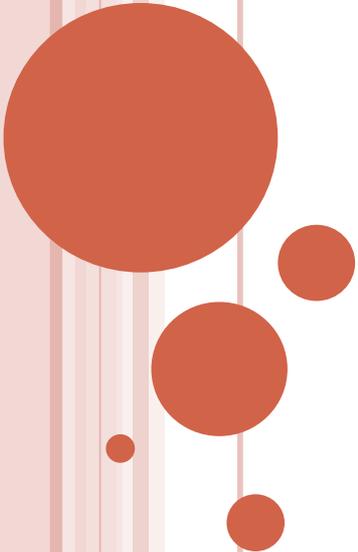
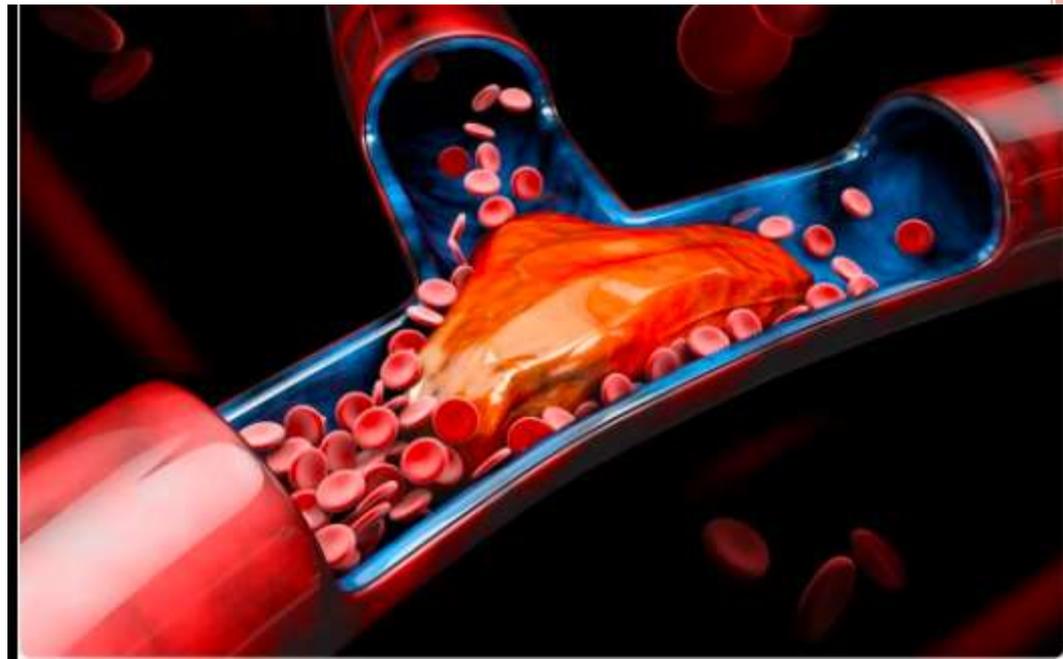
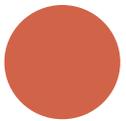
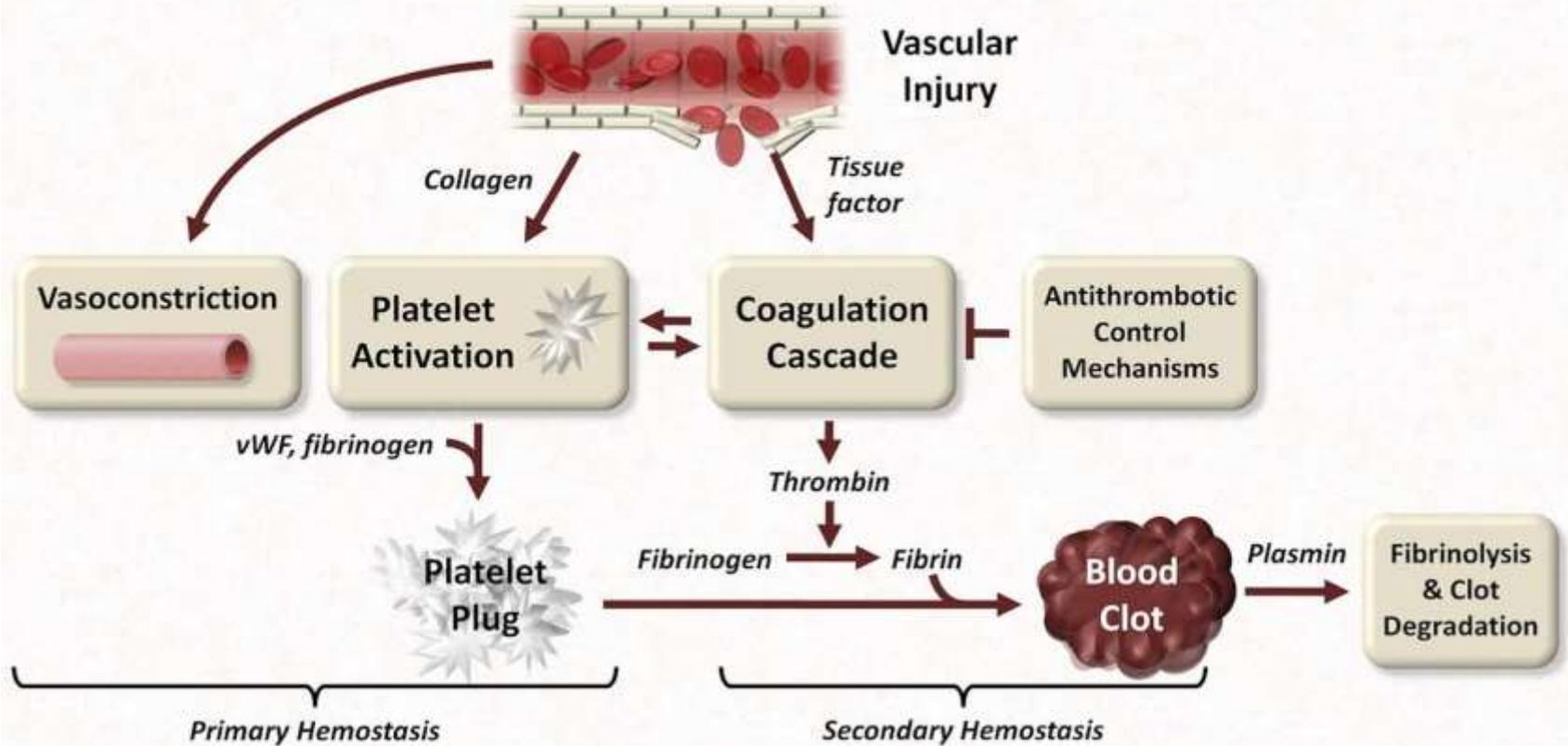


# THROMBOSIS

Izzat Al Jaber, M.D



# Major Components of Hemostasis

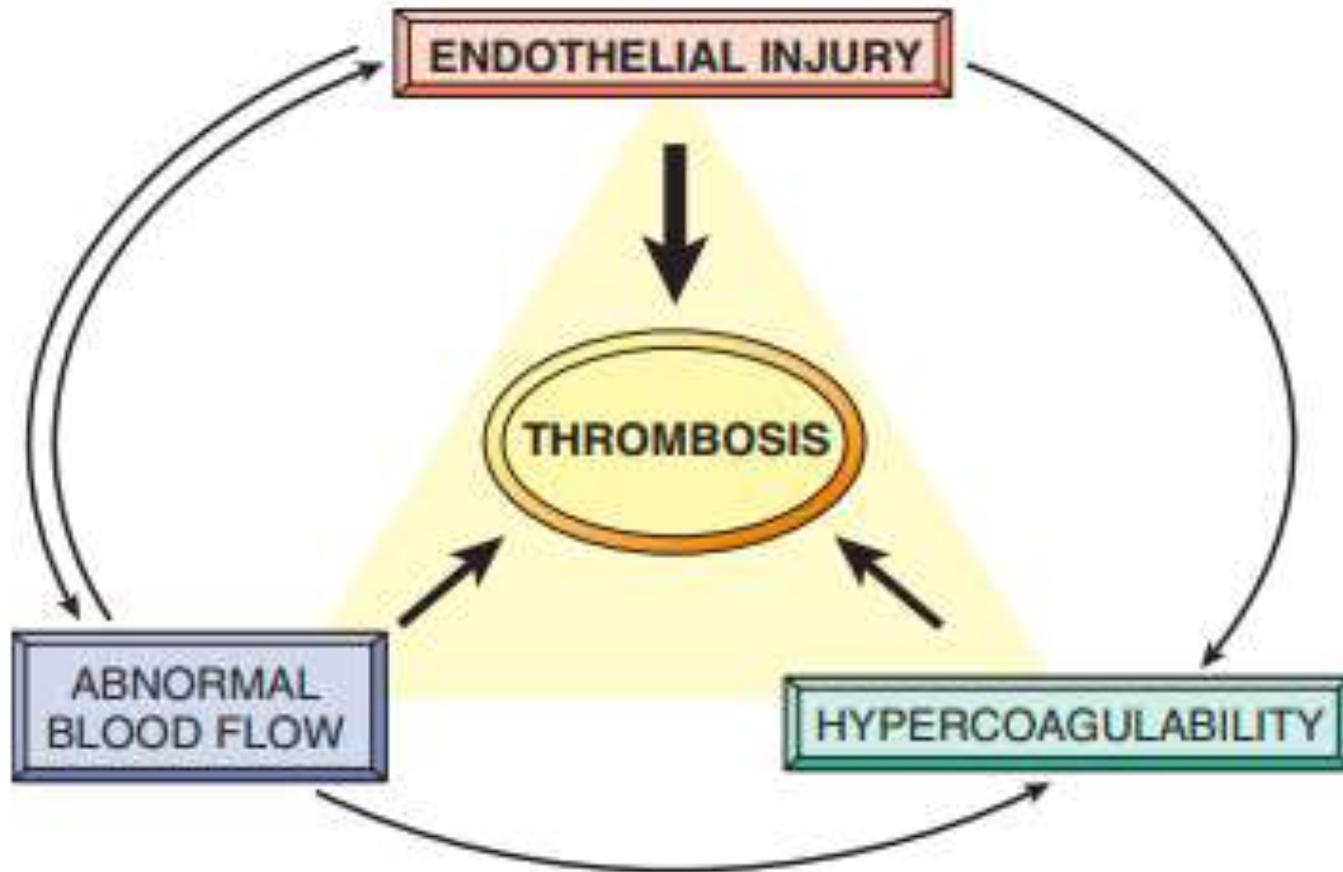


# THROMBOSIS

- **Thrombosis** is the formation of a blood clot, known as a thrombus, within a blood vessel.
  
