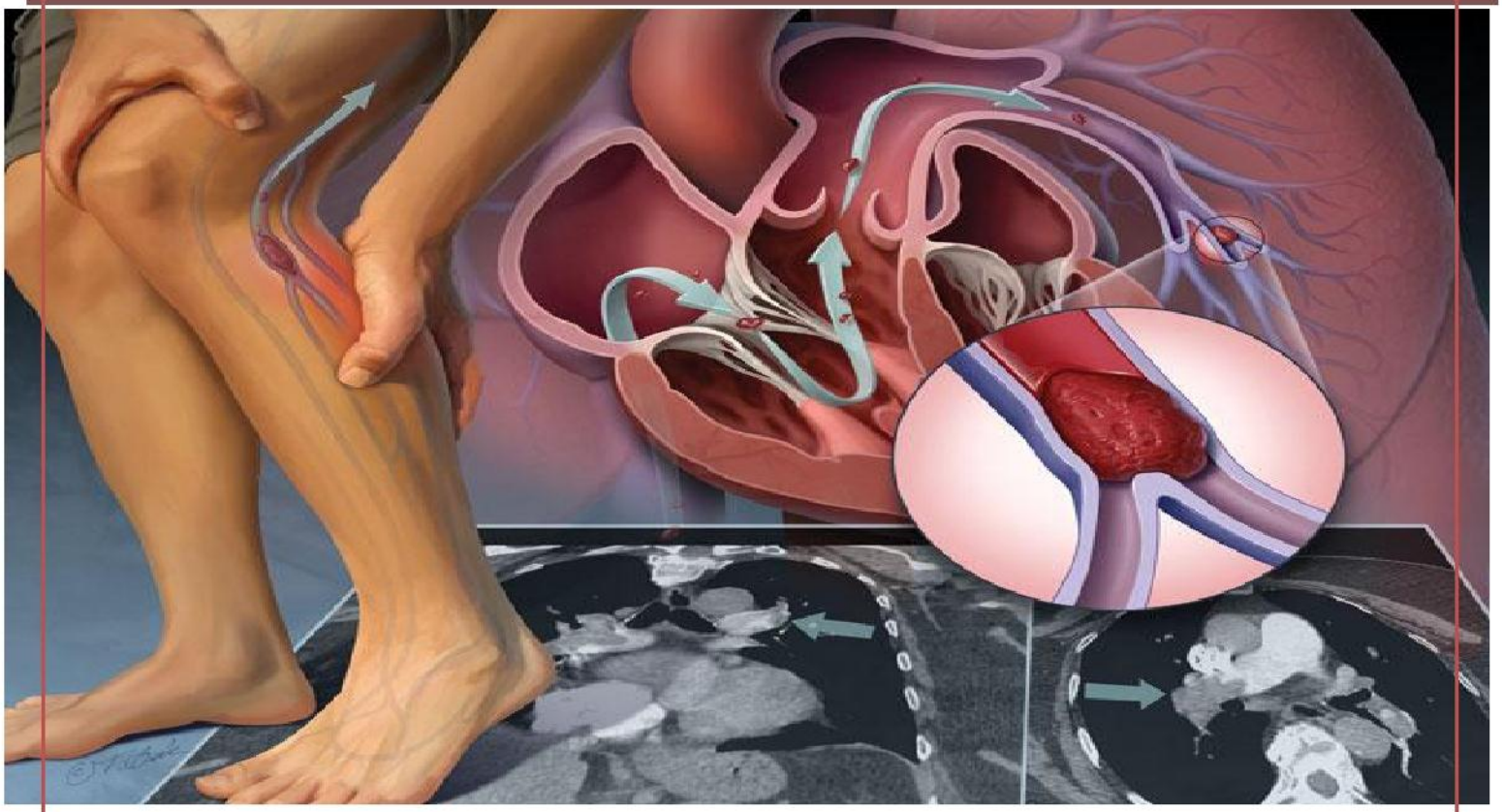

Lecture 6

Hemostasis and thrombosis

432 pathology team

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Objectives :

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

Hemostasis and thrombosis :

- **Normal hemostasis**

A consequence of tightly regulated processes that:

- *maintain blood in a fluid, clot-free state in normal vessels*
- *inducing the rapid formation of a localized hemostatic plug at the site of vascular injury*

N.B. It is different from Homeostasis which is the property of a system that regulates its internal environment and tends to maintain a stable, relatively constant condition of properties such as temperature or pH.

