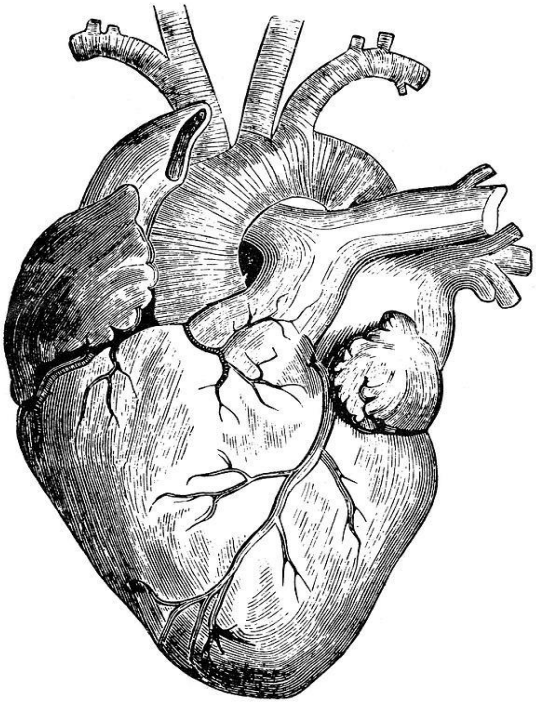


Pathology

teamwork

Lecture (5) :

Thromboembolism

Color Index :-

- **VERY IMPORTANT**
- Extra explanation
- **Examples**
- **Diseases names: Underlined**
- **Definitions**

Objectives :

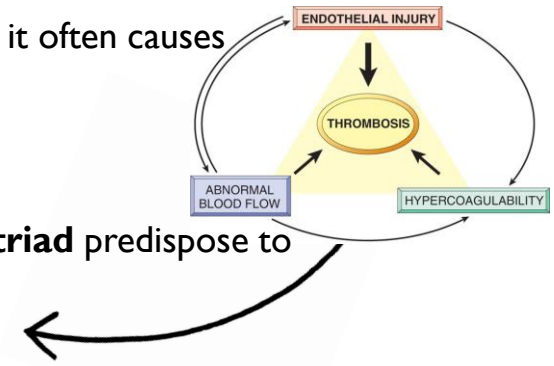
- Understand the basic pathology of thrombogenesis and the risk factors for development of venous and arterial thrombosis.

- Know the types of emboli and to be able to describe the causes and pathology for each one.

* Try to focus on the **red** text, all of it is important.

Thrombosis:

- A thrombus is a solid mass of blood constituents which develops in 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.
2) Stasis or turbulence of blood flow.
3) Blood Hyper-coagulability.

It results from interaction of platelets, damaged endothelial cells and the coagulation cascade. All 3 are components of the hemostatic process.

Thrombosis development & decomposition

Thrombotic factor

1. Platelets
2. Coagulation cascade

Formation of thrombin

Fibrinogen → **Fibrin**

Anti-thrombotic

1. Antithrombin 3
2. Protein S
3. Protein C

If there is a deficiency the patient will develop thrombosis

Fibrinolysis

Generation of plasmin

Splits

Hyper-coagulable States:

1) Primary/Genetic (e.g. mutation in factor V gene or prothrombin gene, anti-thrombin III deficiency protein C or S deficiencies, or fibrinolysis defects). (thrombosis in early ages).
2) Secondary/acquired states they can be high risk or low risk

a) High risk for thrombosis:

- Prolonged bed rest or immobilization
- Myocardial infarction, Atrial fibrillation
- Tissue damage (surgery, fracture, burns)
- Cancer = (release of procoagulant tumor products)
- Prosthetic valves
- Disseminated intravascular coagulation (thrombin generation)
- Antiphospholipid antibody syndrome (Lupus anticoagulant syndrome) (Autoantibodies)

b) Low risk for thrombosis : (Dr. didn't talk about it)

Cardiomyopathy, Nephrotic syndrome, Hyperestrogenic states (pregnancy), Oral contraceptive use, Sickle cell anemia, Smoking.

- **Components of the hemostatic process**

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

2.Endothelial cells are resistant to the thrombogenic influence of platelets and coagulation proteins. Intact endothelial cells are thrombo resistant.

3.Coagulation Cascade 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.

- **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. Endothelial Injury

Endothelial Injury is a major cause of thrombosis in the heart or arteries.