- The primary abnormalities that lead to intravascular thrombosis are:
  - ❖ (1) endothelial injury.
  - ❖ (2) stasis or turbulent blood flow.
  - ❖ (3) hypercoagulability of the blood



➤(the so-called “Virchow triad”)

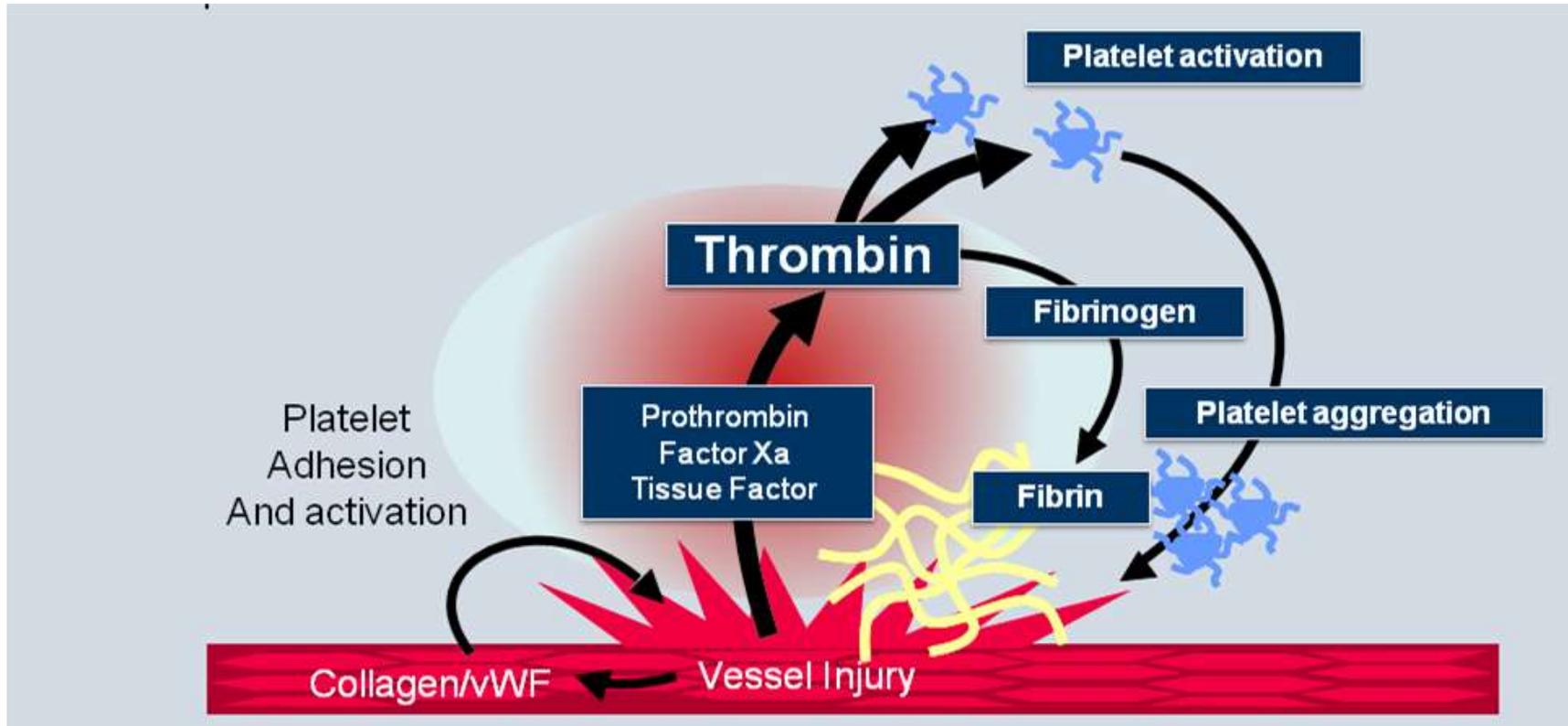


# 1. ENDOTHELIAL INJURY

- Endothelial injury leading to platelet activation.
- cardiac and arterial clots are typically rich in platelets.
- Endothelial injury may be caused by:
  - physical injury.
  - infectious agents.
  - inflammatory mediators.
  - metabolic abnormalities, such as hypercholesterolemia or homocystinemia,
  - toxins absorbed from cigarette smoking.



severe endothelial injury may trigger thrombosis by exposing VWF and tissue factor



- Endothelial injury .....that's mean:
  - platelet activation: exposed VWF, TF.
  - Endothelial dysfunction : prothrombotic endothelium.
  
- Procoagulant changes:
  - ↓thrombomodulin, ↑thrombin
  
- Anti-fibrinolytic effects:
  - ↑ Plasminogen activator inhibitors (PAI).
  - ↓t-PA.



## Plasminogen activators

Tissue plasminogen activator (tPA),  
urokinase, streptokinase  
staphylokinase, vampire bat PA

## PAI-1

(inhibits tPA,  
present in blood  
in small concentration)

Cleave  
plasminogen into  
active plasmin

**Plasminogen** → **Plasmin**

Degrades  
fibrin clot,  
core of  
thrombus

$\alpha_2$ -antiplasmin  
(physiological inhibitor of  
plasmin present in blood in concentration  
6-8X exceeding therapeutic dose of plasmin)

**Fibrin**

**Fibrin degradation  
products**

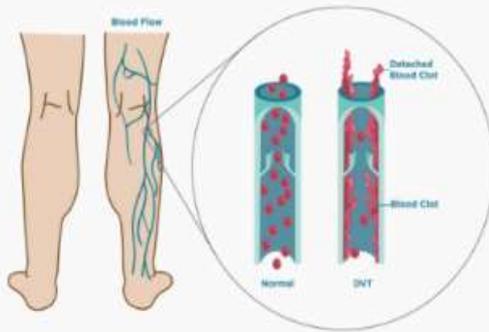


## 2. ABNORMAL BLOOD FLOW

- Stasis is a major factor in the development of venous thrombus.
  
- stasis and turbulence have the following effects:
  - Stasis allows platelets and leukocytes to come into contact with the endothelium when the flow is sluggish.
  - Stasis also slows the washout of activated clotting factors and impedes the inflow of clotting factor inhibitors.



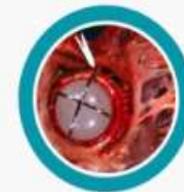
# Factors that contribute to blood flow disturbances - stasis and turbulence



Vessel wall irregularities  
e.g. atherosclerosis



Cardiac arrhythmias  
e.g. atrial fibrillation



Cardiac prosthetic valves



Aneurysms

## Stasis due to impaired venous return

Economy class syndrome  
Post surgery  
Prolonged immobilisation  
Hyperviscosity - PRV, SCD

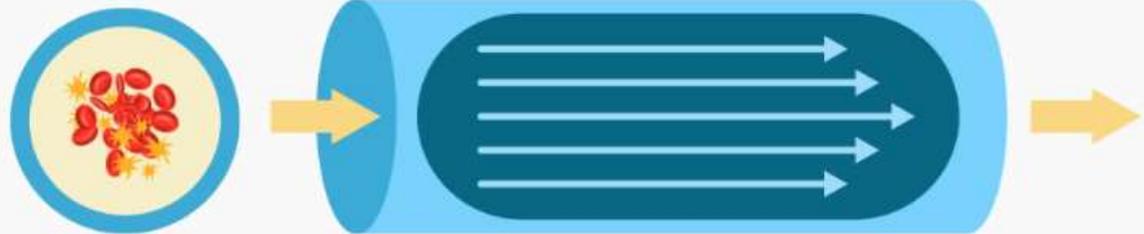
## Vessel obstruction or compression

Pregnancy  
Local compression e.g., tumours

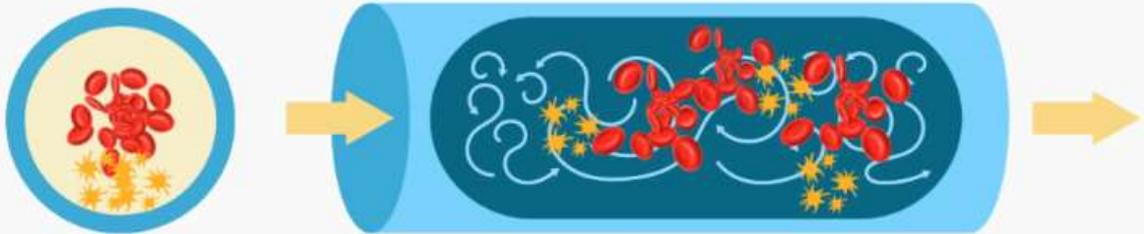


## Blood flow disturbances - stasis and turbulence

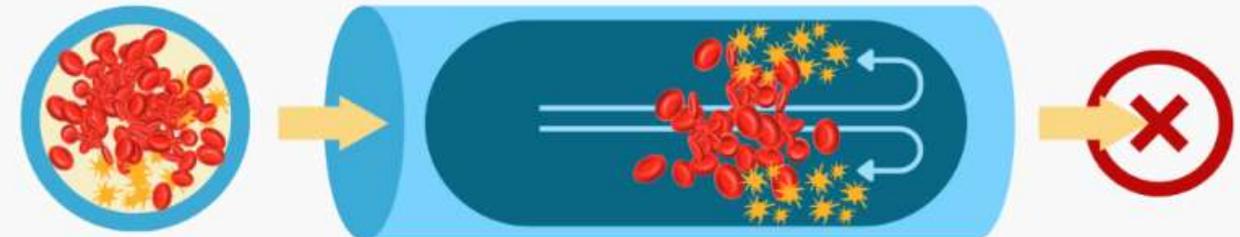
Laminar flow with red cells in axial flow and separation of platelets from endothelial surface. Plasma containing anticoagulants lines the endothelial cells.