- **Thrombosis:**
  - *the pathologic form of hemostasis*
  - *involves blood clot (thrombus) formation in uninjured vessels (or after relatively minor injury)*
    - **Thrombosis can only occur during life**
  - ***Clotting can also occur after death or in a test tube***

Note that:

Hemostasis is a physiological process that occurs during vascular injury to control bleeding → normal process.

Thrombosis is the pathological counterpart of hemostasis

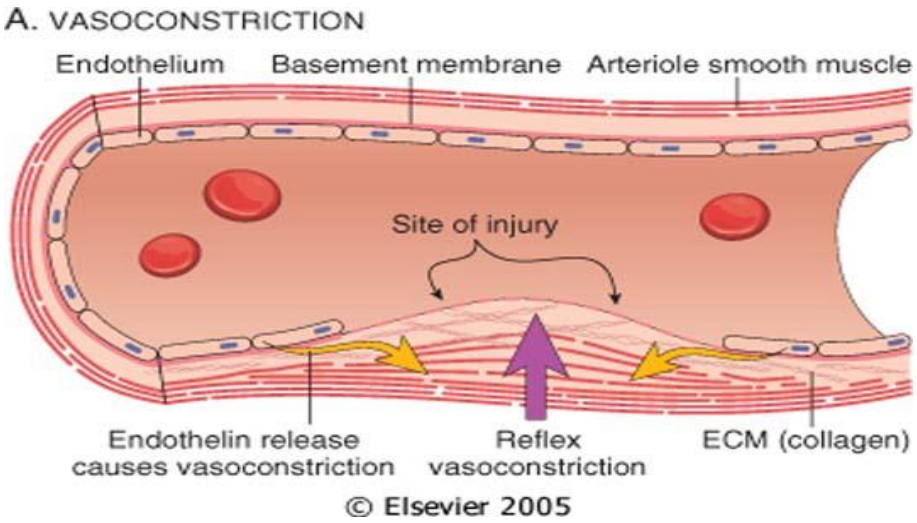
How normal hemostasis occur ? *In 4 steps ..*

1- Vasoconstriction

2- Primary hemostasis — *(control bleeding)*

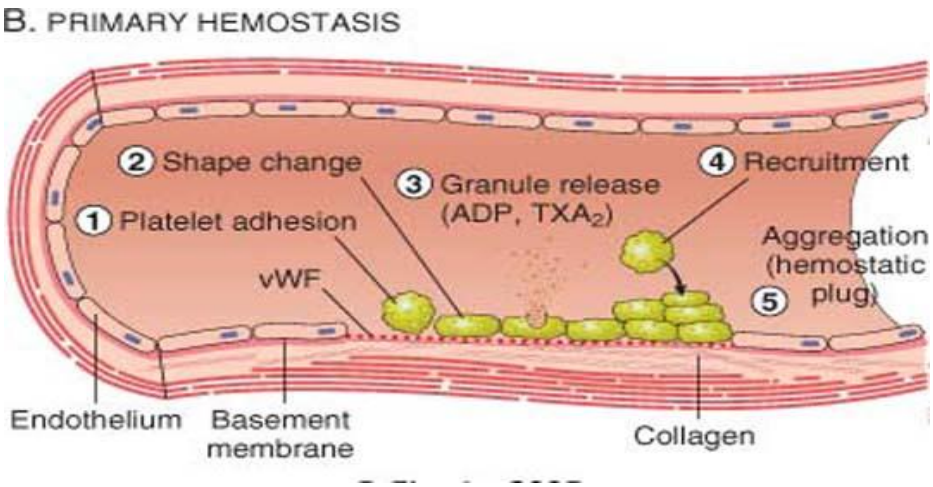
3- Secondary hemostasis

4- Antithrombotic counterregulation — *(control clotting)*



1- Vasoconstriction :

After vascular injury, local neuro-humoral factors induce a transient vasoconstriction. It's a reflex vasoconstriction occurs by secretion of endothelin–a potent vasoconstrictor-