Endothelial injury leads to:

- Exposure of subendothelial ECM, i.e the basement membrane
- Adhesion of platelets
- Release of tissue factor and ultimately thrombosis
- Endothelial injury can contribute to thrombosis in several clinical settings e.g:
- Endocardial injury due to myocardial infarction
- Ulcerated plaques in atherosclerotic arteries
- Traumatic or inflammatory vascular injury

The following conditions lead to chronic subtle endothelial dysfunction/injury:

- Hypertension
- Scarred valves
- Bacterial endotoxins
- Radiation
- Hypercholesterolemia
- Cigarette smoking

2. Abnormal Blood Flow

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

2.Turbulence contributes to arterial and cardiac thrombosis by causing endothelial injury or dysfunction.

- Abnormal blood flow contributes to thrombosis in several clinical settings:
- Ulcerated atherosclerotic plaques
- Abnormal aortic and arterial dilations
- Acute myocardial infarction
- Mitral valve stenosis
- Hyperviscositysyndromes
- Sickle cell anemia

3. Hypercoagulability

- Definition: Any change of the coagulation pathways that predisposes to thrombosis
- Hypercoagulability can be divided into:
- Primary (inherited) hypercoagulable states
- Secondary (acquired) hypercoagulable states

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.
- Characterized by recurrent venous thrombosis and thromboembolism.
- Can be caused by deficiency of antithrombotic proteins e,g. antithrombin3, 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).

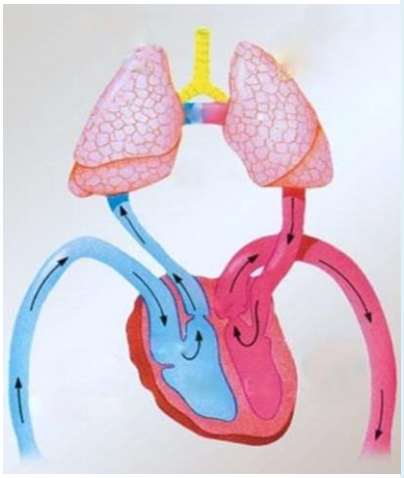
Antiphospholipid antibody syndrome

- Is a prothrombotic hypercoagulable autoimmune multisystem 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.

Morphology of thrombus :

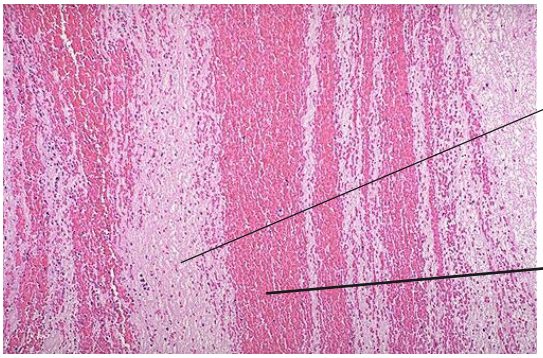
Thrombi may develop anywhere in the cardiovascular system the cardiac chambers, valve cusps, arteries, veins, or capillaries. They vary in size and shape, depending on the site of origin.

