

# Thromboembolism

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REFERENCE: ROBBINS & COTRAN PATHOLOGY AND RUBIN'S PATHOLOGY

# Lecture outline

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

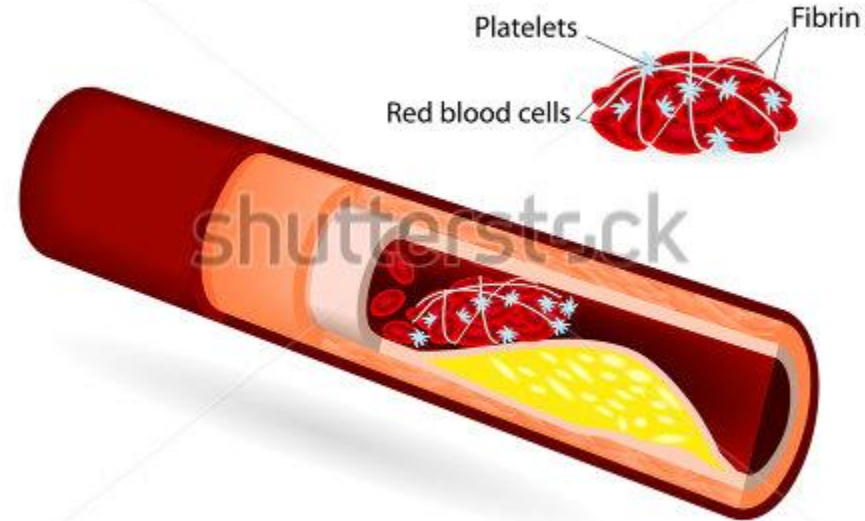
# Thrombosis

It is a process by which a thrombus is formed. It represents hemostasis in the intact vascular system.

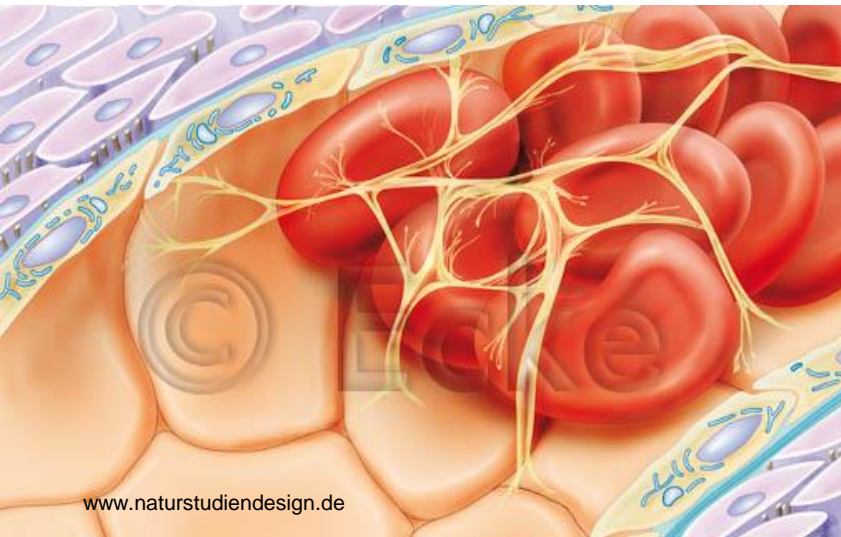
A thrombus is a solid mass (blood clot) made up of blood constituents which develops in artery or vein.

It is intravascular coagulation of blood and it often causes significant interruption to blood flow.

## THROMBUS



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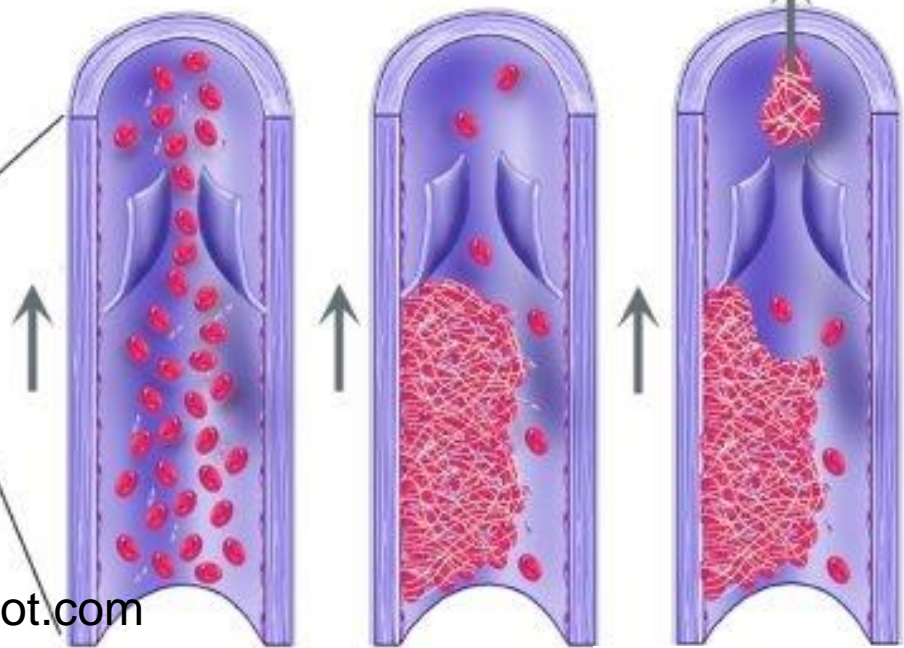
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(aortic thrombus)