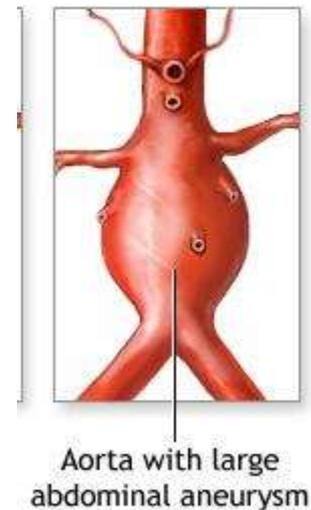
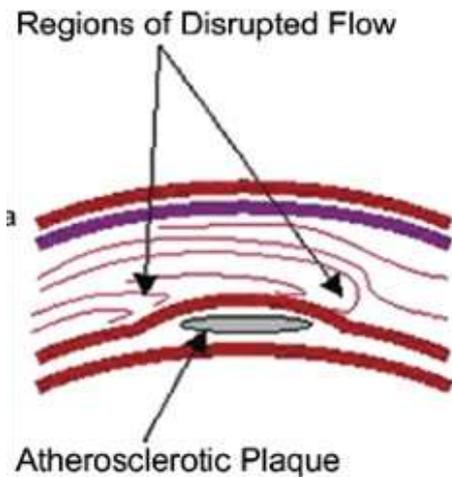
Turbulent flow with eddy currents. Platelets undergo shear stress and activation as they are thrown against the endothelial surface



Stasis due do impaired venous return or obstruction causes congestion, prolonged contact of red cells, platelets and clotting factors with endothelial cells



- Turbulent and static blood flow contributes to thrombosis in a number of clinical setting:
- 1. Ulcerated atherosclerotic plaques.
- 2. aortic aneurysms create local stasis and consequently are fertile sites for thrombosis



- 3. Hyperviscosity syndromes (such as polycythemia vera )increase resistance to flow and cause small vessel stasis.
- 4. sickle cell anemia:
  - The deformed red cells in cause vascular occlusions.



### 3. HYPERCOAGULABILITY

- Hypercoagulability refers to an abnormally high tendency of the blood to clot, and is typically caused by alterations in coagulation factors.
- Is an important underlying risk factor for venous thrombosis



- The alterations of the coagulation pathways that predispose affected persons to thrombosis can be divided into:
  - Primary (genetic):
    - ❖ Mutations in the factor V : Makes factor V resistant to cleavage and inactivation by protein C.
  - Secondary (acquired) disorders:
    - ❖ oral contraceptive.
    - ❖ Pregnancy (Hyperestrogenic state)
    - ❖ Cancers (release of procoagulants from tumors)

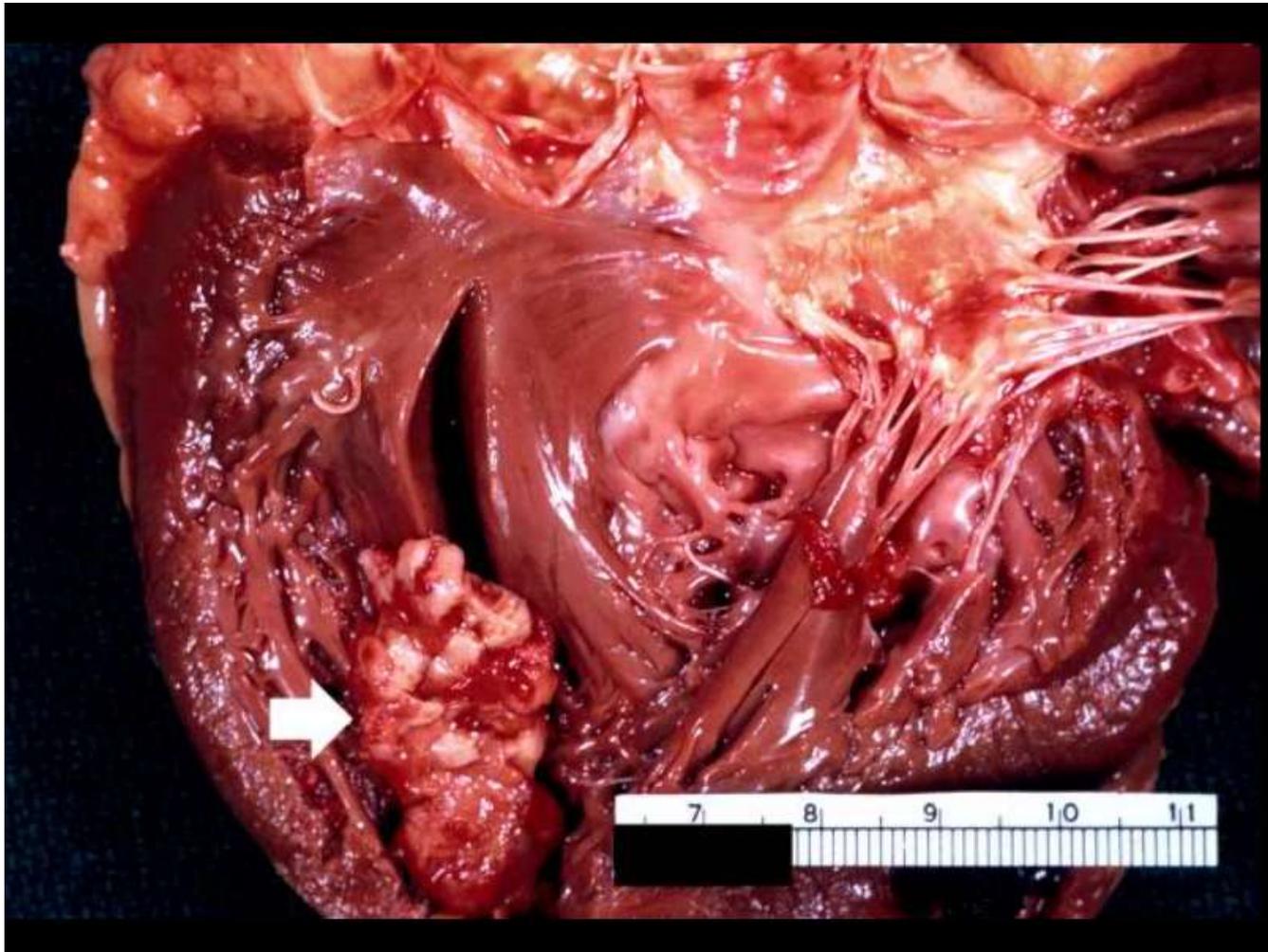


# MORPHOLOGY

- Thrombi can develop anywhere in the cardiovascular system.
- Arterial or cardiac thrombi typically arise at sites of endothelial injury or turbulence.
- venous thrombi characteristically occur at sites of stasis.



- Mural thrombi:
- Thrombi occurring in heart chambers or in the aortic lumen

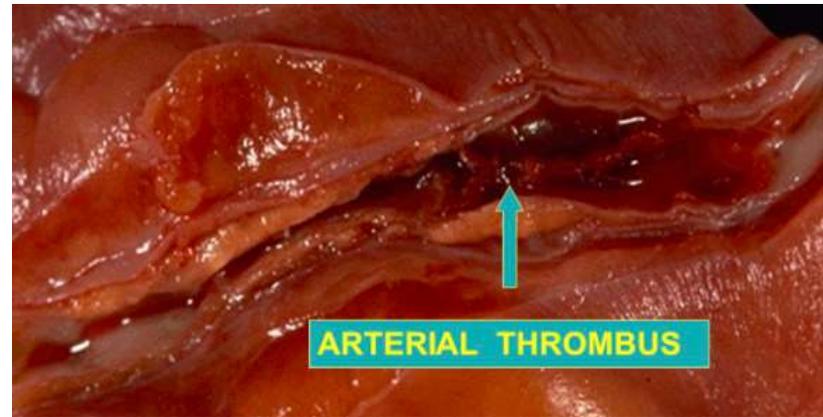
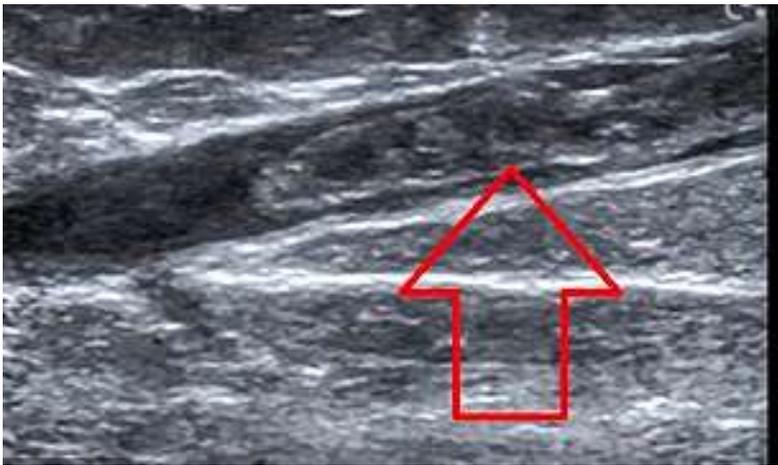




thrombus (1) attached to the myocardium (2)



