Pathology team 441

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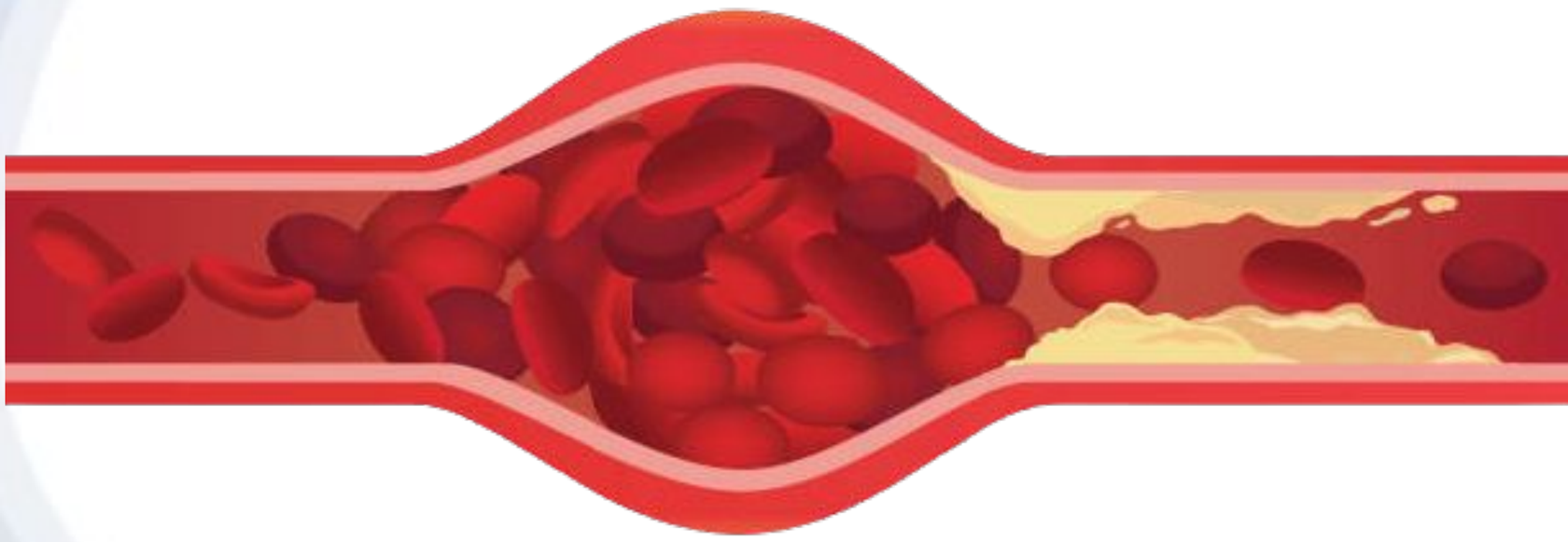
MED441
KING SAUD UNIVERSITY

# Thromboembolism



## Editing File

Color Index:

- Main text
- Important
- Boys slides
- Girls slides
- Dr's notes
- Extra

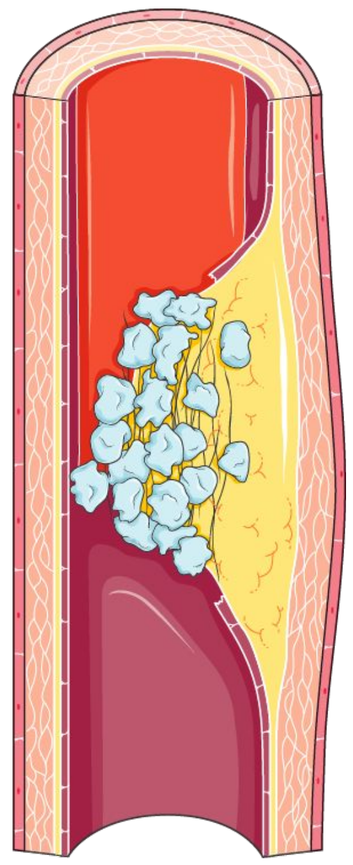
# Objectives

1. 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.
2. Pathological aspects of thrombogenesis: vessel wall abnormality, vascular stasis or turbulent flow and increased blood coagulability. Causes of thrombus and embolism formation.
3. Predisposing factors for deep vein thrombosis.
4. Pathology of pulmonary thrombo-embolism.
5. Brief description of other forms of emboli like: fat embolism, air embolism, atherosclerotic plaque embolism, amniotic fluid embolism, nitrogen embolism and infective endocarditis

# Definitions

## Thrombosis

- It is a process by which a thrombus is formed. It represents hemostasis in the intact vascular system.
- It is intravascular coagulation of blood and it often causes significant interruption to blood flow.



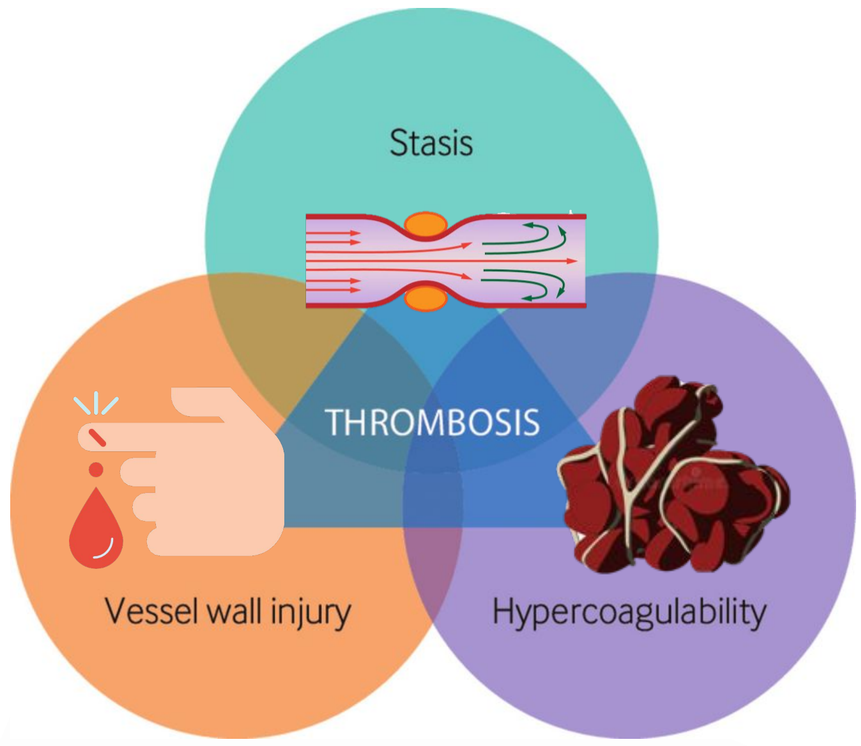
## Thrombus

is a solid mass (blood clot) made up of blood constituents which develops in artery or vein.