Normal Blood Flow

Deep Vein Thrombosis

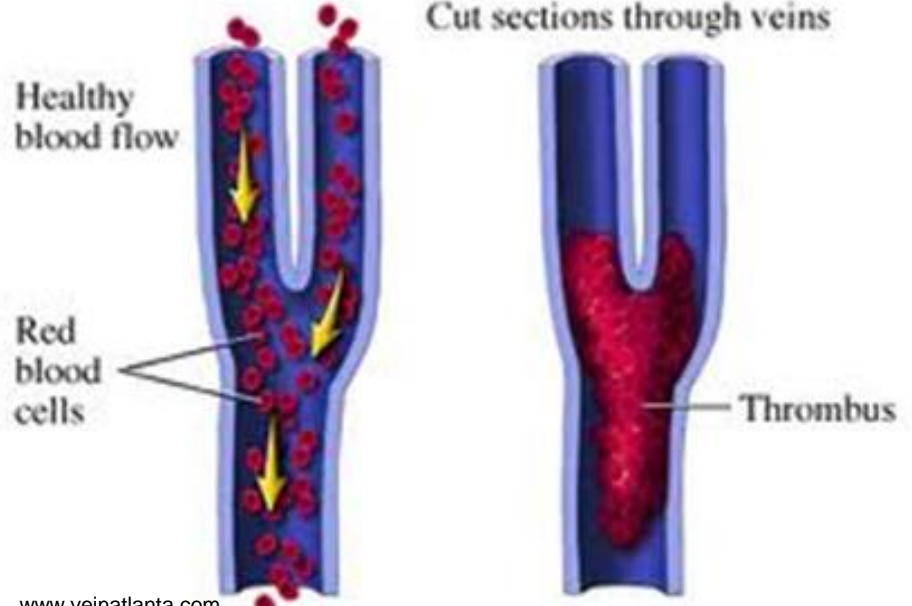
Embolus

Deep Veins of the Leg



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Cut sections through veins



# Pathogenesis

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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.

# Few components of the hemostatic process

- **Platelets** maintain the integrity of the vascular endothelium and participate in endothelial repair through the contribution of PDGF. They form platelet plugs and **promote the coagulation cascade** through the platelet phospholipid complex.
- **Endothelial cells** are resistant to the thrombogenic influence of platelets and coagulation proteins. **Intact endothelial cells oppose coagulation** after injury. They are thromboresistant.
- **Coagulation Cascade** is a **major contributor to thrombosis**. It is a series of enzymatic conversions, turning inactive proenzymes into activated enzymes and resulting 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, and it also triggers the fibrinolytic cascade that limits the size of the final clot. It runs concurrently with thrombogenesis. Fibrinolytic cascade 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 inactive proenzyme plasminogen is converted to active plasmin. **Plasmin then splits fibrin**