\*Arterial thrombi are frequently occlusive. They are typically rich in platelets

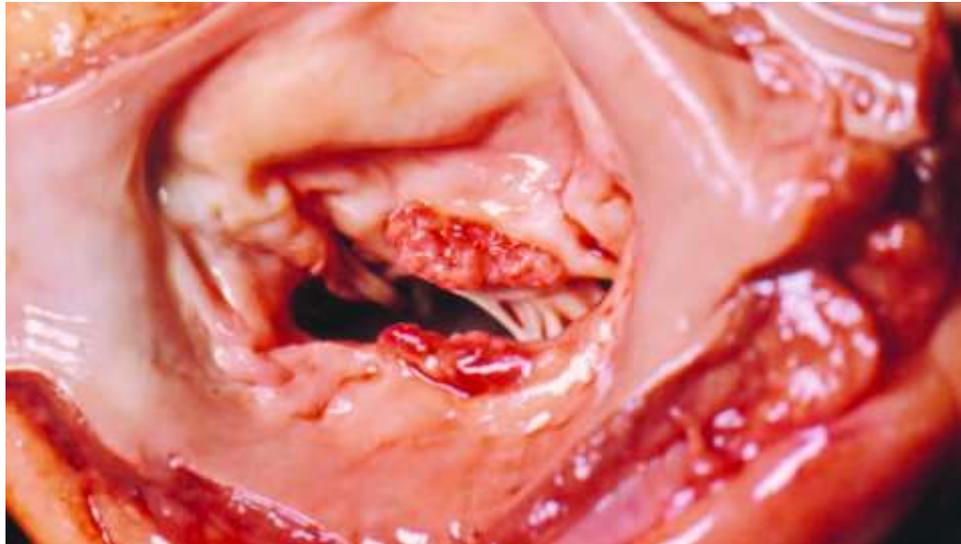


## VENOUS THROMBI (PHLEBOTHROMBOSIS):

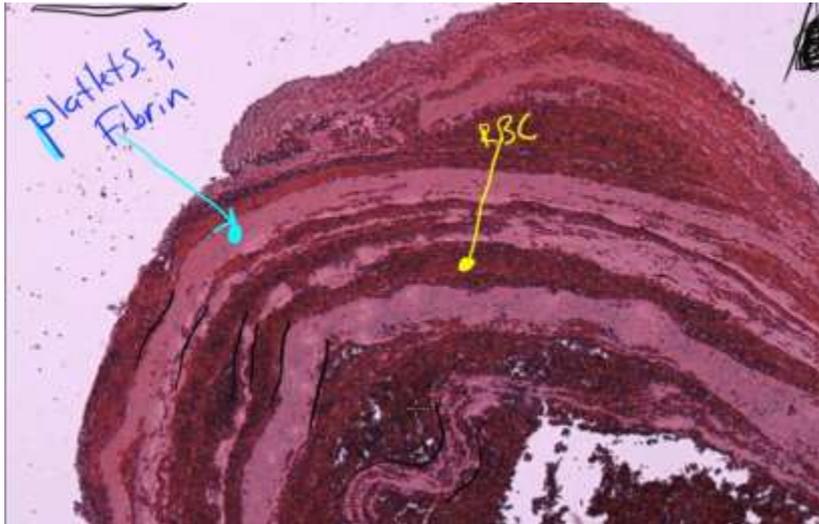
- they frequently propagate some distance toward the heart, forming a long cast within the vessel lumen that is prone to give rise to emboli.
- they tend to contain more red cells.

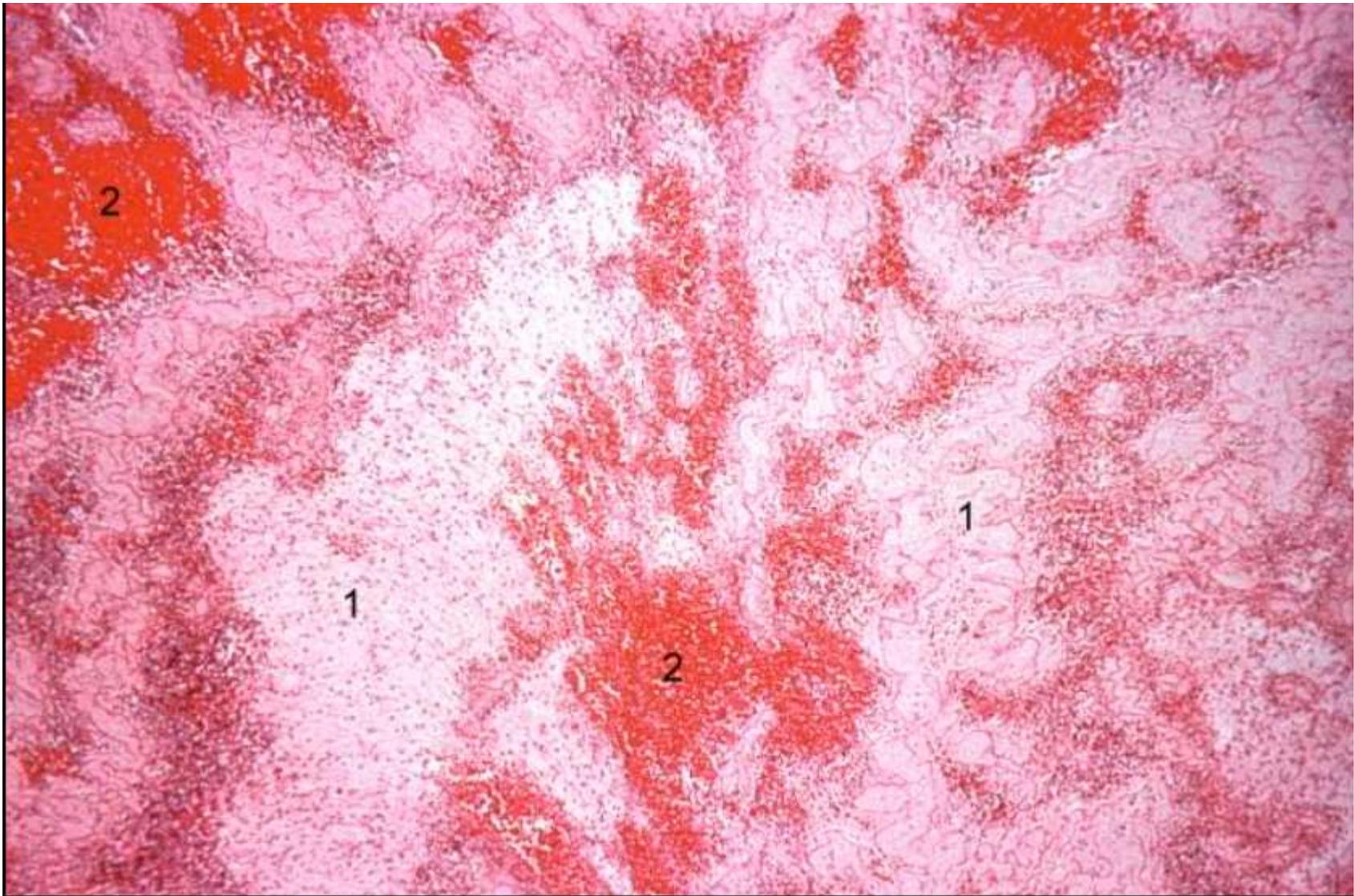


- Vegetations: Thrombi on heart valves , divided into :
  - infective endocarditis: Infective thrombotic masses
  - nonbacterial thrombotic endocarditis: Sterile vegetations.
  - LibmanSacks endocarditis:
    - Sterile, occur in the systemic lupus erythematosus.



- Thrombi can have grossly (and microscopically) apparent laminations called lines of Zahn; these represent pale platelet and fibrin layers alternating with darker red cell-rich layers. >> Thrombus has formed in flowing blood.





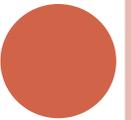
This is a higher-power photomicrograph of the thrombus. Note the pale regions which contain primarily platelets (degranulated platelets) with some fibrin (1), and the red areas which contain RBCs, some leukocytes, and fibrin(2).



# FATE OF THE THROMBUS

- 1. Propagation: The thrombus enlargement.
- 2. Embolization: transported in the vasculature.
- 3. Dissolution: shrinkage and complete dissolution.
- 4. Organization
  - ingrowth of endothelial cells, smooth muscle cells, and fibroblasts.
- 5. Recanalization: capillary channels are formed create canal along the length of the thrombus, thereby reestablishing the continuity of the original lumen.





