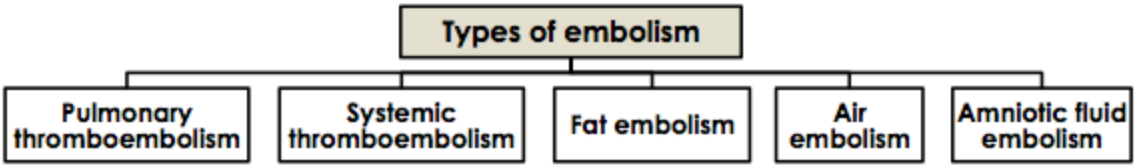
It's a detached intravascular solid, liquid, or gaseous mass that is carried by the blood to a site distant from its point of origin.



Thrombus Vs. Embolism.

Almost all emboli represent some part of a dislodged thrombus, hence the commonly used term ***thromboembolism***. The emboli ultimately lodge in vessels too small to permit further passage, resulting in partial or complete vascular occlusion leading to ischemic necrosis of distal tissue, (infarction). Depending on the site of origin, emboli may lodge in the pulmonary or systemic circulations.



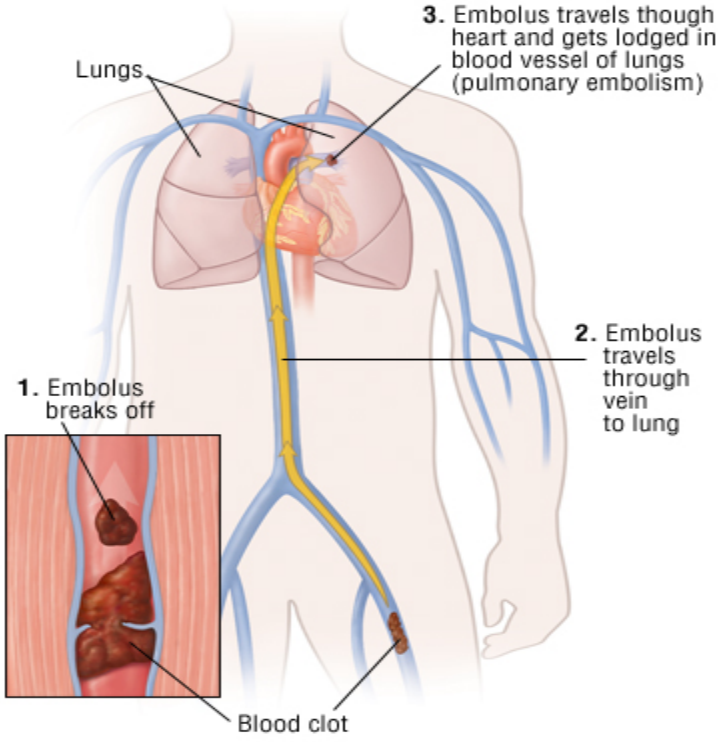
A-PULMONARY THROMBOEMBOLISM.

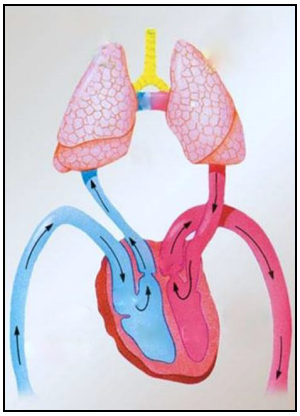
The embolus get lodged in the pulmonary vasculature. Symptoms depend on the size of the embolus & the importance of the artery they occlude. Most pulmonary emboli (60% to 80%) are asymptomatic because they are small.

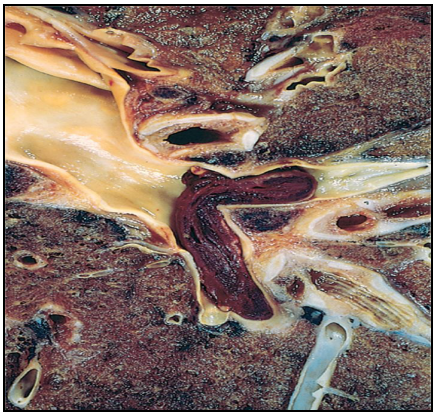
- **Paradoxical embolism**[6] Rarely, an embolus may pass through an interatrial or interventricular defect to gain access to the systemic circulation