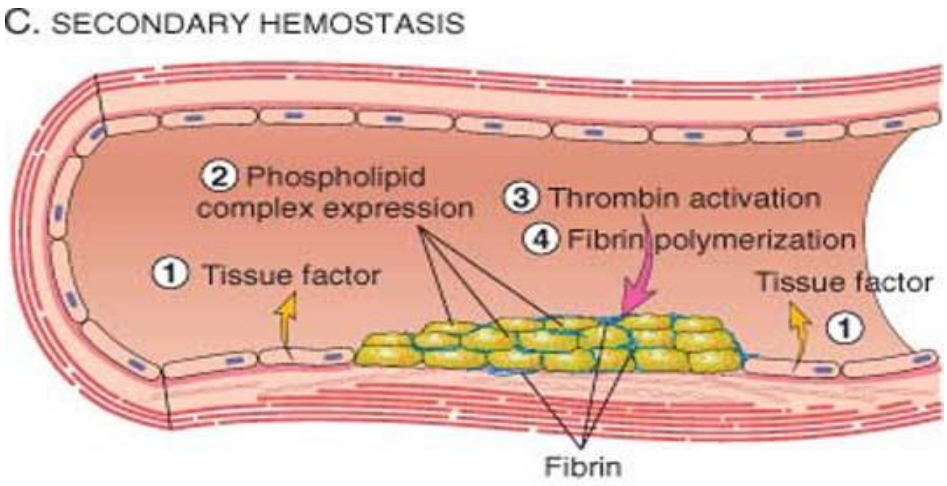


To understand step 2 you should know that :

ECM → highly thrombogenic sub endothelial extracellular matrix, which is hidden by the endothelium in normal conditions. However, when there is an injury it becomes exposed. It contains vWF (von willebrand) factors and glycoprotein I b (GpIb) receptors.

2- Primary hemostasis :

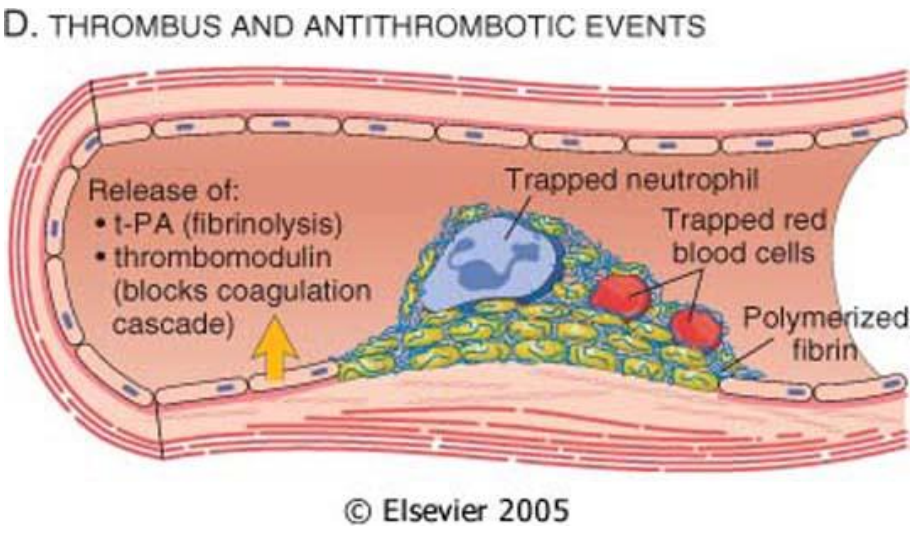
- Platelets adhere to exposed extracellular matrix (ECM) by binding to vWF (through GpIb receptors) and are activated, undergoing a **shape change** and **granule release**.
- Released adenosine diphosphate (ADP) and thromboxane A_2 (TXA_2) lead to **further platelet aggregation** (via binding of fibrinogen to platelet GpIIb-IIIa receptors), to form the **primary hemostatic plug.**



3- Secondary hemostasis :

Endothelial injury also exposes tissue factor (also known as tissue factor III or thromboplstin) a membrane-bound glycoprotein synthesized by endothelial cells. When this factor is released it triggers the coagulation cascade which ultimately leads to activation of thrombin → converts fibrinogen into fibrin.