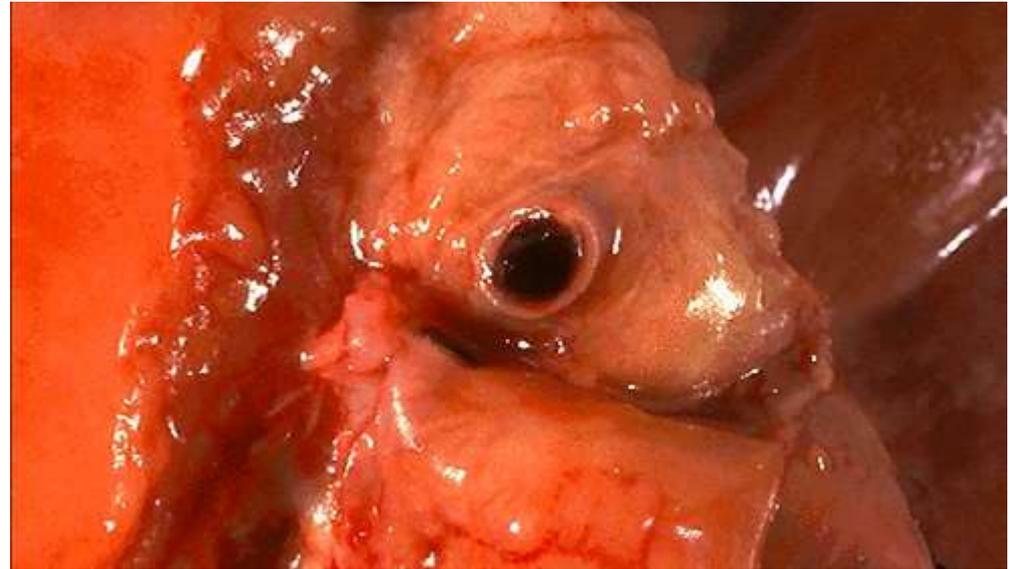
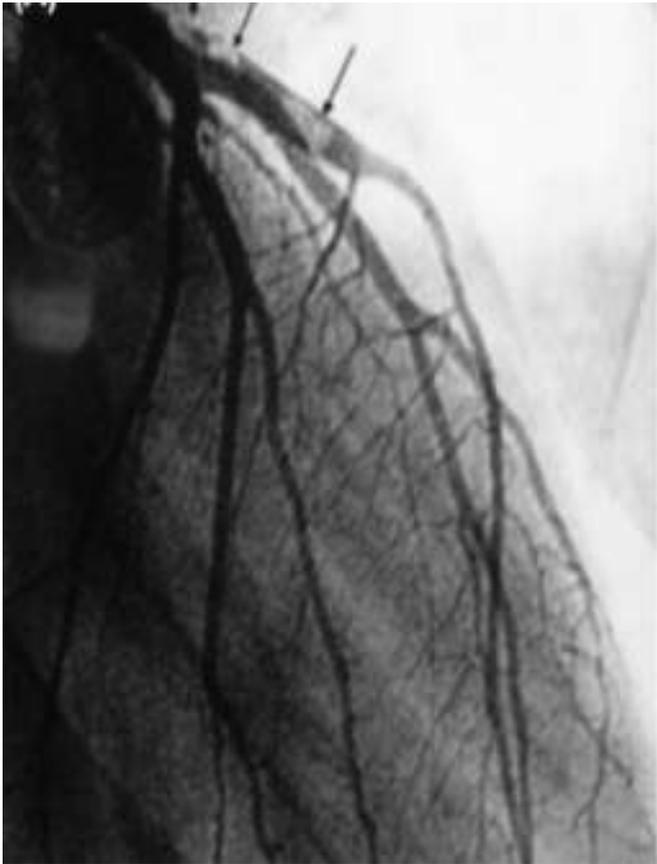
## CLINICAL FEATURES

- 1. Venous Thrombosis (Phlebothrombosis)
  - Superficial leg veins: in cases of varicosities > congestion, swelling, pain, and tenderness.  
**Rarely embolize**
  
  - Deep leg veins: Deep vein thrombosis: **More serious.** involving one of the large leg veins at or above the knee, more often embolize to the lungs and give rise to pulmonary infarction



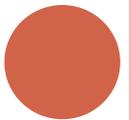
- 2. Arterial and Cardiac Thrombosis;
- Atherosclerosis is a major cause of arterial thromboses because it is associated with the loss of endothelial integrity and with abnormal blood flow.
- Both cardiac and aortic mural thrombi are prone to embolization. . The brain, kidneys, and spleen are particularly likely targets because of their rich blood supply.



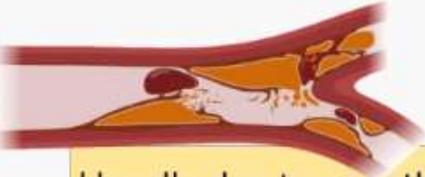


**thrombosis** of a coronary artery

Massive thrombosis (*arrows*) from distal portion of left main coronary artery



## Different characteristics between arterial and venous thrombosis



### Arterial thrombosis

Usually due to endothelial injury, usually resulting from rupture of atherosclerotic plaque. Other uncommon causes include vasculitis, trauma and hypercoagulopathy

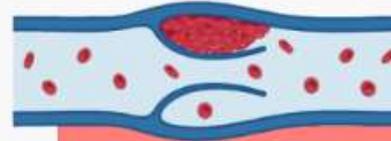
Occurs under high pressure and shear (high flow) conditions

Pale thrombus, composed mainly of platelets and fibrin. May exhibit lines of Zahn

Adherent to vessel wall

Site: coronary arteries, cerebral arteries, carotid arteries, aorta, cardiac chambers

Clinical effects: myocardial infarction, stroke, peripheral vascular disease



### Venous thrombosis

Occurs in non-injured veins, mainly as a result of stasis, turbulence and hypercoagulopathy

Occurs under low pressure and shear (low flow) conditions, often against gravity

Red thrombus, composed of red cells and fibrin

Loosely attached to vessel wall and easily friable

Site: deep veins of leg, portal vein, cerebral venous sinuses

Clinical effects: deep vein thrombosis, pulmonary embolism, cerebral venous sinus thrombosis

# DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

- DIC is widespread thrombosis within the microcirculation that may be of sudden or insidious onset.
- DIC = widespread microvascular thrombosis + fibrinolytic mechanisms activation.
- DIC consumes platelets and coagulation proteins (hence the synonym consumptive coagulopathy).



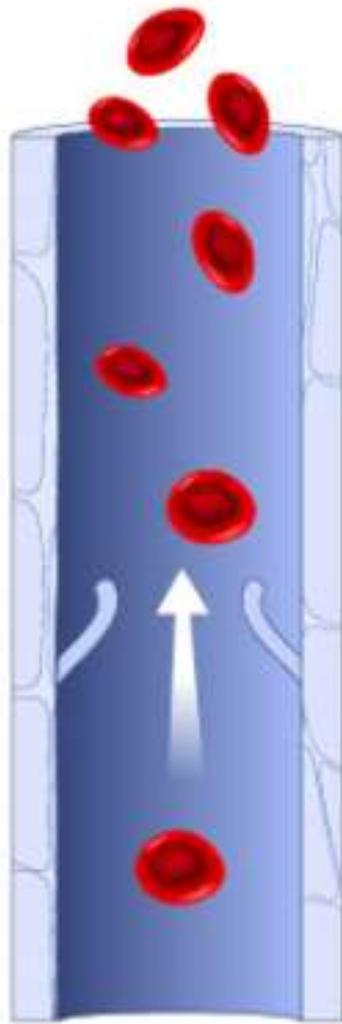


Excessive hemorrhage (Bruising, petechiae).

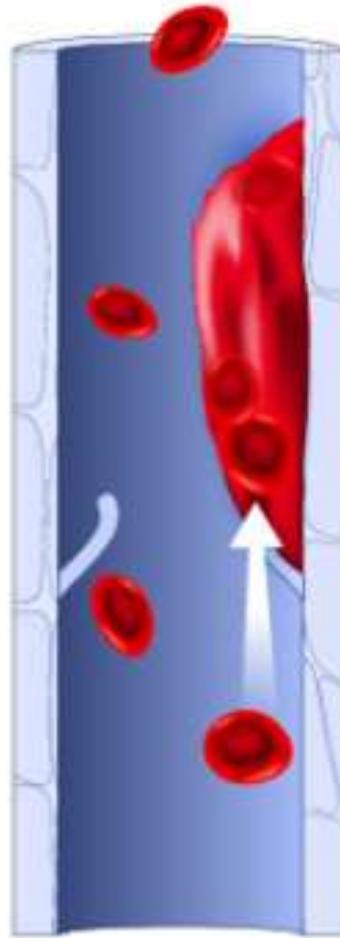


# EMBOLISM

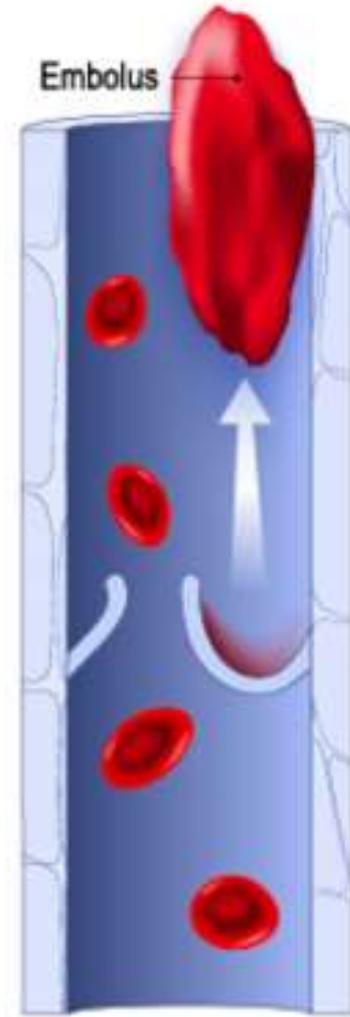
- An embolus is a detached intravascular mass that is carried by the blood from its point of origin to a distant site, where it often causes tissue dysfunction or infarction.
- This mass may be:
  - Solid.
  - Liquid.
  - Gaseous.
- The vast majority of emboli derive from a dislodged thrombus—hence the term thromboembolism.