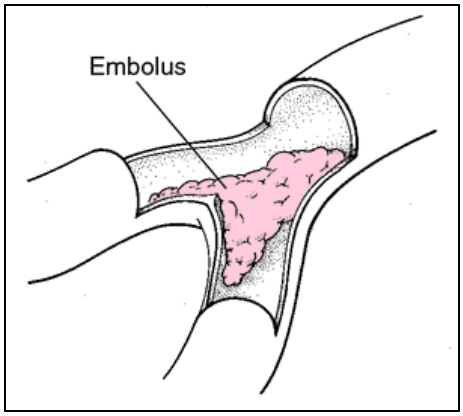
When 60% or more of the pulmonary circulation is obstructed with emboli the following complication may occur:

- Sudden death.
- Right heart failure (cor pulmonale)
- CVS Embolic obstruction of small end-arteriolar pulmonary branches may result in infarction.





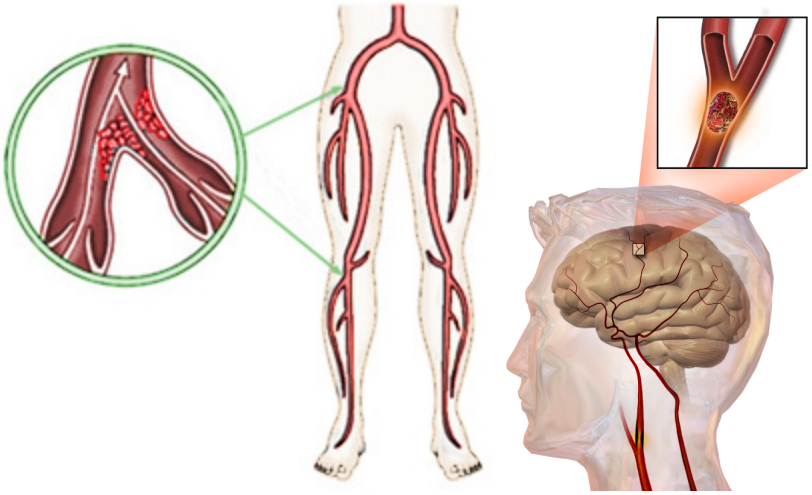




Saddle Embolus

[6] What happens here is that if a patient has a septal defect, where there is communication between the right & left heart, the emboli might skip the lungs & go into this septal defect, and become a systemic emboli that may cause more serious complications The opening is typically an **atrial septal defect**, but can also be a **ventricular septal defect**.

B-SYSTEMIC THROMBOEMBOLISM.



Refers to emboli traveling within the arterial circulation. Most (80%) arise from intracardiac mural thrombi. The major sites for arterial embolization are the **lower extremities (75%)** and the **brain (10%)**.

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[7] of the vessel occluded. In general, arterial emboli cause infarction of tissues supplied by the artery

C-FAT EMBOLISM.

Microscopic fat globules may be found in the circulation after **fractures of long bones** (which have fatty marrow)

Fat is released by marrow or adipose tissue injury and enters the circulation through rupture of the blood vessels and act as an embolus.

Less than 10% of patients with fat embolism have any clinical findings.

Fat embolism syndrome is characterized by pulmonary insufficiency, neurologic symptoms, anemia, and thrombocytopenia.

[7] قطر

D-AIR EMBOLISM

- Gas bubbles within the circulation can obstruct vascular flow (and cause distal ischemic injury) acting as thrombotic masses. Bubbles may coalesce [8]to form frothy masses sufficiently large to occlude major vessels.
- Air may enter the circulation during *obstetric procedures* [9]or as a consequence of chest wall injury.

Decompression sickness.