- Local activation of the coagulation cascade (involving tissue factor and platelet phospholipids) results in fibrin polymerization, "cementing"→(making it firm) the platelets into a definitive **secondary hemostatic plug** (larger and more stable)



4- antithrombotic counterregulation

Counter-regulatory mechanisms, such as release of t-PA (tissue plasminogen activator, a fibrinolytic product) and thrombomodulin (interfering with the coagulation cascade–it binds to thrombin and convers it to anticoagulant), **limit the hemostatic process to the site of injury.**

Both hemostasis and thrombosis involve three structural and molecular components:

- the vascular wall
- platelets
- the coagulation cascade

- **the vascular wall :**
  - *Intact endothelial cells maintain liquid blood flow by actively:*
    - *inhibiting platelet adherence*
    - *preventing coagulation factor activation*
    - *lysing blood clots that may form*

    } ***function of normal endothelium***
  - *Loss of endothelial integrity exposes underlying vWF and basement membrane collagen →platelet aggregation & thrombus formation*
  - ***Dysfunctional** endothelial cells can produce more pro-coagulant factors (e.g., platelet adhesion molecules, tissue factor) or may synthesize less anticoagulant effectors (e.g., thrombomodulin, PGI2)* (normal endothelial cells produce both pro and anticoagulant factors **in balance**, according to which is needed)
  - **Endothelial dysfunction** Can be induced by a wide variety of insults as:

- **Hypertension**
- Turbulent blood flow
- Bacterial endotoxins
- Radiation injury
- Metabolic abnormalities such as homocystinemia or hypercholesterolemia
- Toxins absorbed from cigarette smoke

- **Platelets : functions..**
  - Maintain the integrity of the vascular endothelium.
  - Participate in endothelial repair through the contribution of PDGF (Platelet-derived growth factor)
  - Form platelet plugs
  - Promote the coagulation cascade through the platelet phospholipid complex (that provide an important surface for coagulation-protein activation)

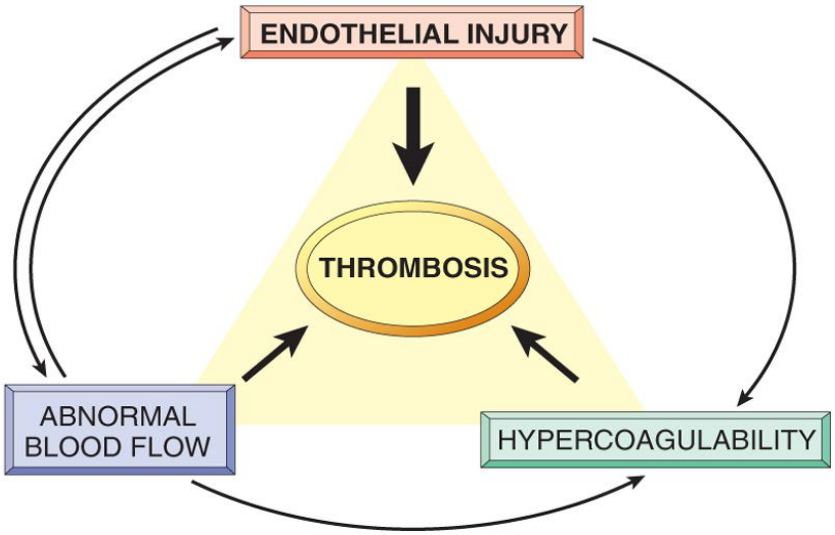
- **Coagulation factors :**
  - Coagulation occurs via the sequential enzymatic conversion of a cascade of circulating and locally synthesized proteins
  - Tissue factor elaborated at sites of injury is the most important initiator of the coagulation cascade
  - At the final stage of coagulation, **thrombin converts fibrinogen into insoluble fibrin,** which helps to form the **definitive** hemostatic plug.

Thrombosis :

Caused by one or more of 3 abnormalities

- Endothelial injury
- Abnormal or turbulent blood flow
- Hypercoagulability

* Causes of abnormal blood flow / ex. Hypertension, aneurysms (abnormal aortic and arterial dilations) → stasis



Virchow's triad in thrombosis

Integrity of endothelium is the most important factor. Injury to endothelial cells can also alter local blood flow and affect coagulability.

Abnormal blood flow (stasis or turbulence), in turn, can cause endothelial injury. The factors may act independently or may combine to promote thrombus formation

- **Hypercoagulability :**

  Any alteration of the coagulation pathways that predisposes to thrombosis.