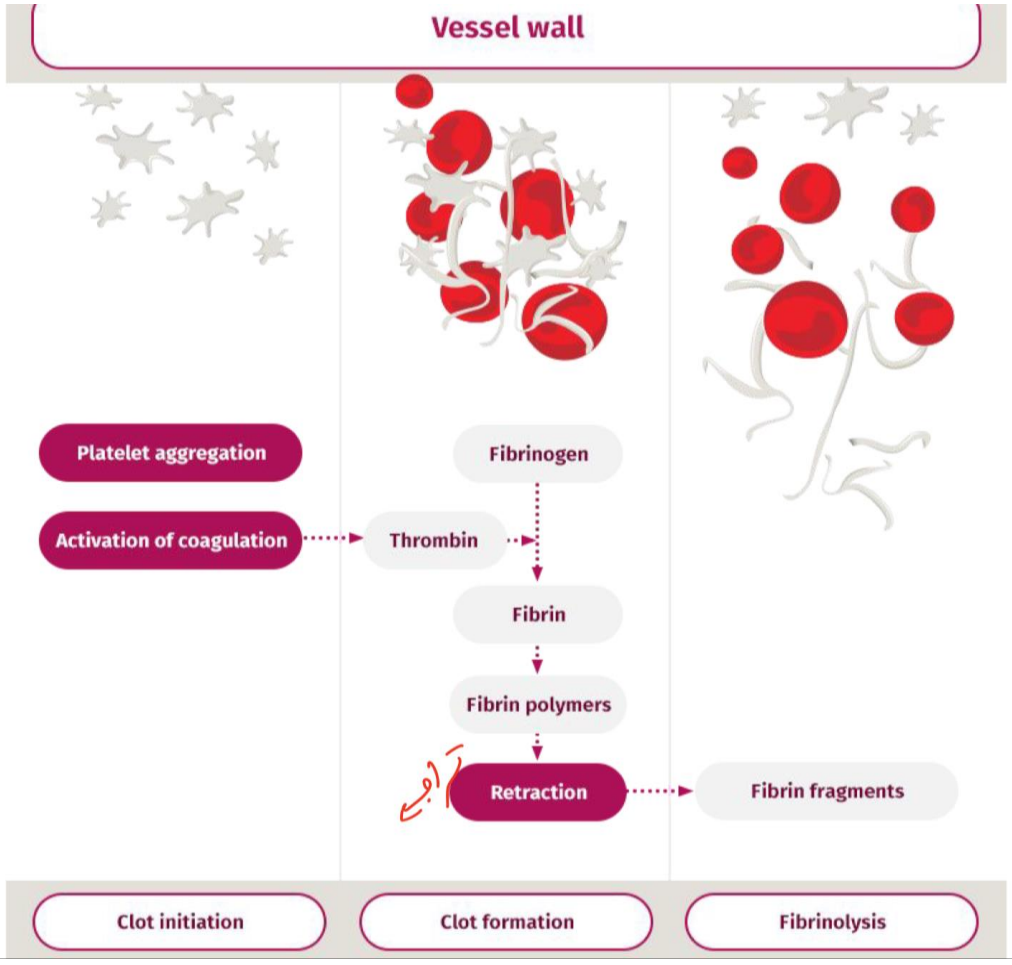
- Arterial or cardiac thrombi usually begin at a site of endothelial injury (e.g., atherosclerotic plaque) or turbulence (vessel bifurcation)
- Venous thrombi characteristically occur in sites of stasis.
- The propagating tail of either thrombi may not be well attached (particularly in veins) is prone to fragmentation, creating an embolus.



Lines of Zahn

They are composed of platelets, fibrin, and RBCs.





Arterial Thrombi

- Are usually occlusive
- Most common sites in descending order, are coronary, then cerebral, and then femoral arteries.
- It is usually superimposed on an atherosclerotic plaque and are firmly adherent to the injured arterial wall (mural). When thrombi are attached to the wall, we call them mural
- Gray-white and friable.

Venous Thrombi

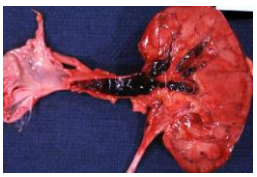
- Also called Phlebothrombosis, almost invariably occlusive
- The thrombus often takes the shape of the vein
- Because these thrombi form in a relatively static environment, they contain more enmeshed erythrocytes and are therefore known as red, or stasis thrombi.
- Phlebothrombosis most commonly affects the veins of the lower extremities (legs) (90% of cases).

Postmortem clots: (after death)

- At autopsy, postmortem clots may be confused for venous thrombi.
- Post-mortem clots are gelatinous with a 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.
- Thrombi are firmer, almost always have a point of attachment, and on transection reveal vague strands of pale gray fibrin.

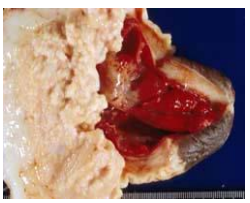
Venous thrombus

- Firm
- Rich admixture of RBCs and appear red
- Attached to the vessel wall



Postmortem clots

- Rubbery and gelatinous
- Dark red in one side and yellow in the other.
- Not attached to the vessel wall