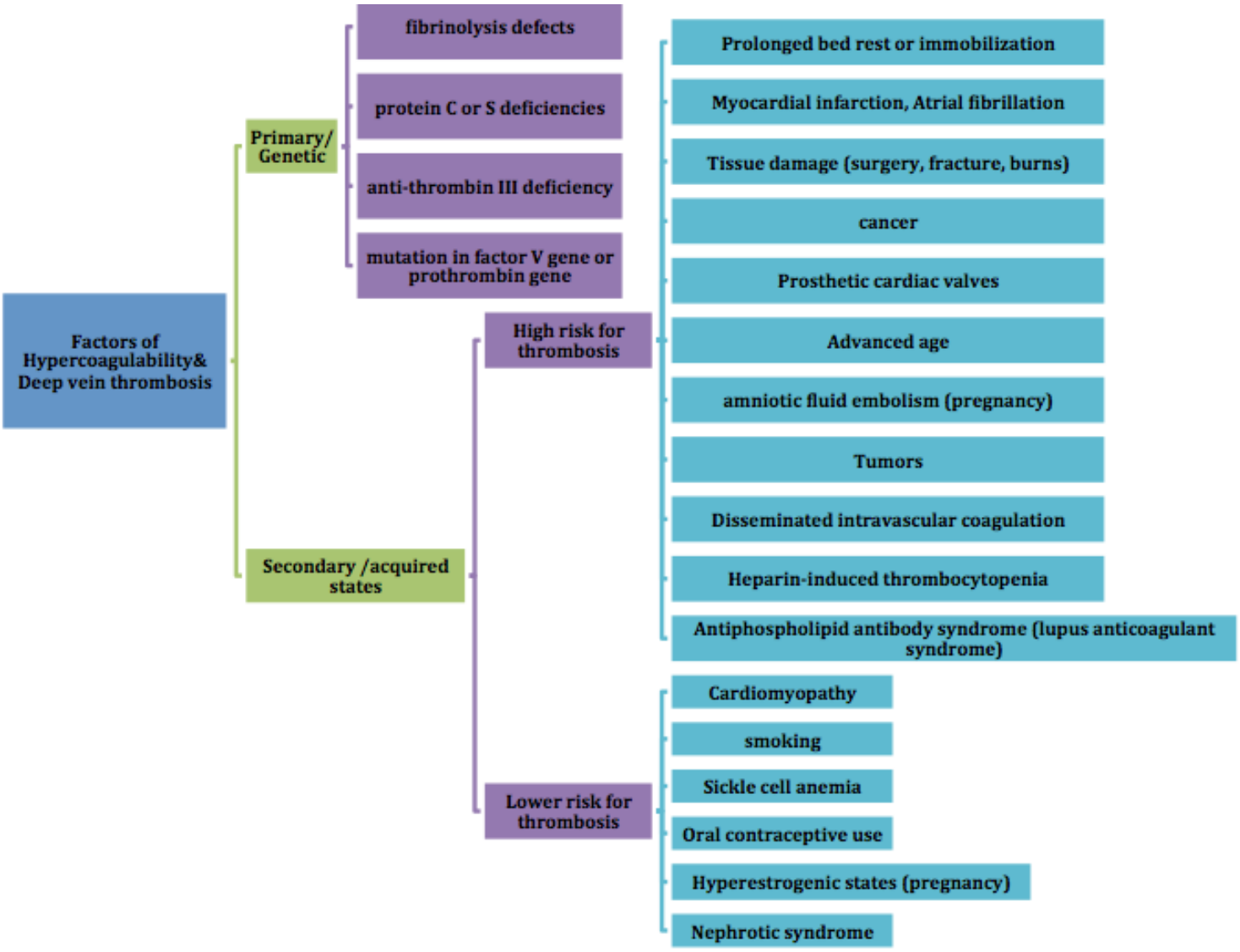
- Occurs when individuals are exposed to sudden changes in atmospheric pressure.
- Scuba and deep sea divers, underwater construction workers, and individuals in unpressurized aircraft in rapid ascent are all at risk.
- When air is breathed at high pressure (e.g. during a deep sea dive), increased amounts of gas (particularly nitrogen) become dissolved in the blood and tissues. If the diver then ascends (depressurizes) too rapidly, the nitrogen expands in the tissues and bubbles out of solution in the blood to form gas emboli.
- 'Bends' i.e. joint/muscle pain and 'chokes' i.e. respiratory distress.
- Treatment: placing the individual in a compression chamber where the barometric pressure may be raised, thus forcing the gas bubbles back into solution followed by subsequent slow decompression.
- A more chronic form of decompression sickness is called caisson disease in which, persistence of gas emboli in the skeletal system leads to multiple foci of ischemic necrosis; the more common sites are the heads of the femurs, tibia, and humeri.

E-AMNIOTIC FLUID EMBOLISM

An 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.
Characterized by 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, lanugo hair, fat from vernix caseosa, and mucin derived from the fetal respiratory or gastrointestinal tract. Marked pulmonary edema and diffuse alveolar damage are also present. Systemic fibrin thrombi indicative of DIC can also be seen.

[8] Unite, or come together
[9] Procedures done on pregnant women

Summary.