# Pathogenesis

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

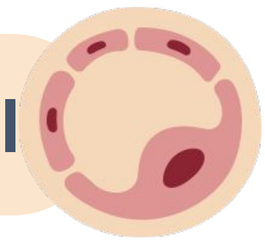
**(1) endothelial injury**
**(2) stasis or turbulence of blood flow**
**(3) blood hypercoagulability**




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

**component of the hemostatic process.**

## Endothelial cell



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

## Platelets

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

## 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)

**Definition**

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.

**Function**

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

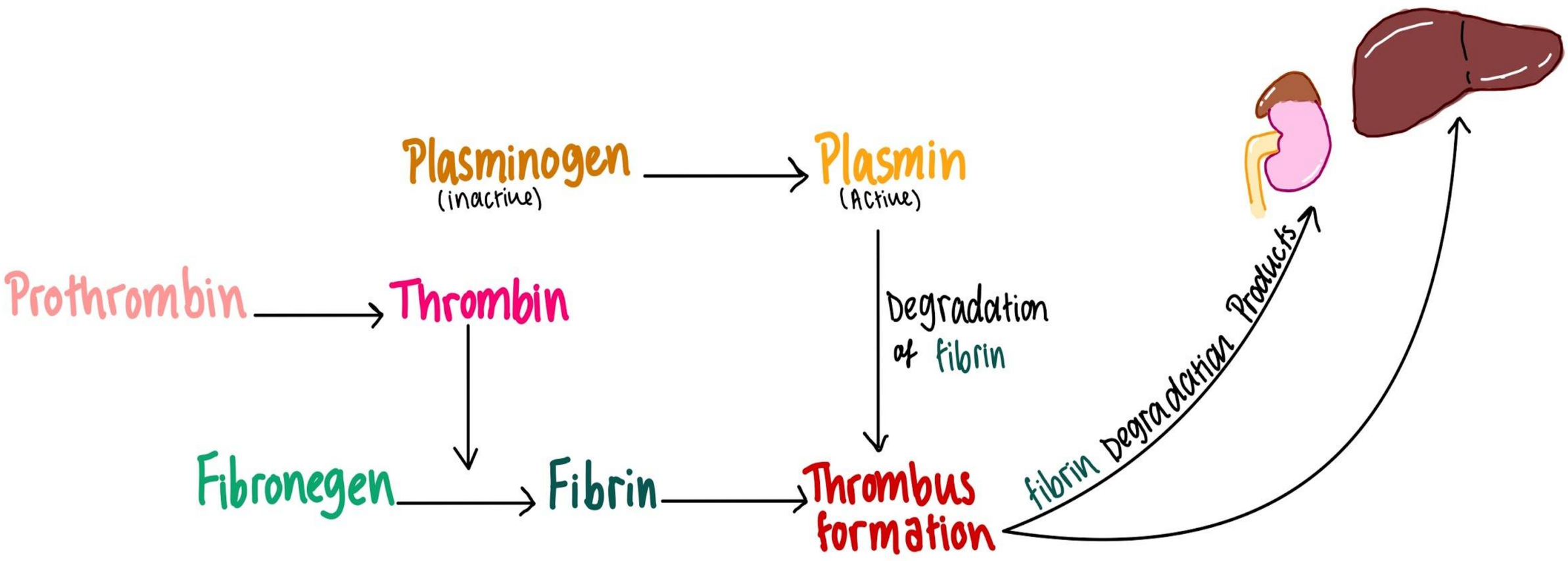
## Mechanism

**inactive proenzyme plasminogen**

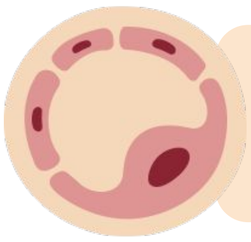
**Conversion**

**active plasmin**

**plasmin then splits the fibrin in the thrombus.**
The thrombus is dissolved by plasmin.



# Virchow Triad



## Endothelial cells

**Definition**

The endothelium is a single cell thick lining of endothelial cells and it is the inner lining of the entire cardiovascular system (arteries, veins and capillaries) and the lymphatic system.

**Location**

It is in direct contact with the blood/lymph and the cells circulating in it.

**Importance**

Endothelial structural and functional integrity is fundamental to the maintenance of vessel wall homeostasis and normal circulatory function.