Thrombi on Heart Valves

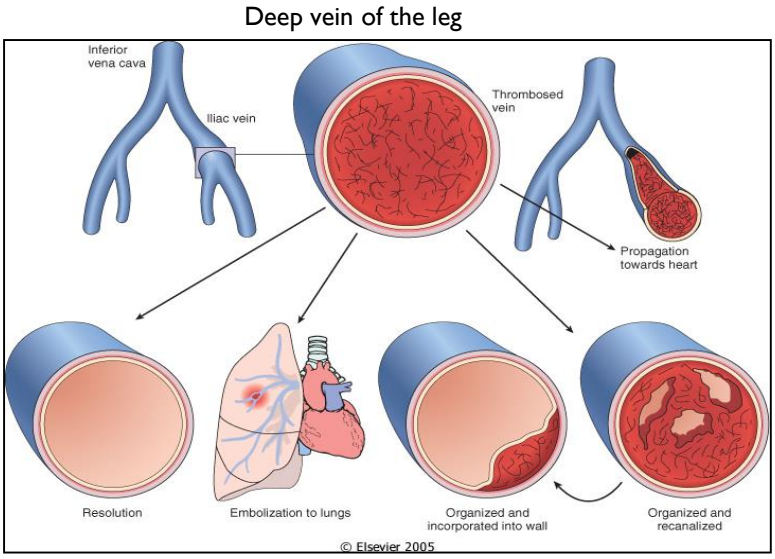
- Thrombi on Heart Valves are called vegetations.
- Are infective or sterile:

1) Bacterial or fungal blood-borne infections may result in the development of large thrombotic masses on heart valves, called as **vegetations** (**infective endocarditis**).
2) Sterile vegetations can also develop on noninfected 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:

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



*Resolution, the thrombus is completely gone by fibrinolysis.
*Propagation, the thrombus propagates in the same place without going somewhere else.
*Embolism, the thrombus detaches and goes somewhere else.
*Organization, which means that the thrombus doesn't change in size. It either incorporates into the wall or forms small canalizations.

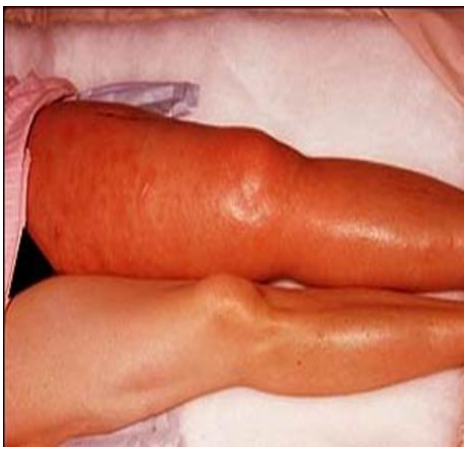
Deep vein thrombosis & Thrombophlebitis

- Venous thrombosis often arises in the deep veins of the legs and then it is called deep vein thrombosis (DVT).
- They occur with stasis or in hypercoagulable states.
- Often associated with inflammation and then it is termed thrombophlebitis
- Such thrombi more often embolize to the lungs and give rise to pulmonary infarction.
- 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

Usually happens is stasis conditions

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

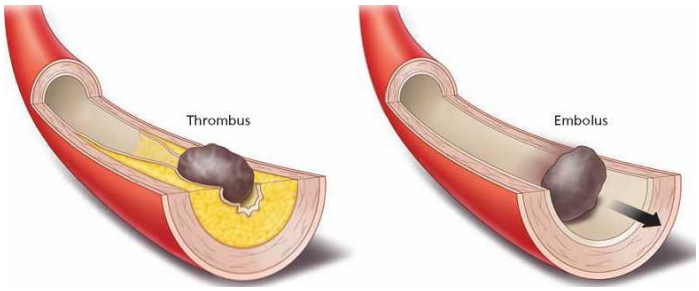
1. **Bed rest and immobilization**
2. **Congestive heart failure** (a cause of impaired venous return)
3. **Trauma, surgery, and burns**
4. **Pregnancy**:
   - the potential for amniotic fluid infusion into the circulation at the time of delivery can cause thrombogenesis
   - late pregnancy and the postpartum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



Embolism

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

- 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.



Types of embolism

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

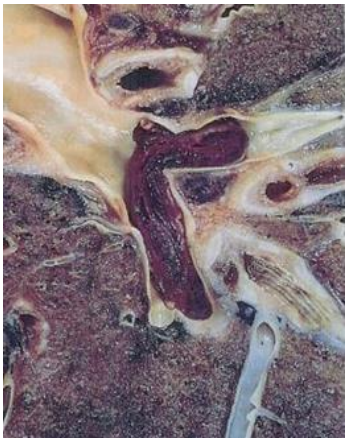
Pulmonary thromboembolism

In more than 95% percent of the cases, venous emboli originate from deep leg vein thrombi above the knee.