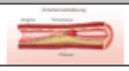


Thrombotic disorders:

1- anti-thrombotic (hemorrhagic): e.g : hemophilia &Christmas disease and von Willebrand disease.

2- prothrombotic e.g : hereditary thrombophilia and antiphospholipid antibody syndrome

Hereditary Thrombophilia:	Factor V Leiden thrombophilia:	Antiphospholipid antibodysyndrome	Disseminated intravascularcoagulation:
prothrombotic familial syndrome. 1- recurrent venous thrombosis and thromboembolism caused by: deficiency of antithrombotic proteins including antithrombin 3, protein C, and protein S.	prothrombotic disorder. Mutated form of human factor V	(lupus anticoagulant): prothrombotic disorder associated Systemic Lupus Erythematosus	both prothrombotic and antithrombotic

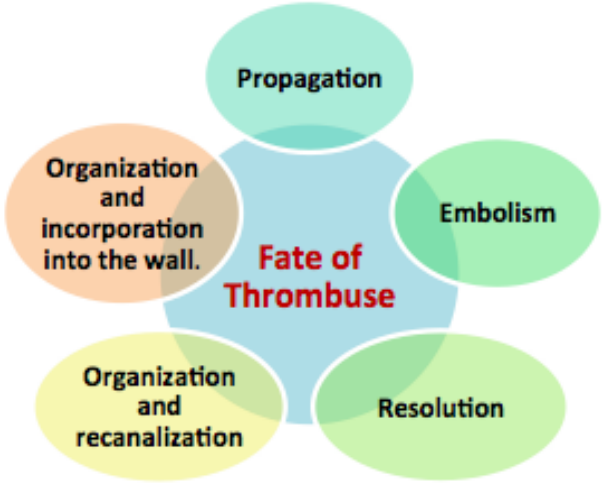
Arterial thrombi	Venous thrombi (phlebothrombosis)	Postmortem clots	Thrombi	Thrombi on Heart Valves (vegetation's)
At a site of: 1- endothelial injury (e.g., atherosclerotic plaque) 2- turbulence (vessel bifurcation)	In sites of: Stasis. (Red, or stasis thrombi)	Not attached to the underlying wall	Have a point of attachment	1-Infective vegetations: (Infective endocarditis) 2- Sterile vegetation's: (Nonbacterial thrombotic endocarditis) (Libman-Sacks) endocarditis
Grow in a retrograde direction (i.e. toward the heart).	In the direction of blood flow (i.e. toward the heart).	dark red dependent portion where red cells have settled by gravity and a yellow chicken fat supernatant resembling melted and clotted chicken fat. They are not attached to the underlying wall.	Vague strands of pale gray fibrin.	
Occlusive				
Most common sites are: Coronary, cerebral, and femoral arteries.	Commonly affects The veins of the lower extremities			
usually superimposed on an atherosclerotic plaque 				

Deep vein thrombosis (DVT).& Thrombophlebitis
In the deep veins of the legs
Because stasis prolong period of rest & other reasons mentioned before.
Embolize to the lungs and give rise to pulmonary infarction.
Asymptomatic in 50%


When arterial thrombi arise in heart chambers or in the aortic lumen they are termed mural thrombi. (cut section) --> lines of Zahn

propagating tail prone to fragmentation, creating an embolus

Thrombus is made up of : fibrin & platelets & red blood cell & few inflammatory cells .



EMBOLISM (thromboembolism) ultimately lodge in vessels too small to permit further passage, resulting in partial or complete vascular occlusion leading to ischemic necrosis of distal tissue, (infarction).					
Pulmonary thromboembolism	Systemic thromboembolism	FAT EMBOLISM	AIR EMBOLISM	Nitrogen Embolism (Decompression sickness)	Amniotic fluid embolism
originating from venous may occlude main pulmonary artery, or impact across the bifurcation (saddle embolus)	Originating from : artery or heart champers	Originating from: Marrow (fracture) or adipose tissue injury or burns or trauma. Enters the circulation through rupture of the blood vessels and act as an embolus.	Air may enter the circulation during: obstetric procedures or as a consequence of chest wall injury.	At high pressure increased amounts nitrogen become dissolved in the blood and tissues. If the diver then ascends (depressurizes) too rapidly, the nitrogen bubbles expand out of solution in the blood to form gas emboli. Treatment: Forcing the gas bubbles back into solution by placing the individual in a compression chamber where the barometric pressure may be raised. Followed by subsequent slow decompression.	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
embolus may pass through an interatrial or interventricular defect to gain access to the systemic circulation (paradoxical embolism)	The major sites for arteriolar embolization are : The lower extremities and the brain.		*An excess of 100 cc Is required to have a clinical effect.		If the patient survives the initial crisis: Pulmonary edema develops, along with disseminated intravascular coagulation, owing to release of thrombogenic substances from amniotic.
Silent clinically because they are small 		Fat embolism syndrome: 1- Pulmonary insufficiency 2-neurologic symptoms 3-anemia 4- Thrombocytopenia.			