## Endothelial injury

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

**conditions lead to chronic subtle endothelial dysfunction/injury**

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

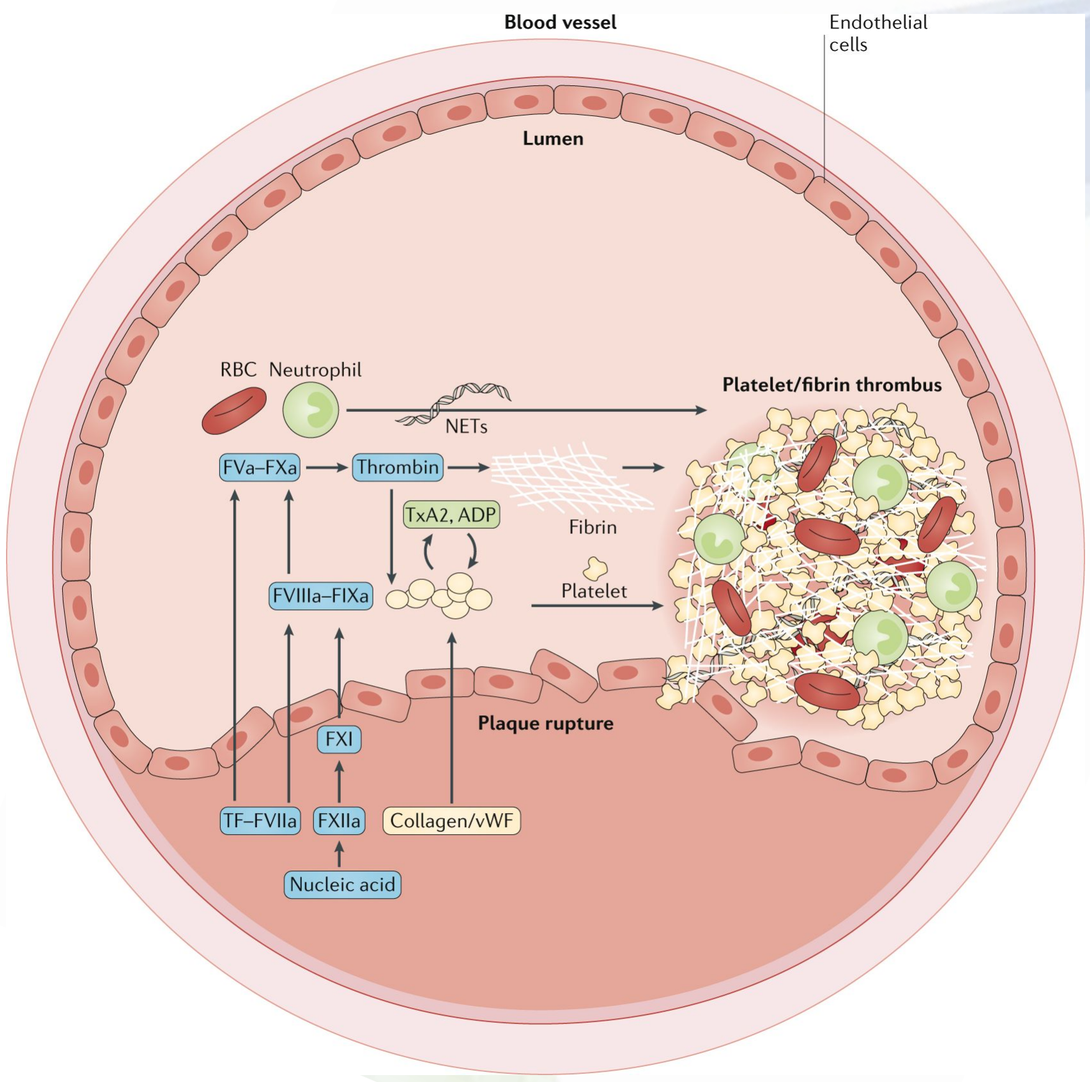
**NOTE**

**Endothelial injury can contribute to thrombosis in several clinical settings e.g:**

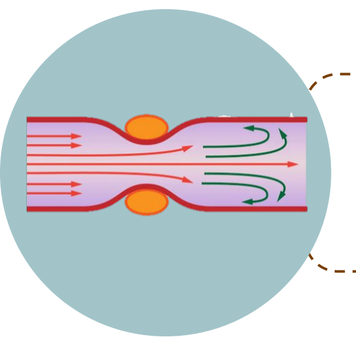
- Endocardial injury due to myocardial infarction
- Ulcerated plaques in atherosclerotic arteries
- Traumatic or inflammatory vascular injury

**Endothelial injury leads to:**

- Exposure of subendothelial ECM i.e : the basement membrane
- Adhesion of platelets
- Release of tissue factor and ultimately thrombosis



# Virchow Triad



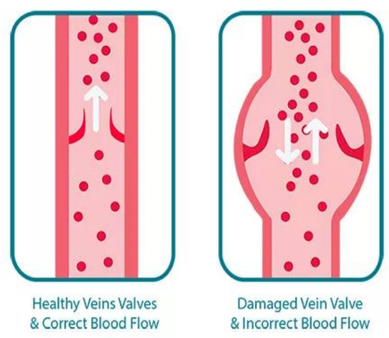
## Stasis or turbulence of blood flow

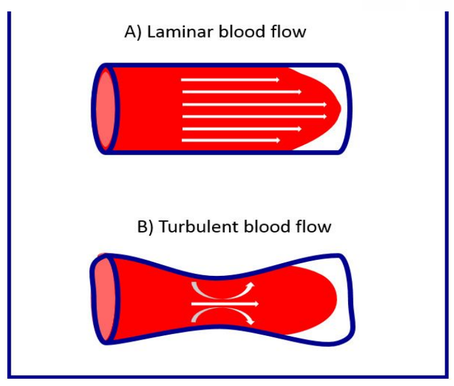
**Definition**

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




**NOTE**

**Abnormal blood flow contributes to thrombosis in several clinical settings**

- Ulcerated atherosclerotic plaques
- Abnormal aortic and arterial dilations
- Acute myocardial infarction
- Mitral valve stenosis
- Hyperviscosity syndromes
- Sickle cell anemia

## Blood hypercoagulability

**Definition**

Any change of the coagulation pathways that predisposes to thrombosis.

| Primary/Genetic | Secondary/acquired states |
|---|---|
| (e.g. mutation in factor V gene or prothrombin gene, anti-thrombin III deficiency, protein C or S deficiencies, or fibrinolysis defects. | **High risk for thrombosis**<br>• Prolonged bed rest or immobilization<br>• Myocardial infarction, Atrial fibrillation<br>• Tissue damage (surgery, fracture, burns)<br>• Cancer<br>• Prosthetic cardiac valves<br>• Disseminated intravascular coagulation<br>• Heparin-induced thrombocytopenia<br>• Antiphospholipid antibody syndrome (lupus anticoagulant syndrome)<br>**Lower risk for thrombosis**<br>Cardiomyopathy, Nephrotic syndrome, Hyperestrogenic states (pregnancy), Oral contraceptive use, Sickle cell anemia, Smoking. |

# Thrombotic disorders

## 1- Anti-thrombotic (hemorrhagic)

leading to pathologic bleeding states such as
hemophilia, Christmas disease and von Willebrand disease.