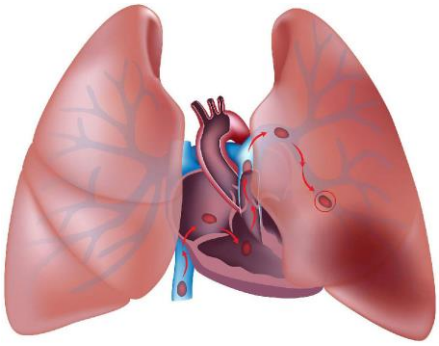
Depending on size of embolus, it may occlude main pulmonary artery, or impact across the bifurcation *(saddle embolus)* *or* pass into a smaller branching arterioles of the pulmonary circulation.

- An embolus may pass through an interatrial or interventricular defect to gain access to the systemic circulation but its **rare** *(paradoxical embolism)*.
- 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.

*When there is an embolus in the pulmonary circulation that is obstructing 60% or more, the right ventricle is unable to pump blood to the lungs due to the occluded artery. That is why right heart failure (cor pulmonale) occurs.



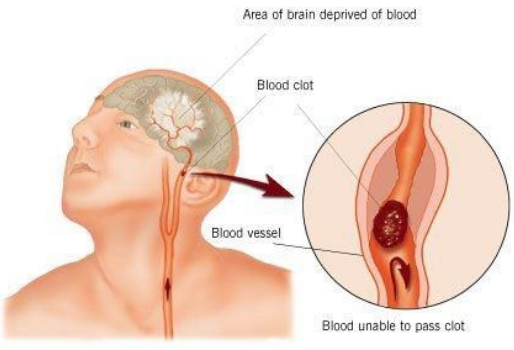
< Saddle embolus

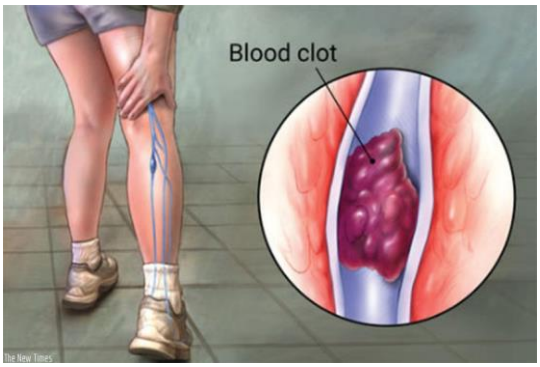


Systemic Thromboembolism

Refers to emboli traveling within the arterial circulation.

- About (80%) arise from **intracardiac mural thrombi.**
- The major sites for arteriolar embolization are the lower extremities (75%) and the brain (10%).
- Arterial emboli usually cause infarction of tissues supplied by the artery
- (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).





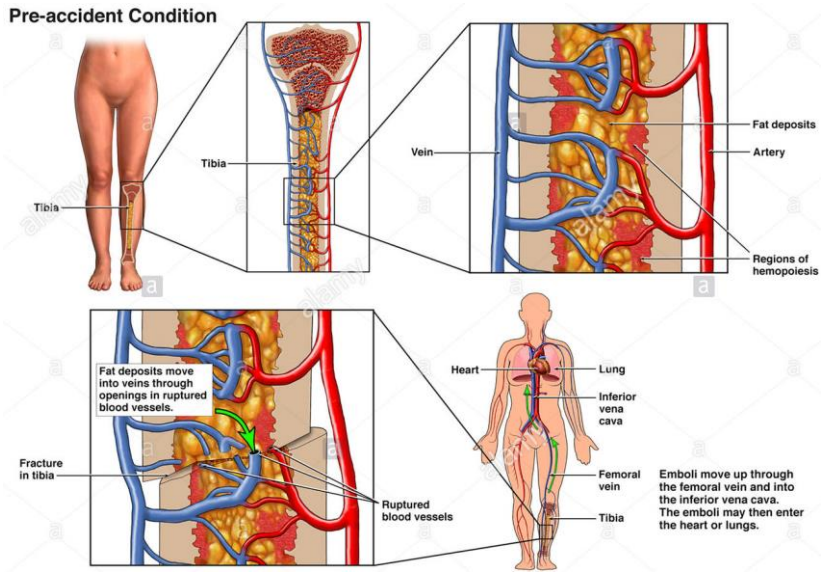
Fat embolism

Microscopic fat globules may be found in the circulation after fractures of long bones (which have fatty marrow) or, rarely, in soft tissue trauma and burns.