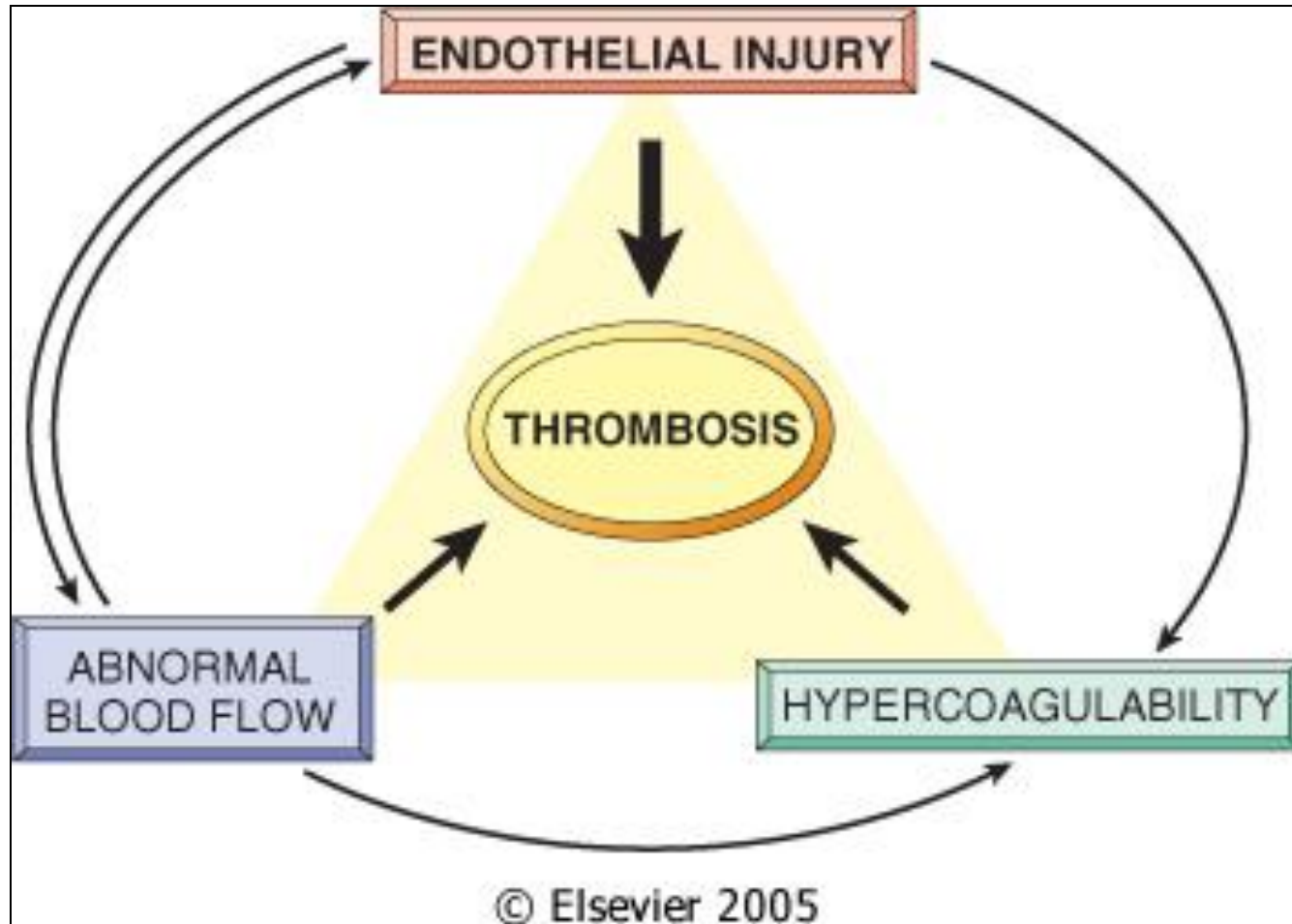


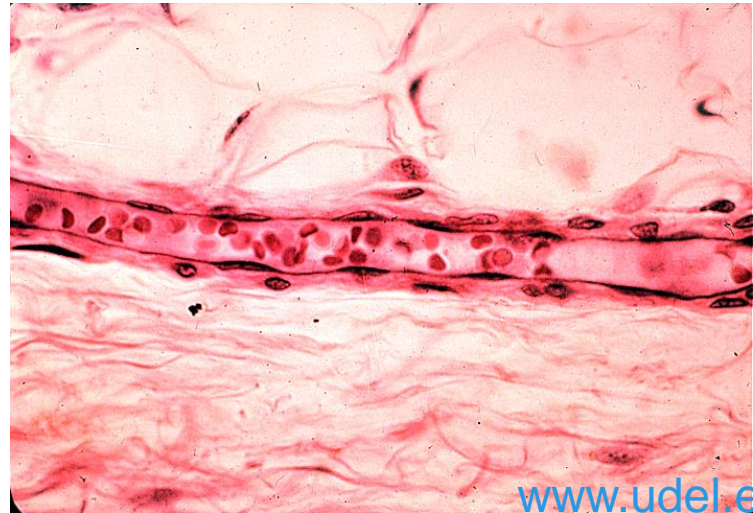
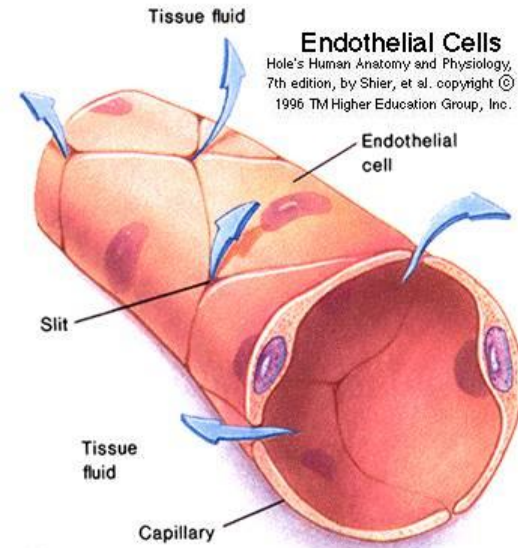
Figure 4-13 Virchow triad in thrombosis. Endothelial integrity is the single most important factor. Note that injury to endothelial cells can affect local blood flow and/or coagulability; abnormal blood flow (stasis or turbulence) can, in turn, cause endothelial injury. The elements of the triad may act independently or may combine to cause thrombus formation.