## 2- Prothrombotic

le ıding to hypercoagulability with pathologic thrombosis e.g. hereditary thrombophilia and antiphospholipid antibody syndrome.

| | Hereditary Thrombophilia | Antiphospholipid antibody syndrome |
|---|---|---|
| **Definition** | Is a **prothrombotic** familial syndrome. | Is a **prothrombotic** hypercoagulable autoimmune multisystem disorder caused by the presence of antiphospholipid antibodies. |
| **characteristic** | Characterized by recurrent venous thrombosis and thromboembolism | Is characterized by recurrent thrombosis and embolism and fetal loss in pregnancy. |
| **others** | • **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).<br>• Can be caused by deficiency of antithrombotic proteins e,g. antithrombin 3, protein C, and protein S. | • Patients have prolonged partial thromboplastin time (PTT).<br>• It is sometimes associated Systemic Lupus Erythematosus and so this antibody is also known as lupus anticoagulant. |

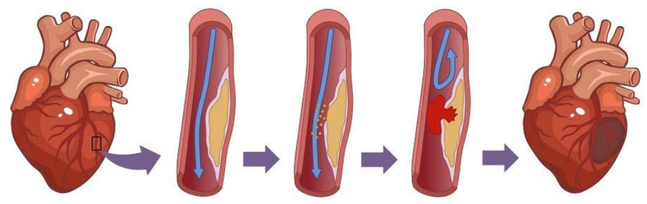
## 3-DISSEMINATED INTRAVASCULAR COAGULATION

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

# Morphology of Thrombus

1 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.

2 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.

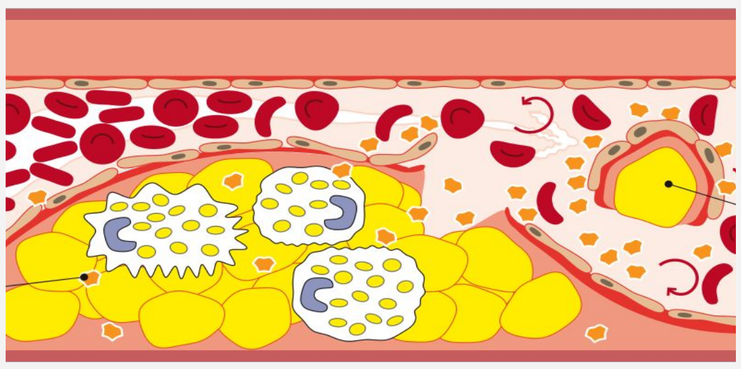


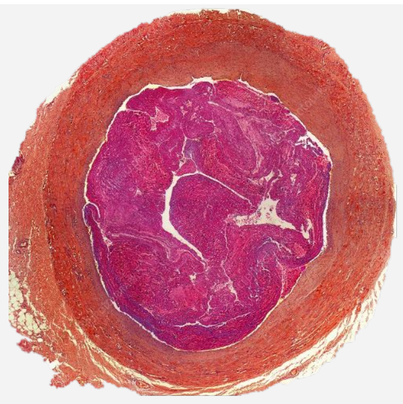

3 The propagating tail of either thrombi may not be well attached (particularly in veins) is prone to fragmentation, creating an embolus

4 Arterial thrombi grow in a retrograde direction from the point of attachment (i.e. toward the heart). Venous thrombi extend in the direction of blood flow (i.e. toward the heart).

5 A thrombus is made up of

- Fibrin
- platelets
- red blood cell
- few inflammatory cells

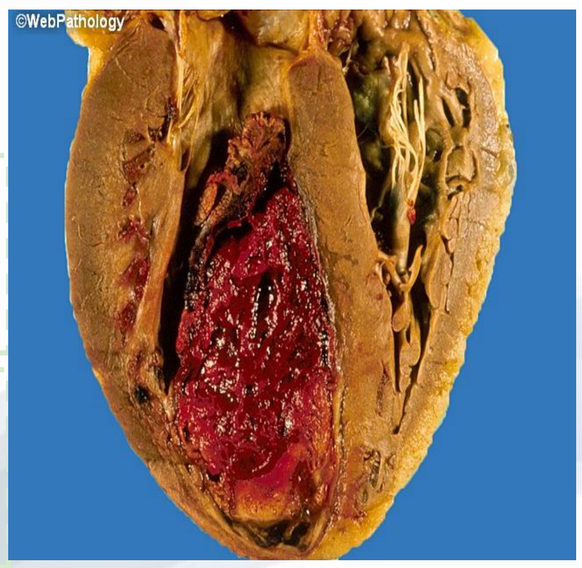




## Mural Thrombus

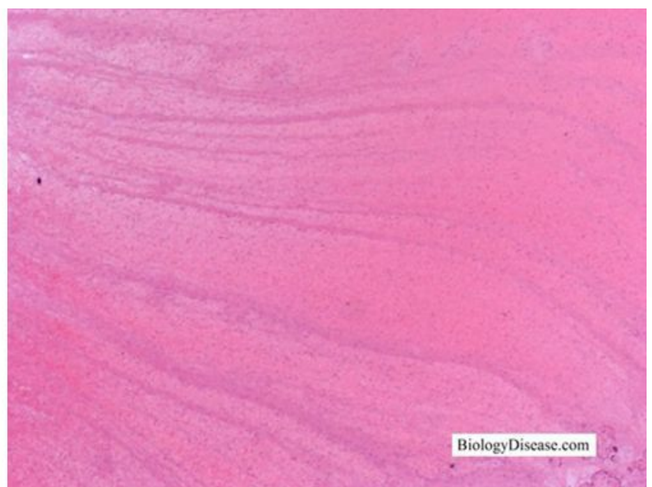
**Definition** When arterial thrombi arise in heart chambers or in large blood vessels such as the aortic lumen

**Cause** Abnormal myocardial contraction or endomyocardial injury promotes cardiac mural thrombi.




## Lines of Zahn

Thrombi formed in the heart or aorta may have apparent laminations, called **lines of Zahn** seen grossly (and microscopically). Lines of Zahn are produced by alternating pale layers of platelets admixed with some fibrin and darker layers containing more red cells.