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

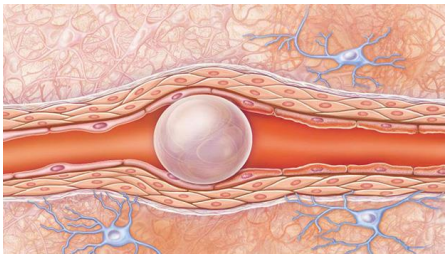
Less than 10% of patients with fat embolism have any clinical findings.

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



Air embolism

- Gas bubbles within the circulation 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.
- **Air may enter the circulation during obstetric procedures or as a consequence of chest wall injury, or in decompression sickness.**
- An excess of 100 cc is required to have a clinical effect.



Decompression sickness

Occurs when individuals are exposed to **sudden changes** in atmospheric pressure, Such as 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.

Symptoms: '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.

- 'Grecian Bend' i.e. joint/muscle pain, and 'chockes' in respiratory distress

Amniotic fluid embolism

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.

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.

Summary

Embolus: is a detached intravascular solid, liquid, gaseous mass that is carried by the blood to a site distant from its point of origin.

- **Types of embolism**

- **Pulmonary thromboembolism:**
- -**originate from** deep leg vein thrombi.
- -occlude *main pulmonary artery* or impact across the *bifurcation* (saddle embolus).
- -sudden death , right heart failure occurs **when 60% or more** of the pulmonary artery obstructed with emboli.

- **Systemic thromboembolism:**
- -refers to emboli traveling within the ***arterial circulation***.
- - most (80%) arise from **intracardiac mural thrombi .**
- - the major sites for arteriolar embolization are the ***lower extremities*** (75%) and the ***brain*** (10%).

- **Air embolism:**
- *Air inters the circulation during:*
- 1- obstetrics procedures (not normal delivery)
- 2- chest wall injury
- 3- decompression sickness (caisson disease) or grecian bend. Mainly deep see divers.

- **Fat embolism:**
- -occurs after fractures of long bones --> fat released.

- **Amniotic fluid embolism:**
- -uncommon complication of labor (normal delivery) and the immediate postpartum period.
- -**microscopy** you will see:
- -fetal skin
- -hair

Thrombus: is a solid mass of blood constituents which develops in artery or vein.

- Organization and incorporation into the wall

- Organization and recanalization

- ***Fate of thrombus***

- Embolism

- Resolution

- Propagation

Questions

1. Which of the following leads to thrombosis?
A. Deactivated platelets.
B. Protein C
C. Protein S
D. Coagulation cascade

2. Which of the following belongs to Virchow triad?
A. Endothelial injury
B. Protein C
C. Protein S
D. All of the above.

3. Which of the following is a fate of thrombus?
A. Resolution
B. Propagation
C. Embolism
D. All of the above

4. A detached intravascular solid, liquid, or gaseous mass that is carried by the blood to a site distant from its point of origin. Is:
A. Embolus
B. Vessels
C. Blood
D. None of the above

5. Which of the following is not a type of embolus?
A. Air
B. Fat
C. Food
D. Pulmonary

6. During an X-ray of a 27 years old woman, fragments of hair where found in the lungs, this is most likely:
A. Air embolus
B. Amniotic fluid embolus
C. Fat embolus
D. Pulmonary embolus

7. 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

8. deep vein thrombosis (DVT) may lead to:
A. pulmonary infarction
B. renal infraction
C. brain infraction
D. peripheral infarctions

9. Decompression sickness → high risk of:
A. An air EMBOLISM
B. An AMNIOTIC FLUID EMBOLISM
C. A FAT EMBOLISM
D. Septic embolism

1.d/2.a/3.d/4.a/5.c/6.b/7.d/8.a/9.a

10. What substances dissolve fibrin?

A. Plasmin
B. Plasminogen
C. Thrombin
D. Factor XII

11. What are the lighter lines in the line of zahn?

A. Fibrin And Platelet
B. White Blood Cells
C. Fat
D. RBCs

12. What are the red lines in the line of zahn?

A. Red Blood Cells
B. Lymphocytes
C. Neutrophils
D. Fibrin And Platelet

13. What do the arterial thrombi look like?

A. Red And Friable
B. Gray-White And Friable
C. Red Taking The Shape Of The Artery
D. Non of the above

10.a/11.a/12..a/13.b

Match the following:

1) Intracardiac mural thrombi cerebrum or gangria
2) Caisson disease
3) Saddle embolus
4) Fractures of long bones
5) Obstetric procedures
6) Decompression sickness
7) Grecian Bend
8) Deep vein thrombosis
9) Complication of labor and the immediate postpartum period
10) Deep sea divers
11) Presence of squamous cells, lanugo hair, fat, and mucin in pulmonary circulation

A) Pulmonary thromboembolism
B) Systemic thromboembolism
C) Fat embolism
D) Air embolism
E) Amniotic fluid embolism

Answers:
1- B
2- D
3- A
4- C
5- D
6- D
7- D
8- A
9- E
10- D
11- E

CASES

1- 50-year-old man has sudden onset of severe substernal chest pain that radiates to the neck. Emergent coronary angiography shows a thrombotic occlusion of the left circumflex artery. Which of the following complications of this disease is most likely to occur within 1 hour of these events?

(A) Ventricular fibrillation

(B) Pericarditis

(C) Myocardial rupture

(D) Ventricular aneurysm

(E) Thromboembolism

2- A 60-year-old man has experienced angina on exertion for the past 6 years. A coronary angiogram performed 2 years ago showed 75% stenosis of the left anterior descending coronary artery and 50% stenosis of the right coronary artery. For the past 3 weeks, the frequency and severity of the anginal attacks have increased, and pain sometimes occurs even when he is lying in bed. Which of the following is most likely to explain these findings?

(A) Hypertrophy of ischemic myocardium with increased oxygen demands

(B) Increasing stenosis of right coronary artery

(C) Fissuring of plaque in left coronary artery with superimposed mural (partial) thrombosis

(D) Sudden complete thrombotic occlusion of right and left coronary arteries

(E) Reduction in oxygen-carrying capacity owing to pulmonary congestion

Q1) The answer is A

In the period immediately after coronary thrombosis, arrhythmias are the most important complication and can lead to sudden cardiac death. It is believed that, even before ischemic injury manifests in the heart, there is greatly increased electrical irritability.Pericarditis and rupture occur several days later.An aneurysm is a late complication of healing of a large transmural infarction; a mural thrombus may fill an aneurysm and become a source of emboli.If portions of the coronary thrombus break off and embolize, they enter smaller arterial branches in the distribution already affected by ischemia.

Q2) The answer is C

This patient has 75% stenosis of the left anterior descending branch of the coronary artery. This degree of stenosis prevents adequate perfusion of the heart when myocardial demand is increased, which occurs during exertion. The patient had angina on exertion. The patient has recently developed unstable angina, which is manifested by increased frequency and severity of the attacks and angina at rest. In most patients, unstable angina is induced by disruption of an atherosclerotic plaque followed by a mural thrombus and possibly distal embolization, vasospasm, or both. Hypertrophy of the heart is unlikely in this case because there is neither hypertension nor a valvular lesion. The remaining choices theoretically can give rise to a similar picture, but plaque disruption with mural thrombosis is the most common anatomic finding when the patient develops unstable angina. It is important to recognize this because unstable angina is a harbinger of myocardial infarction.

Males:

منصور العبرة : Leader-

خالد العقيلي

عبدالجبار اليماني

بندر الجماز

محمد المحيميد

راكان الغنيم

سليمان الزميع

طارق العلوان

أحمد الصبي

أنس السيف

تركي آل بنهار

خالد المطيري

سعد الفوزان

سعود الأحمري

سيف المشاري

عبدالعزيز العبدالكريم

عبدالله العبيدان

عبدالله السرجاني

فهد الفايز

محمد الأصفه

محمد بن معيوف

Females:

فاطمة بالشرف : Leader-

ريناد الغريبي

منيرة المسعد

شوق القحطاني

رزان الزهراني

الرحيمي بتول

فاطمة الديحان

الجوهرة الشنيفي

نورة القاضي

غادة الحيدري

مها العمري

غرام الجليدان

آلاء الصويغ

ال فهدة السليم

شيرين حمادي

رناد الفرم

نورة الحربي

ميعاد النفيعي

PATHOLOGY
TEAM 437

Kindly contact us if you have any questions/comments and suggestions:

* EMAIL: pathology437@gmail.com
* TWITTER : @pathology437

GOOD LUCK ! ☺

*references:
- Robbins Basic Pathology
- Slides

Pathology
teamwork