Normal  
blood flow



Blood clot  
formation



Blood clot, that  
travels through the

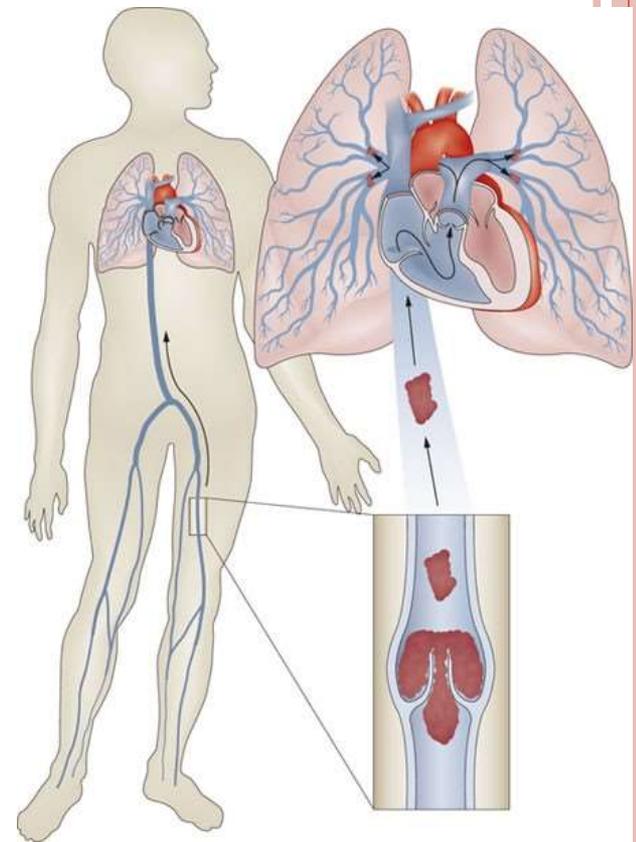


- ◎ The primary consequence of systemic embolization is ischemic necrosis (infarction) of downstream tissues.
- ◎ whereas embolization in the pulmonary circulation leads to hypoxia, hypotension, and right-sided heart failure

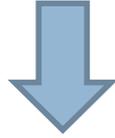


# 1. Pulmonary thromboembolism

- Originate from deep venous thromboses and are responsible for the most common form of thromboembolic disease.



◎ Fragmented thrombi from DVT



◎ are carried through progressively larger venous channels



◎ pass through the right side of the heart

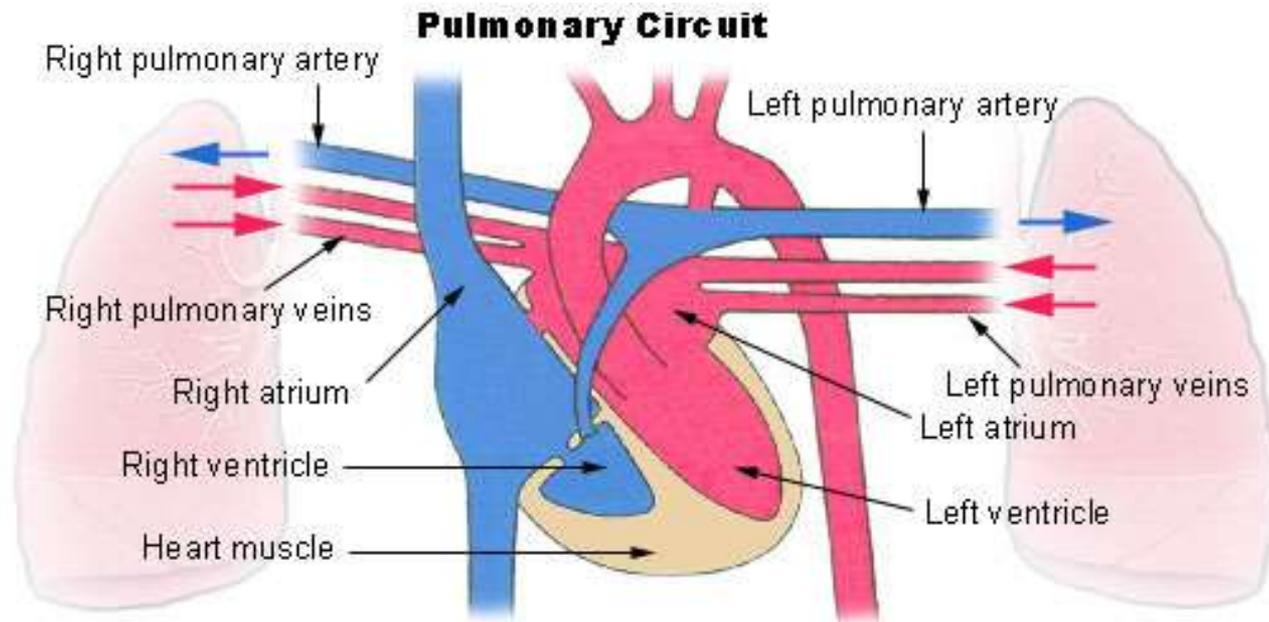


◎ arresting in the pulmonary vasculature.



## ◎ PE can occlude:

- the main pulmonary artery,
- lodge at the bifurcation of the right and left pulmonary arteries (saddle embolus),
- pass into the smaller, branching arterioles

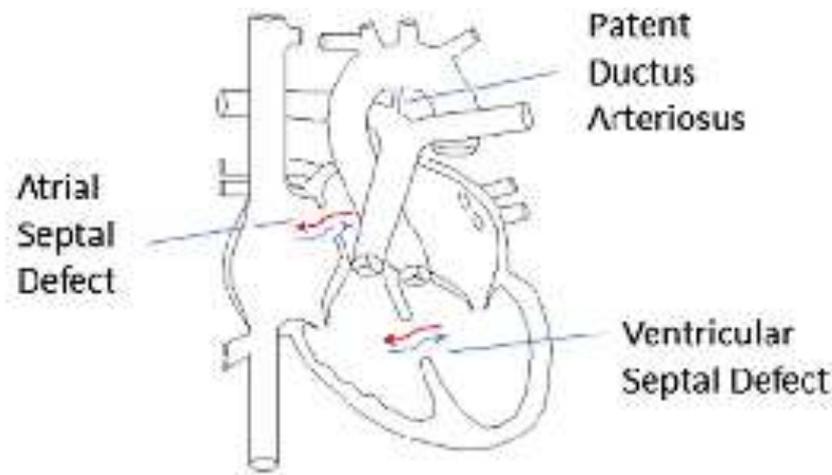




**Figure 4.16** Embolus from a lower extremity deep venous thrombosis, lodged at a pulmonary artery branchpoint.

● paradoxical embolism:

● an embolus passes through an atrial or ventricular defect and enters the systemic circulation.



# Fate of pulmonary embolism

- (60%–80%) of pulmonary emboli are clinically silent, they undergo organization.
- A large embolus that blocks a major pulmonary artery can cause sudden death.
- Embolic obstruction of medium-sized arteries : rupture >>can cause pulmonary hemorrhage, but not pulmonary infarction, why?
- Multiple emboli occurring through time can cause pulmonary hypertension and right ventricular failure (cor pulmonale).



## 2. Systemic thromboembolism

### ● Origin:

1. Intracardiac mural thrombi (80%).
2. Aortic aneurysms.
3. Thrombi overlying ulcerated atherosclerotic plaques.
4. Fragmented valvular vegetations .
5. The venous system (paradoxical emboli).



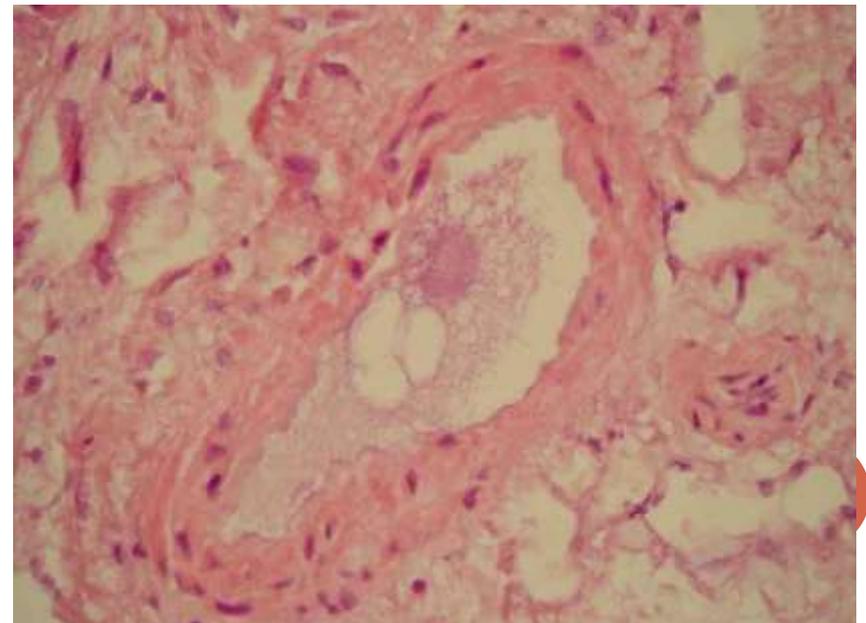
◎ Common arteriolar embolization sites include:

- the lower extremities (75%).
- central nervous system (10%).
- intestines.
- Kidneys
- spleen



# 3. Fat Embolism

- Soft tissue crush injury or rupture of marrow vascular sinusoids (eg, due to a **long bone fracture**) release microscopic fat globules into the circulation.



# Fat embolism syndrome

- ◎ fat embolism syndrome characterized by:
  - pulmonary insufficiency.
  - neurologic symptoms.
  - anemia\*
  - thrombocytopenia\*
  - diffuse petechial rash\*
- ◎ fatal in 10% of cases.
- ◎ Clinical signs and symptoms appear 1 to 3 days after injury.