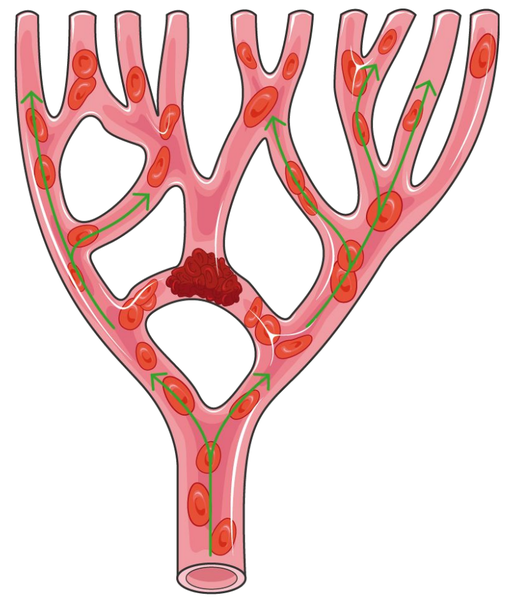




Looks like the wave rock in Arizona

# Clinical effects of thrombosis

**Thrombi are significant because**

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



**Clinical effects depend 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.

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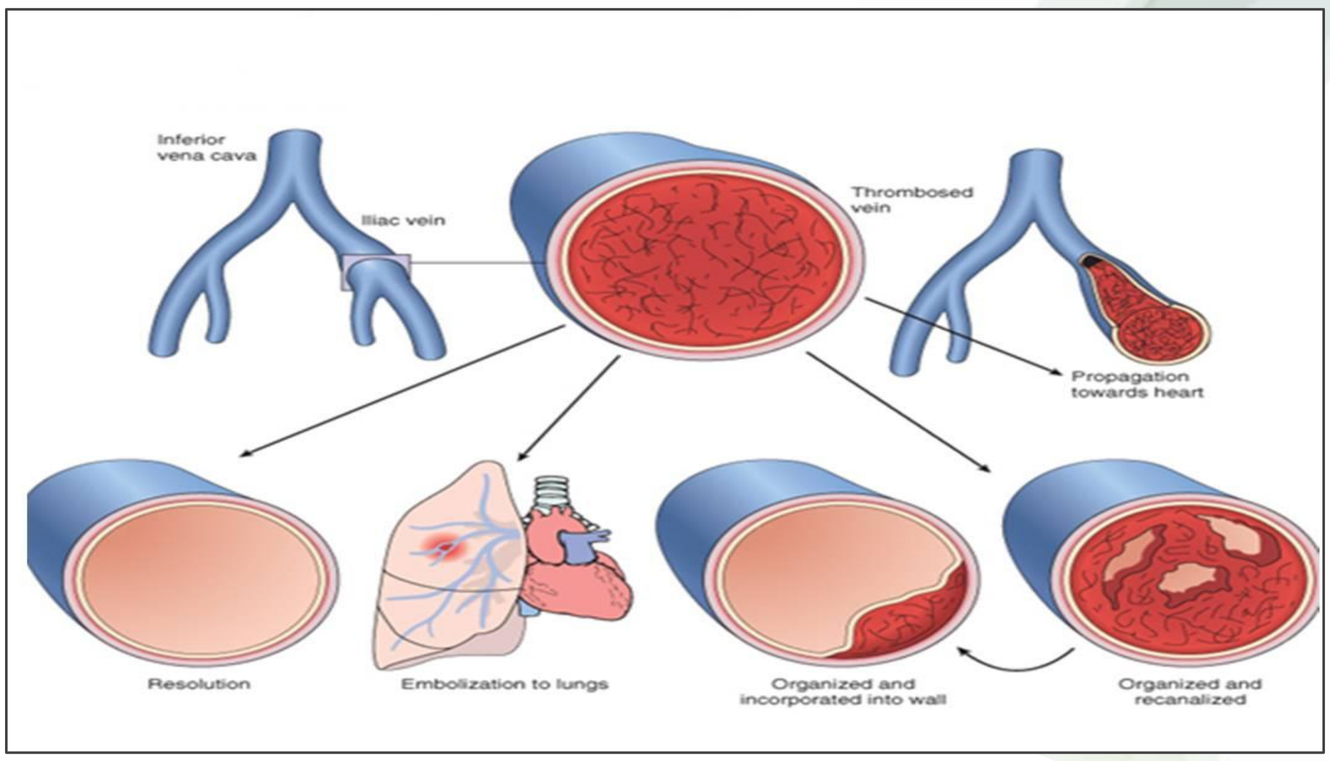
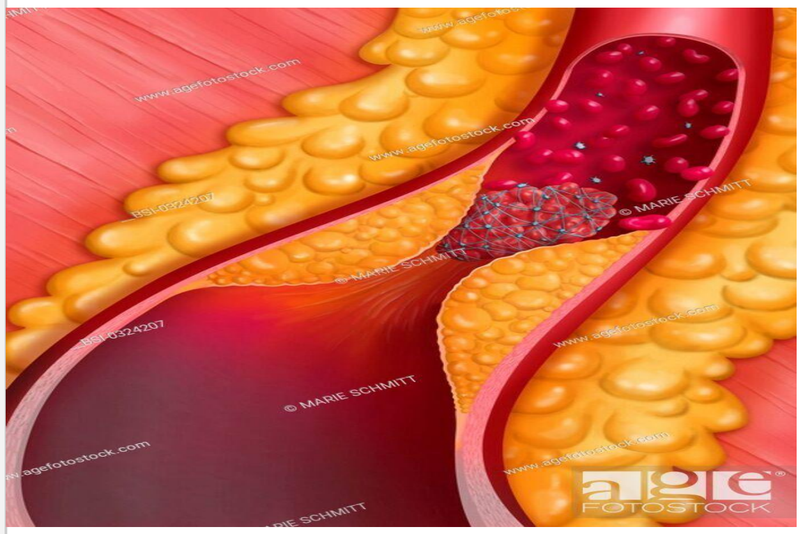
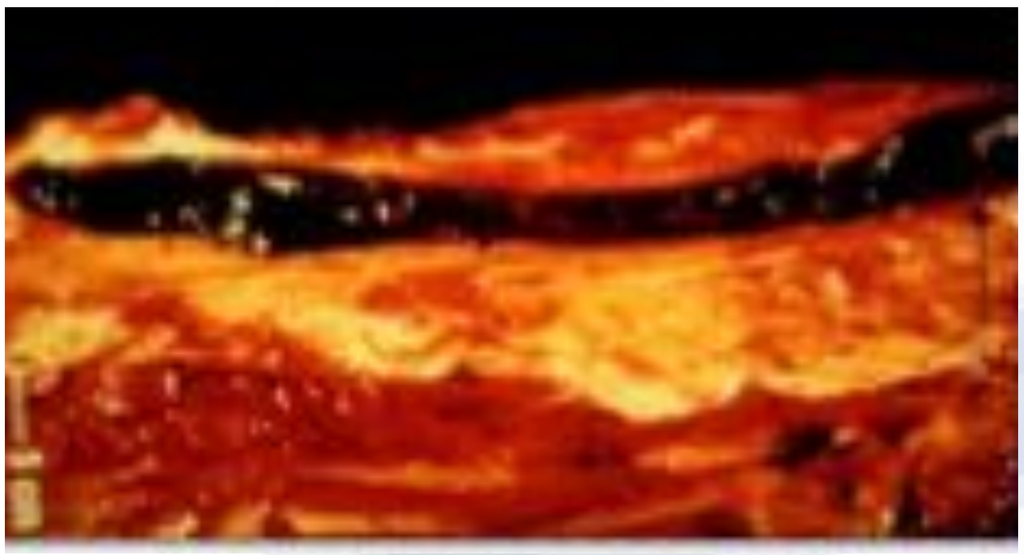
## FATE OF THROMBUS