Another summary:

- Thrombosis is a bad pathological clot.
- Endothelial injury, abnormal blood flow, & hypercoagulability are risk factors for thrombosis.
- Normally, there is a balance between the endothelial cells & platelets in terms of platelet aggregation. Platelets want to aggregate (TXA2) & endothelium doesn't (PGI2).
- Fibrinolysis: plasminogen → plasmin
- Examples of hypercoagulability states & thrombotic disorders.
- Lines of Zahn help in differentiating premortem & postmortem clots (to identify the cause of death).
- Mural thrombi are due to vegetations of the heart endothelium lining the valves. Bacteria are the most common cause (infective endocarditis). The heart would then keep shooting emboli to the systemic circulation.
- Arterial thrombi are most common in coronary arteries. Usually hits areas with atherosclerotic plaques.
- Venous thrombi (most common is DVT) → lungs causing a pulmonary emboli. Rarely this thrombi could pass through a septal defect causing a paradoxical embolism.
- Fat embolism → long bone fractures
- Air emboli → operations or decompression sickness
- Amniotic fluid embolism → bad prognosis

MCQs.

1- Which of the following is false regarding thrombosis :

a) It affects both arteries and veins
b) It often causes significant interruption to blood flow
c) It only consists of aggregated platelets
d) It is a response to blood vessel injury

ANSWER: C

2- Which of the following does not belong to the " Virchow triad "

a) endothelial injury
b) blood hyper fibrinogenolytic inducers
c) stasis or turbulence of blood flow
d) blood hypercoagulability

ANSWER: B

3- which of the following is a high risk factor that causes hypercoagulability and therefore forming thrombosis :

a) smoking
b) cardiomyopathy
c) nephrotic syndrome
d) myocardial infarction

ANSWER: D

4- which of the following disorders is a prothrombotic disorder:

a) factor V Leiden thrombophilia
b) hemophilia
c) Disseminated intravascular coagulation
d) Non

ANSWER: A

5- Which of the following is the main feature OF Antiphospholipid antibody syndrome:

a) Reduction of partial thromboplastin time (PTT).
b) Recurrent venous thrombosis
c) associated Systemic Lupus Erythematosus
d) it is an anti-thrombotic disorder

ANSWER: C

6- mural thrombi is :

a) a blood clot originating from the heart chambers and aorta
b) is a mobile thrombi
c) is an inflamed thrombi
d) Thrombi on Heart Valves

ANSWER: A

7- comparison table:

Vessel	Site of thrombosis	Growth direction	Erythrocytes concentration
Arteries			
Veins			

ANSWER:

Vessel	Site of thrombosis	Growth direction	Erythrocytes concentration
Arteries	Bifurcations	Against the blood flow	Lower
Veins	Sites of stasis	With the blood flow	Higher

8- A 55 year old male has died of unknown reason. Autopsy has shown an obstruction of a major blood vessel with by a blood clot involve an adhesion of the vessel's endothelial wall. The clot had no lines of Zahn

9- Which of the following is True based on the case scenario.

a) It is a Postmortem clot
b) It is a venous thrombi

Answer: A

10- Thrombi on Heart Valves are called:

a) Embolus
b) Postmortem clot
c) Vegetations
d) Venous thrombi

Answer: C

11- deep vein thrombosis (DVT) may lead to:

a) pulmonary infarction
b) renal infraction
c) brain infraction
d) peripheral infarctions

Answer: A

12- which of the following is NOT a feature of Fat embolism syndrome:

a) anemia
b) pulmonary insufficiency
c) neurologic symptoms
d) retinal diseases

Answer: D

13- Decompression sickness → high risk of:

a) An air EMBOLISM
b) An AMNIOTIC FLUID EMBOLISM
c) A FAT EMBOLISM
d) Septic embolism

Answer : A

Contact us on: Pathology434@gmail.com

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Good Luck!

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	Najlaa2020