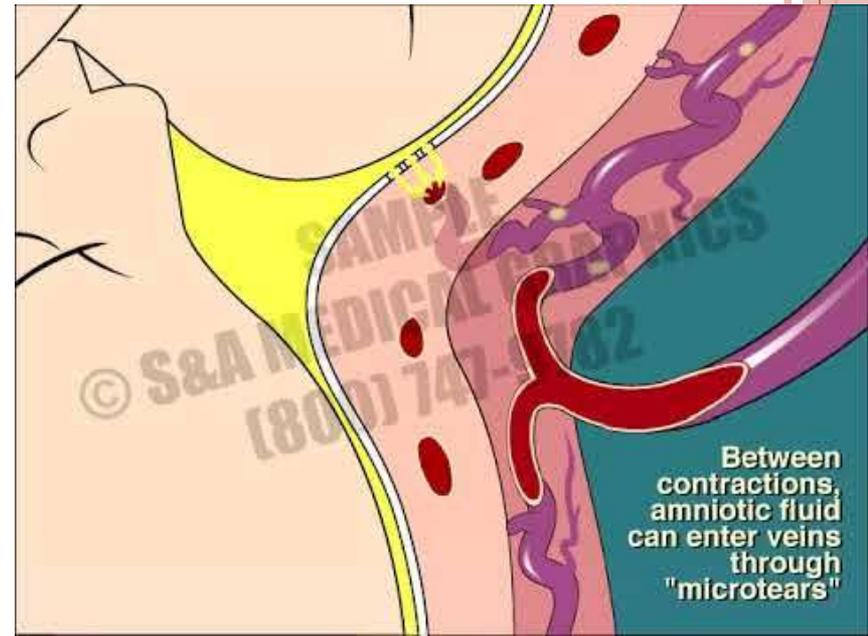


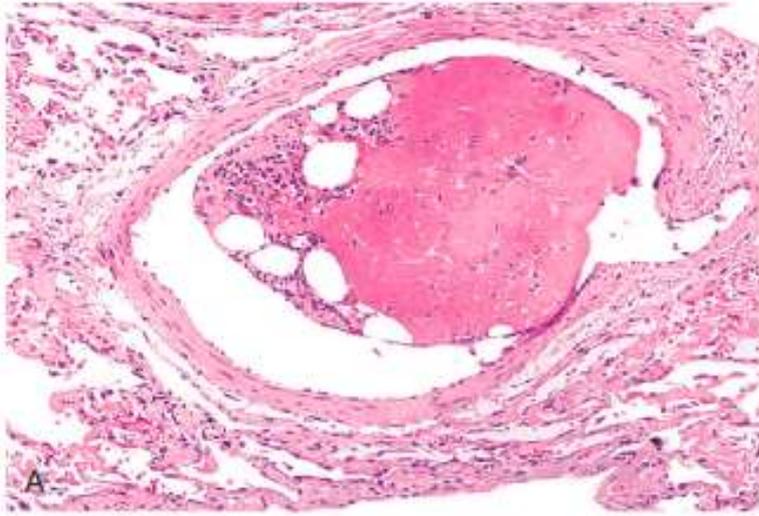
# 4. Amniotic Fluid Embolism

- Onset is characterized by:
  - sudden severe dyspnea.
  - cyanosis
  - hypotensive shock,
  - seizures and coma.
  
- If the patient survives the initial crisis, pulmonary edema typically develops, along with disseminated intravascular coagulation secondary to release of thrombogenic substances from amniotic fluid.

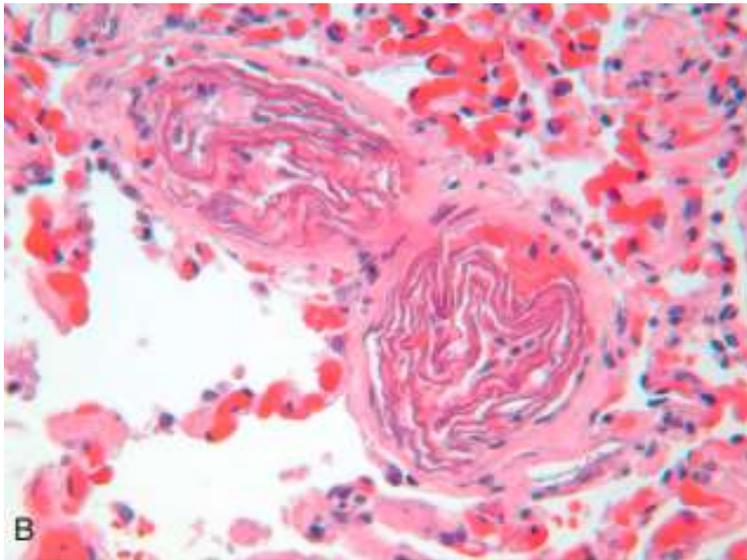


- ◎ mortality in such cases results from :
  - mechanical obstruction of pulmonary vessels .
  - biochemical activation of the coagulation system and the innate immune system caused by substances in the amniotic fluid





Bone marrow embolus



Amniotic fluid emboli



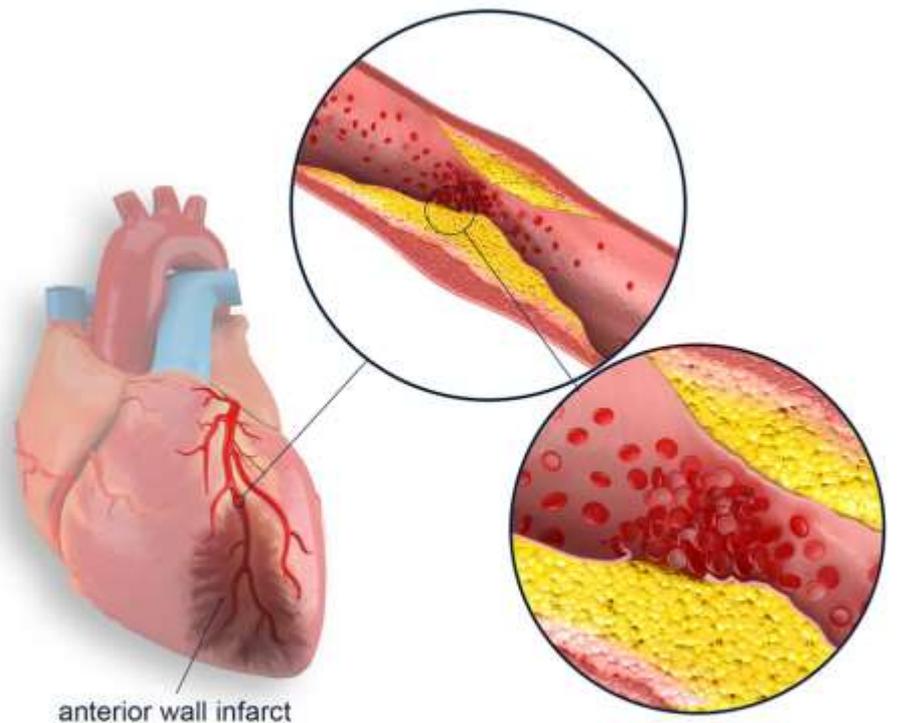
# 5. Air Embolism

- Gas bubbles within the circulation can coalesce and obstruct vascular flow and cause distal ischemic injury.
- Can occur during bypass surgery, laproscopic procedures, chest wall injury or introduced into the cerebral arterial circulation by neurosurgery.



# INFARCTION

## Myocardial Infarction



anterior wall infarct

Red thrombus on a ruptured atherosclerotic plaque, causing blood flow blockage

- ◎ An infarct is an area of ischemic necrosis caused by occlusion of the vascular supply to the affected tissue.
- ◎ Commonly affect heart and brain.
- ◎ Arterial thrombosis or arterial embolism underlies the vast majority of infarctions.

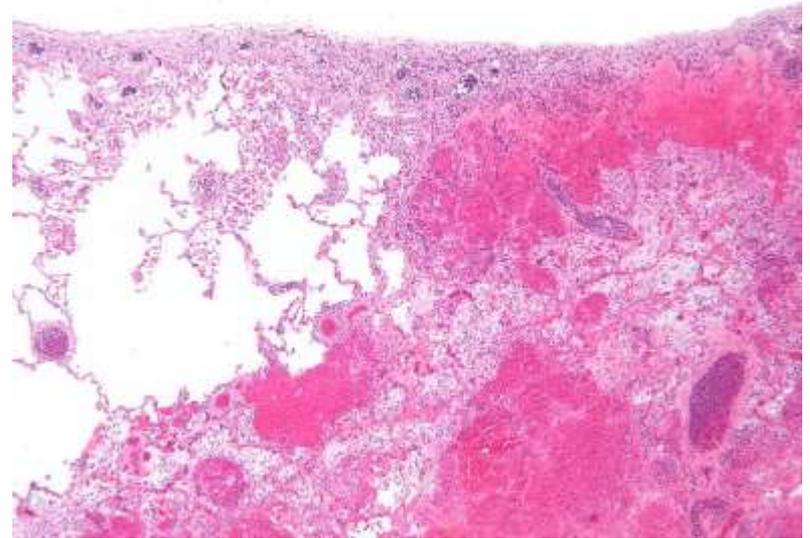


- ◎ Infarcts are classified based on:
  - \*their color
- ◎ (reflecting the amount of hemorrhage)
  - ❖ may be either red (hemorrhagic) or white (anemic)
- \*the presence or absence of microbial infection.
  - ❖ may be either septic or bland.