1. **Resolution**
2. **Propagation**
3. **Embolism**
4. **Organization and recanalization**
5. **Organization and incorporation into the wall**



# Types of Thrombus

| | 1.Arterial Thrombi | 2.Venous Thrombi<br>Also called **phlebothrombosis** |
|---|---|---|
| **Nature** | Usually **occlusive** | almost invariably occlusive, and often takes the **shape of the vein** |
| **Location** | Usually superimposed on an **atherosclerotic plaque** and are firmly adherent to the injured arterial wall. | Because these thrombi form in a relatively static environment, they contain more enmeshed erythrocytes and are therefore known as **red**, or **statis thrombi.** |
| **Most common affected sites** | In descending order,are 1-**coronary**,2-**cerebral** ,3- **femoral arteries**. | The veins of the **lower extremities** (90% of cases) |
| **Gross appearance** | **Gray-white friable**<br>  | Red<br>  |

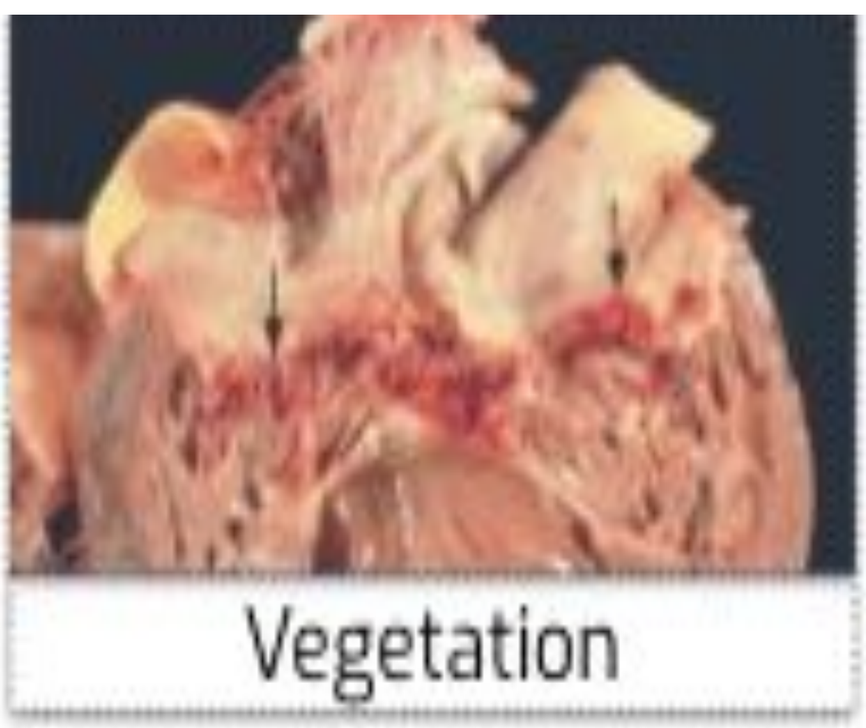
# Types of Thrombus

## 3. Thrombi on Heart Valves

-Also called **Vegetations**.

### Infective vegetations

**Infective endocarditis:**
Bacterial or fungal blood-borne infections may result in the development of large thrombotic masses on heart valves.



Vegetation

### sterile vegetations

**Non-bacterial thrombotic endocarditis:**
Is non-infective vegetations on valves in patients with:

- **hypercoagulable states**
- **subtle endothelial abnormalities**
- **malignancy and other debilitating diseases.**
- patients with **systemic lupus erythematosus** can have noninfective, verrucous **(Libman-sacks) endocarditis**

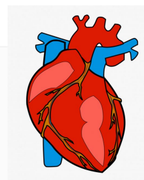
# Deep vein thrombosis (DVT) & Thrombophlebitis

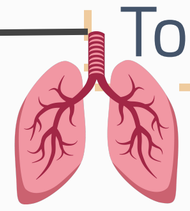
## Definition

**Deep vein thrombosis is a venous thrombosis that arises in the deep veins of the legs.** They occur with stasis or in hypercoagulable states.
Often associated **with inflammation** and then it is termed **thrombophlebitis**.

## Complications

**Deep vein thrombosis** → **Embolize** → Travels to the right side of the heart → To the lungs → **Pulmonary embolism** with resultant pulmonary infarct.