# *ENDOTHELIAL CELLS*

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.

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

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





# 1) Endothelial Injury

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❖ 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 endothelial dysfunction/injury:

➤ Hypertension

➤ Scarred valves

➤ Bacterial endotoxins

➤ Radiation

➤ Hypercholesterolemia

➤ Cigarette smoking

## 2) Abnormal Blood Flow

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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
- Hyperviscosity syndromes
- Sickle cell anemia

# 3) Hypercoagulability

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Definition: Any change of the coagulation pathways that predisposes to thrombosis

Hypercoagulability can be divided into:

- Primary (inherited) hypercoagulable states
- Secondary (acquired) hypercoagulable states

# Hypercoaguable States

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Hypercoagulable states can be

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).
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
    - Prosthetic cardiac valves
    - Disseminated intravascular coagulation
    - Heparin-induced thrombocytopenia
    - Antiphospholipid antibody syndrome (lupus anticoagulant syndrome)
  - b) **Lower risk for thrombosis**

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

# Thrombotic disorders

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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.

# Hereditary Thrombophilia

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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.

**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

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Is a **prothrombotic** disorder characterized by autoantibodies directed against a number of protein antigens that form complexes with phospholipids

Is characterized by recurrent venous and arterial thromboembolism, fetal loss, thrombocytopenia and a variety of neurological manifestations.

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

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



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



# Morphology of thrombus (cont.)

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A thrombus is made up of fibrin, platelets and red blood cell and few inflammatory cells.

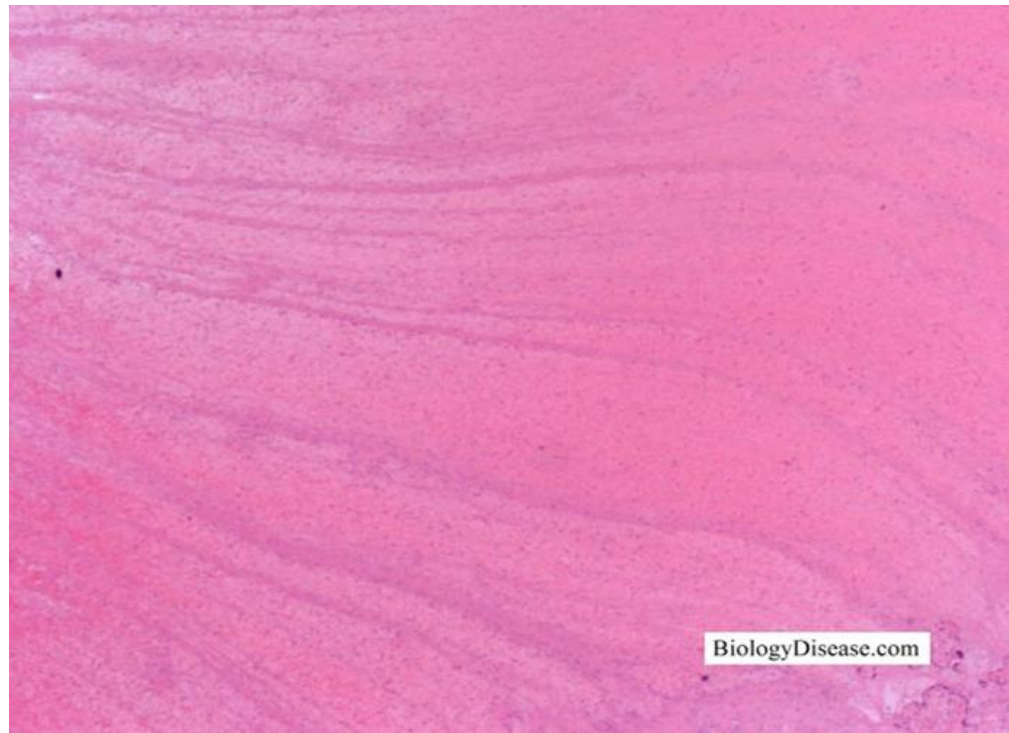
When formed in the heart or aorta, thrombi may have grossly (and microscopically) apparent laminations, called **lines of Zahn**; these are produced by alternating pale layers of platelets admixed with some fibrin and darker layers containing more red cells.