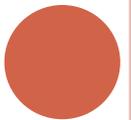
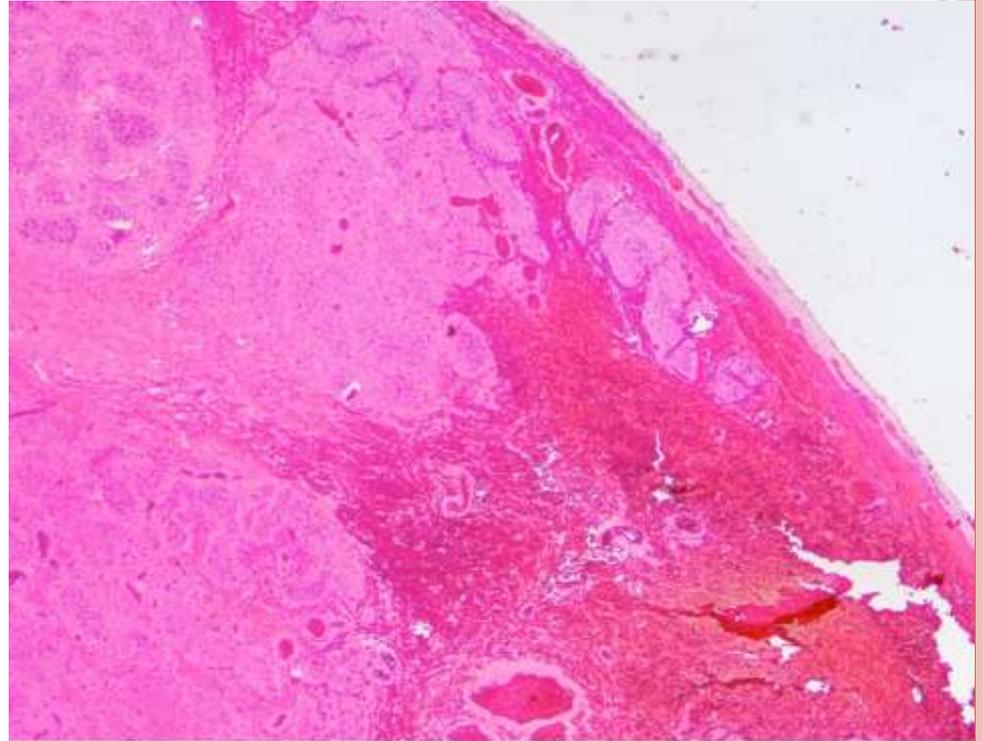
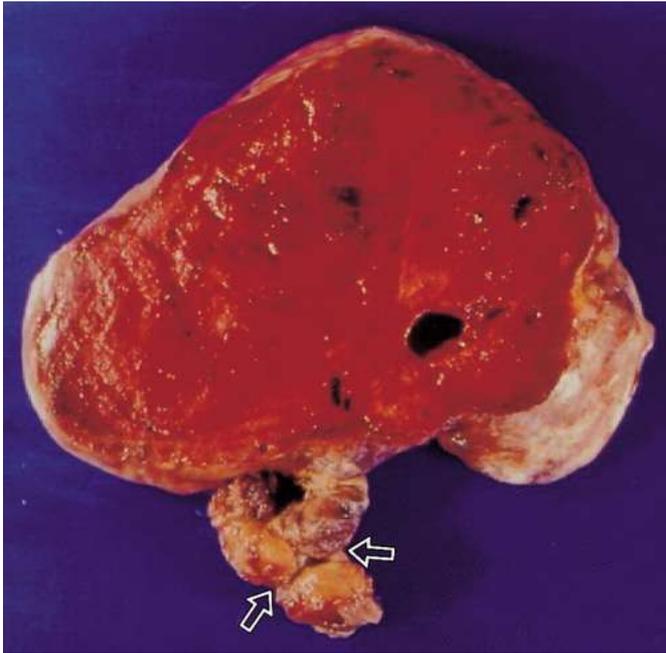


◎ Red infarcts occur :

◎ (1) in loose tissues (e.g., lung) where blood can collect in infarcted zones.



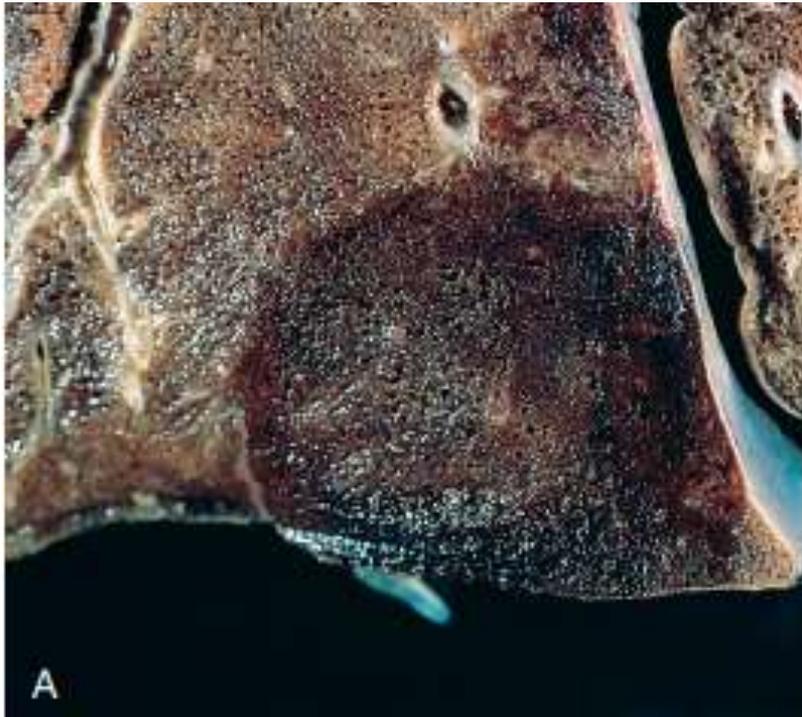
- ◎ (2) as a result of venous occlusions (such as in ovarian torsion).

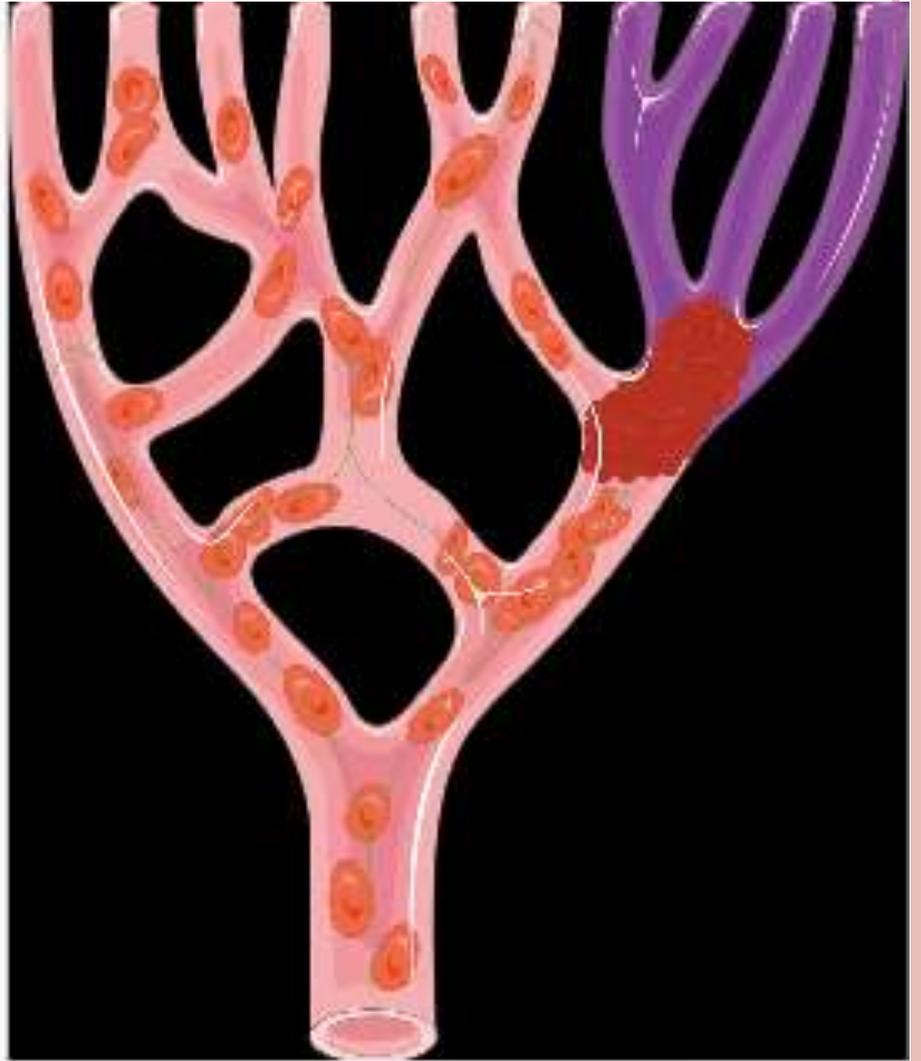


- ◎ (3) in tissues with dual circulations such as lung where partial, inadequate perfusion by collateral arterial supplies is typical.
- ◎ (4) in previously congested tissues (as a consequence of sluggish venous outflow).



- ⦿ White infarcts
- ⦿ occur with arterial occlusions in solid organs with end-arterial circulations (e.g., heart, spleen, and kidney),





# Factors That Influence Infarct Development

- 1. Anatomy of the vascular supply. The presence or absence of an alternative blood supply is the most important factor.
- Organ with the dual supply are resistant to infarction:
  - Liver
  - Lung
  - hand and forearm.
- Organ with end-arterial circulation are more susceptible for infarction:
  - Kidney
  - spleen



◎ 2. Rate of occlusion

◎ 3. Tissue vulnerability to hypoxia.

- Neurons undergo damage after 3 to 4 minutes.
- Myocardial cells, die after 20 to 30 minutes.
- fibroblasts within myocardium remain viable after many hours of ischemia.