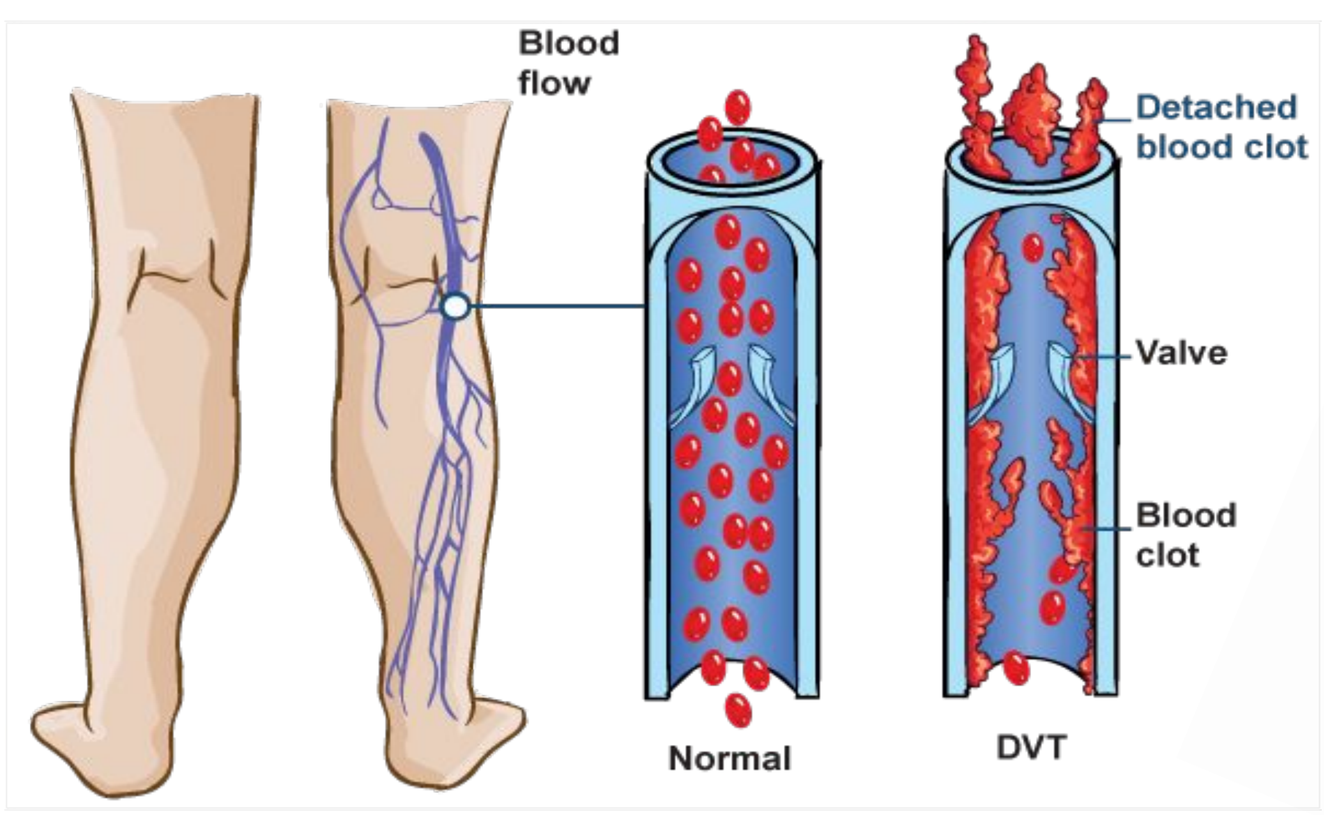


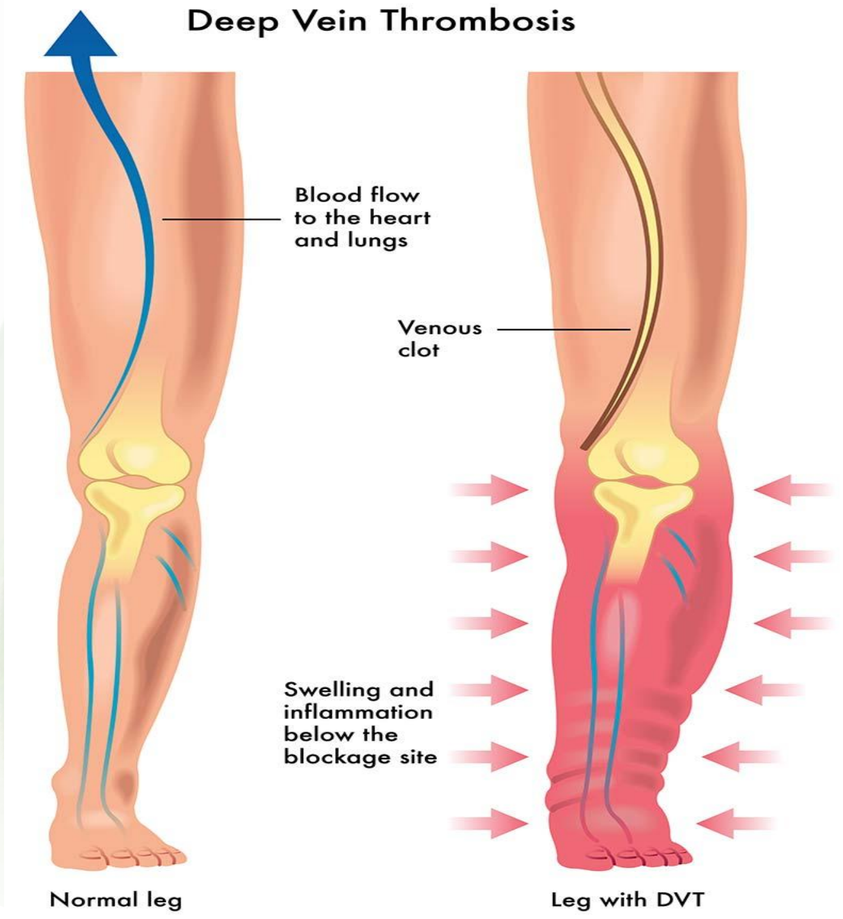
## Clinical features

DVTs are **asymptomatic** in approximately 50% of affected individuals.