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.



# Lines of Zahn

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# Arterial thrombi

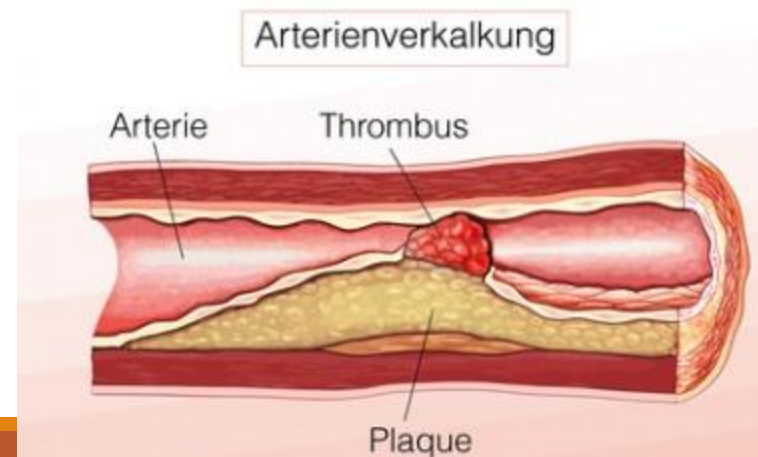
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are usually **occlusive**

most common sites in descending order, are coronary, cerebral, and 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.



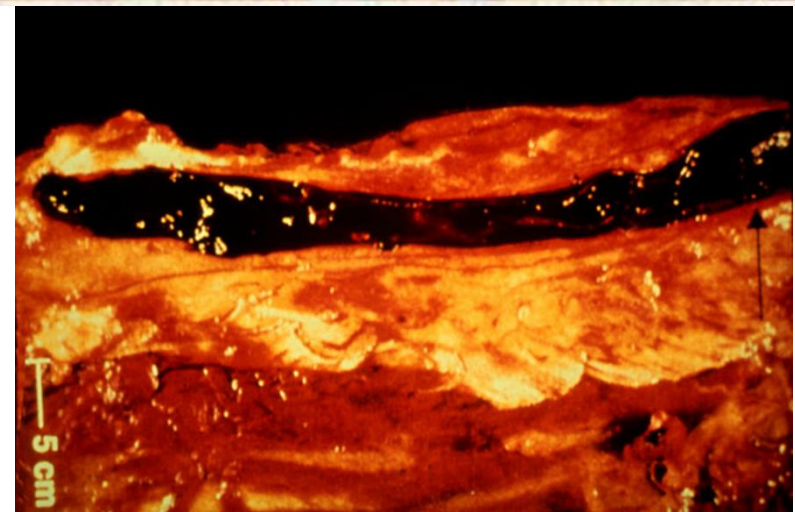
# Venous thrombosis

Also called **phlebothrombosis**, is 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 (90% of cases).



# Postmortem clots

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

Postmortem 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.

# Thrombi on Heart Valves

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Thrombi on Heart Valves are called as vegetations.

**Are infective or sterile:**

1) **Infective vegetations:** 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, patients with systemic lupus erythematosus can have noninfective, **verrucous (Libman-Sacks) endocarditis**.

# Fate of Thrombus

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Resolution

Propagation

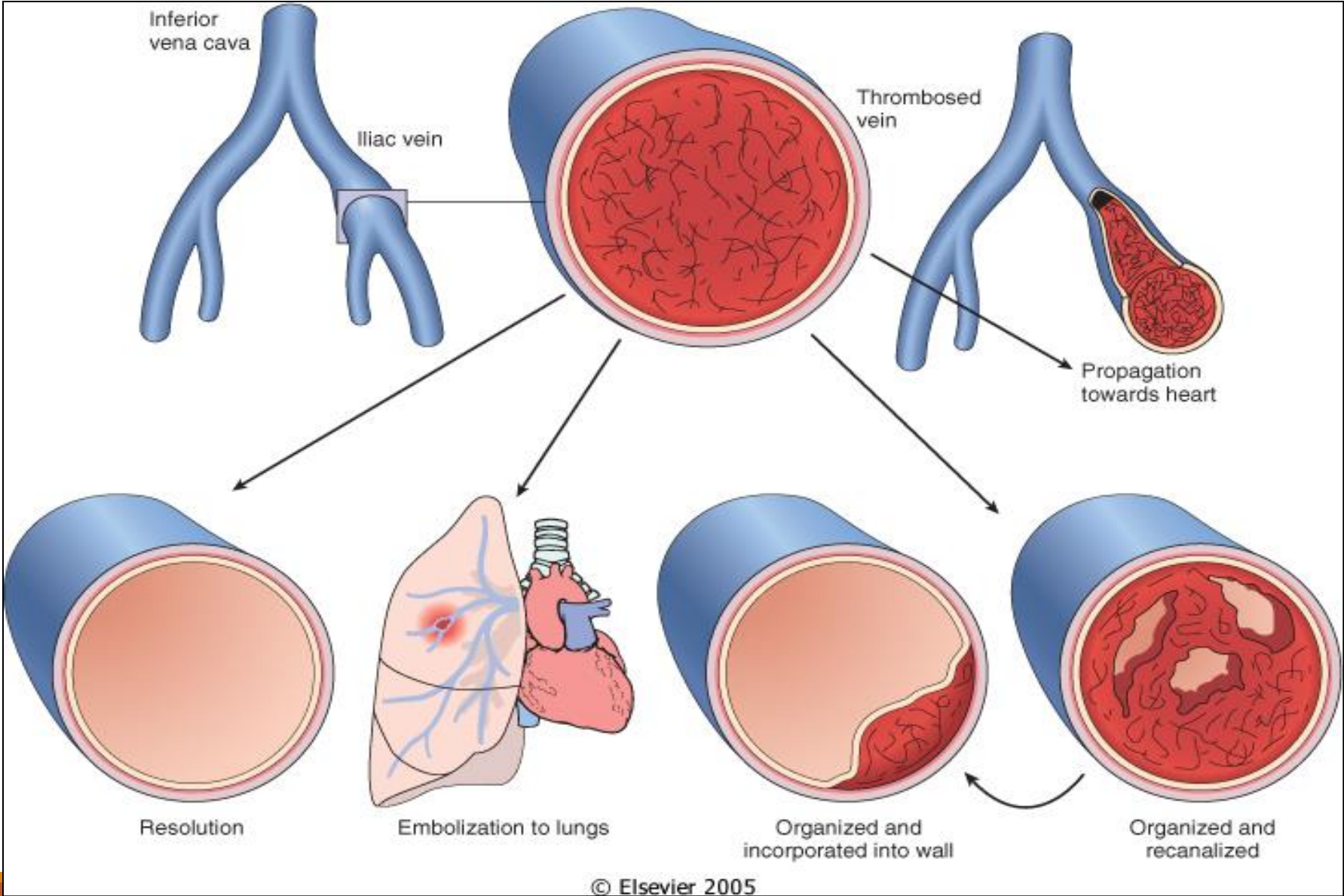
Embolism

Organization and recanalization

Organization and incorporation into the wall.