## Site

common in deep the larger leg veins at or above the knee
(e.g. Popliteal, femoral, and iliac veins)



common
**predisposing factors**
for DVT
(Same as factors predisposing to hypercoagulable state)

**Bed rest and immobilization**

**Trauma, surgery, and burns**

congestive heart failure
(A cause of impaired venous return)

**Tumors**

**Advanced age**

**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

## Postmortem clots

At autopsy postmortem clots  may be confused for venous thrombi.

| Postmortem clots | Red thrombi |
|---|---|
| Are gelatinous. | Are firmer |
| They have a **dark red dependent portion** where red cells have settled by gravity and a **top layer of yellow** fat supernatant resembling melted and clotted chicken fat. | On cut sections reveal vague strands of pale gray fibrin. |
| They are **not attached** to the underlying wall. | Almost always **have a point of attachment.** |

# Embolism

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

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

1

2

3

4

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

## Pulmonary embolism

| | |
|---|---|
| **Site of lodging & occlusion** | Pulmonary vasculature<br>1. Depending on the size: occlude main pulmonary artery, or impact across the bifurcation **(saddle embolus)** or pass out into smaller, branching arterioles of the pulmonary circulation.<br>2. **Paradoxical embolism:** embolus may pass through interatrial or interventricular defect to gain access to the systemic circulation. |
| **Complications** | • Most (60-80%) are clinically silent because they are small.<br>• When **more than 60%** of the pulmonary circulation is obstructed by emboli. Sudden death, infarction, right heart failure (cor pulmonale) occurs. |

## Systemic thromboembolism (arterial emboli)

| | |
|---|---|
| **Site of lodging & occlusion** | - Arterial circulation<br>- Major sites are the lower extremities (75%) and the brain (10%).<br>- Most arise from the **intracardiac mural thrombi (80%).** |
| **Complications** | consequences 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.<br>• Causes infarction of tissues supplied by the artery. |

# Fat embolism

**Site of lodging & occlusion**

- 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 embolus..

**Complications**

- Less than 10% of patients have any clinical findings.
- Fat embolism syndrome is characterized by pulmonary insufficiency, neurologic symptoms, anemia, and thrombocytopenia.

# Amniotic fluid embolism

**Site of lodging,occlusion & characteristics**

- Uncommon and grave 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.
- Microscopy: presence in the pulmonary microcirculation of squamous cells shed from fetal skin, fetal hair, fetal fat,etc.
- Characterized by sudden severe dyspnea, cyanosis, and hypotensive shock, followed by seizures and coma.
- Marked pulmonary edema and diffuse alveolar damage are also present. Systemic fibrin thrombi indicative of DIC can also be seen.

**Complications**

- If the patient survives the intial crisis, pulmonary edema develops, along with disseminated intravascular coagulation, owing to release thrombogenic substances from amniotic.

# Air embolism

**Site of lodging & occlusion**

- 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.

**Complications**

An excess of 100 cc is required to have a clinical effect .

e.g.:

- Decompression sickness.

# Decompression Sickness

**Causes**

Occurs when individuals are exposed to sudden changes in atmospheric pressure.

- 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) to rapidly,

**Risk**

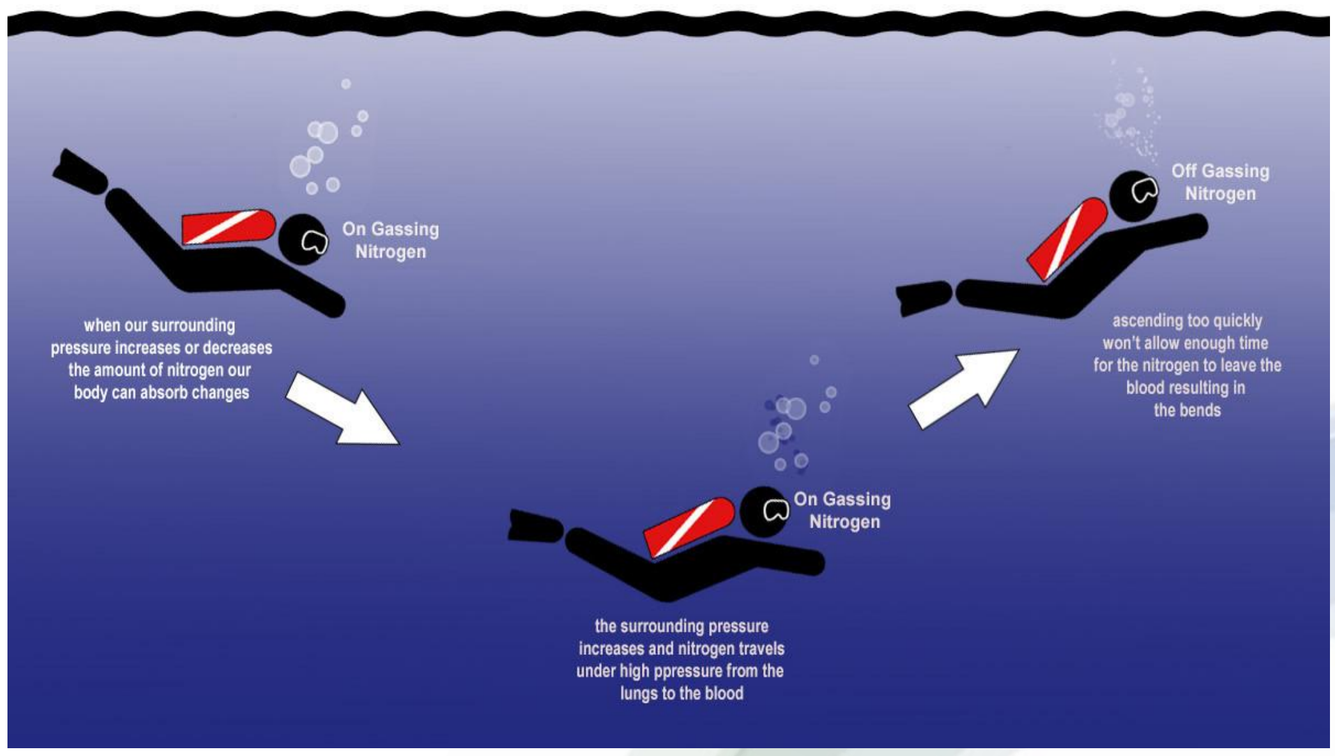
- High for scuba and deep sea divers, underwater construction workers, and individuals in unpressurized aircraft in rapid ascent

**Symptoms**

’ ‘Bends‘ i.e. joint/muscle and ‘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.




A more chronic 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 hemuri.

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Maisa Alaql

Faisal alshuaibi
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