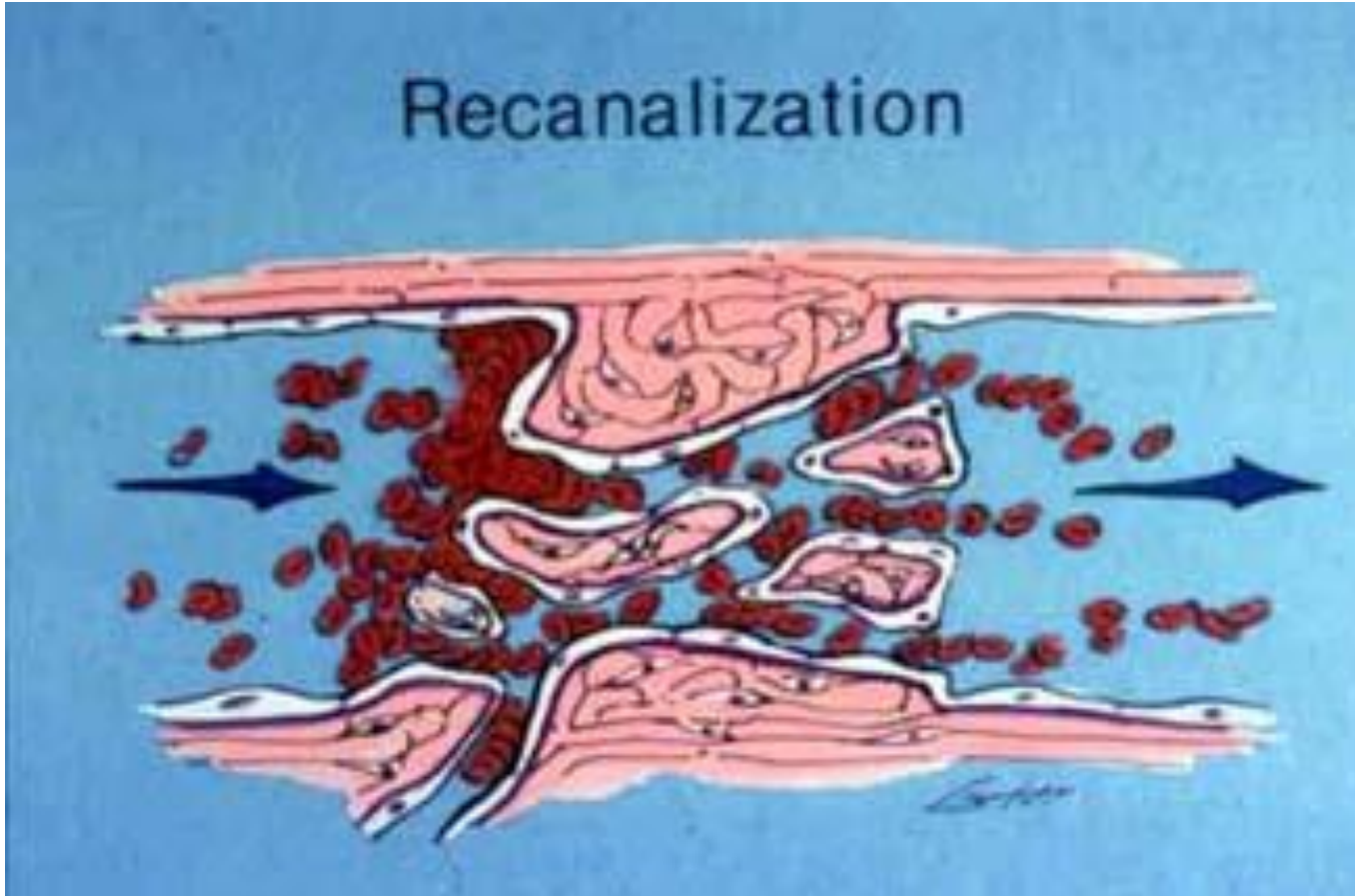


# Fate of thrombus



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# Recanalization



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# Deep vein thrombosis & Thrombophlebitis

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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

DVT may embolize to the lungs giving rise to pulmonary embolism with resultant pulmonary infarct.

- *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.



# Deep vein thrombosis

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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**

# Clinical effects of thrombosis:

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It depends on the site of thrombosis.

Thrombi are significant because:

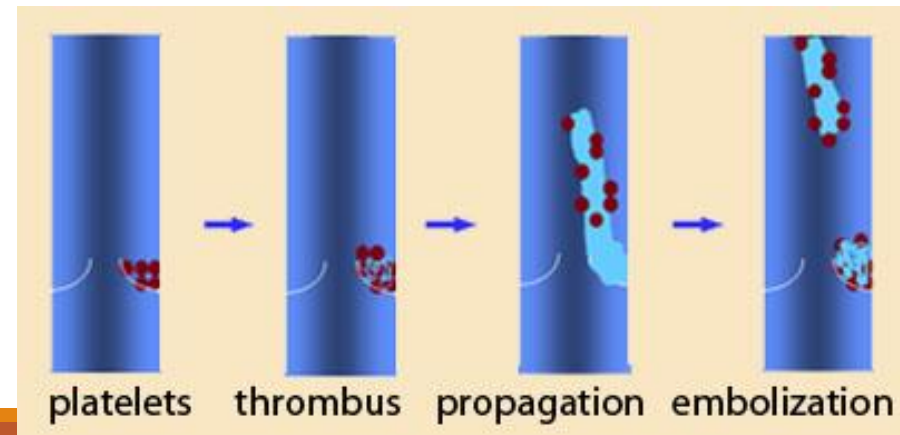
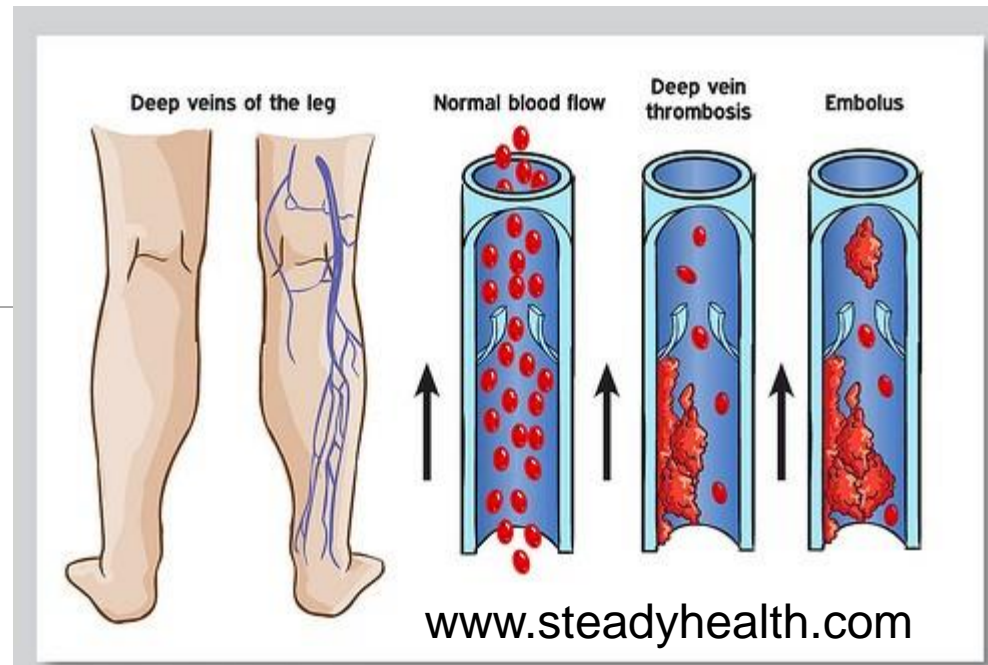
- They cause obstruction of arteries and veins
- They are potential sources of emboli

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.

# 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. Emboli impaction cause partial or complete vascular occlusion.



# Types of embolism

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Pulmonary thromboembolism

Systemic thromboembolism

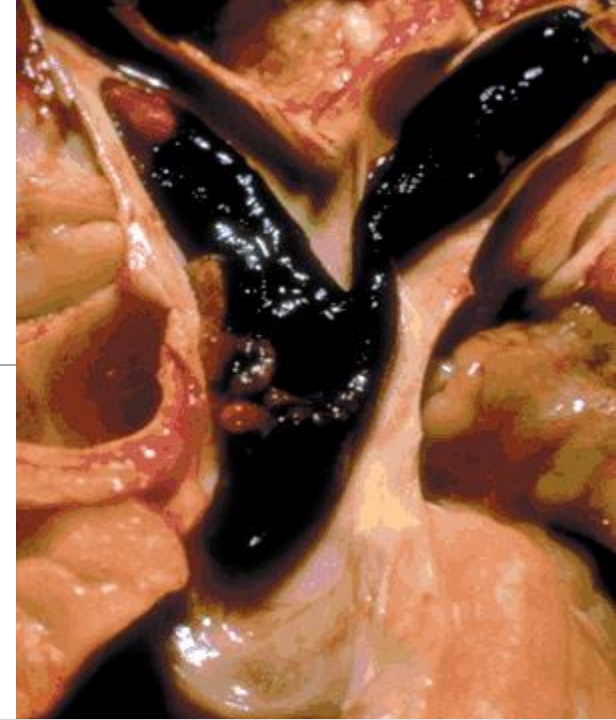
Fat embolism

Air embolism

Amniotic fluid embolism

# PULMONARY THROMBOEMBOLISM

- Here the embolus get lodged in the pulmonary vasculature.
- Depending on size of embolus, it may occlude main pulmonary artery, or impact across the bifurcation (*saddle embolus*), or pass out into the smaller, branching arterioles of the pulmonary circulation.
- Rarely, embolus may pass through an interatrial or interventricular defect to gain access to the systemic circulation (*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.







# SYSTEMIC THROMBOEMBOLISM

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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%).

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

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- 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

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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.

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.
- 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.

# *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.