- **Causes of Hypercoagulability :**

<table>
<tr><th>Genetic</th><th>Secondary (acquired)</th></tr>
<tr><td>Common
• Mutation in factor V Leiden
an autosomal dominant condition which exhibits incomplete dominance
Only a moderately increased risk of thrombosis (inherited hypercoagulability state) when otherwise healthy patients are free of thrombotic complications
• Mutation in prothrombin gene</td><td rowspan="2">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</td></tr>
<tr><td>Rare
• Protein C deficiency
• Protein S deficiency</td></tr>
<tr><td>Very rare
• Fibrinolysis defects</td><td>Lower risk for thrombosis
• Cardiomyopathy
• Nephrotic syndrome
• Hyperestrogenic states (pregnancy)
• Oral contraceptive use
• Sickle cell anemia
• Smoking</td></tr>
</table>

- **Antiphospholipid antibody syndrome**

– *Clinically, the findings include:*

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

– Fetal loss is attributable to **antibody-mediated inhibition of t-PA activity** necessary for trophoblastic invasion of the uterus

– Antiphospholipid antibody syndrome can be:

- *primary*, only the manifestations of a hypercoagulable state and lack evidence of other autoimmune disorders
- *Secondery*, Individuals with a well-defined autoimmune disease, such as SLE

N.B / The name *antiphospholipid antibody syndrome* is a bit of a misnomer, as it is believed that the most important pathologic effects are mediated through binding of the antibodies to epitopes on plasma proteins (e.g., prothrombin) that are somehow induced or "unveiled" by phospholipids.

- **DISSEMINATED INTRAVASCULAR COAGULATION (DIC)**

– Sudden or insidious onset of widespread fibrin thrombi in the microcirculation (microthrombi spread throughout the circulation → "everywhere")

– Although these thrombi are not grossly visible, they are readily apparent microscopically

– Can cause **diffuse circulatory insufficiency**, particularly in the brain, lungs, heart, and kidneys

– It can evolve into a bleeding catastrophe :

- platelet and coagulation protein consumption → ***consumption coagulopathy***
  - Since platelets and coagulation factors are consumed because of DIC there is no enough platelets for clotting incase of on an injury
- At the same time, fibrinolytic mechanisms are activated.

DIC is not a primary disease but rather a potential complication of any condition associated with widespread activation of thrombin. Ex. If someone has septicaemia, as a result of bacterial infection there will be **widespread** activation of thrombin → fibrin formation → thrombus

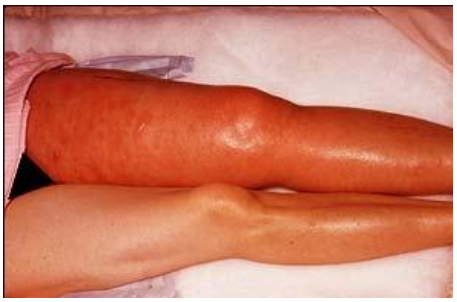
DIC is usually seen in ICU patients.

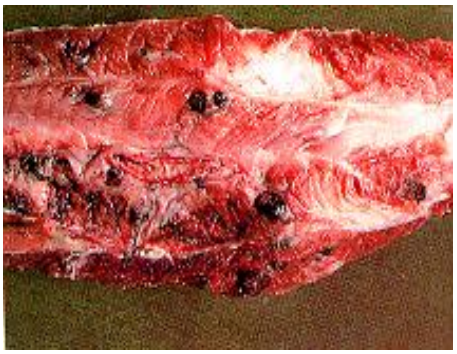
Thrombi :

- Thrombi are focally attached to the underlying vascular surface
- Thrombi often have grossly and microscopically apparent laminations called lines of Zahn → alternating pale and dark lines the pale represent platelets and fibrin layers while the darker lines represent rid cell rich layers. Only seen in flowing blood → indicate ante mortem (not dead) thrombosis.
- Post mortem clots can sometimes be mistaken for ante mortem venous thrombi but they differ in :
    - Gelatinous
    - Have a red portion and yellow (*chicken fat*) portion.
    - Usually not attached to the underling wall.
- **Thrombi on heart valves are called vegetations**

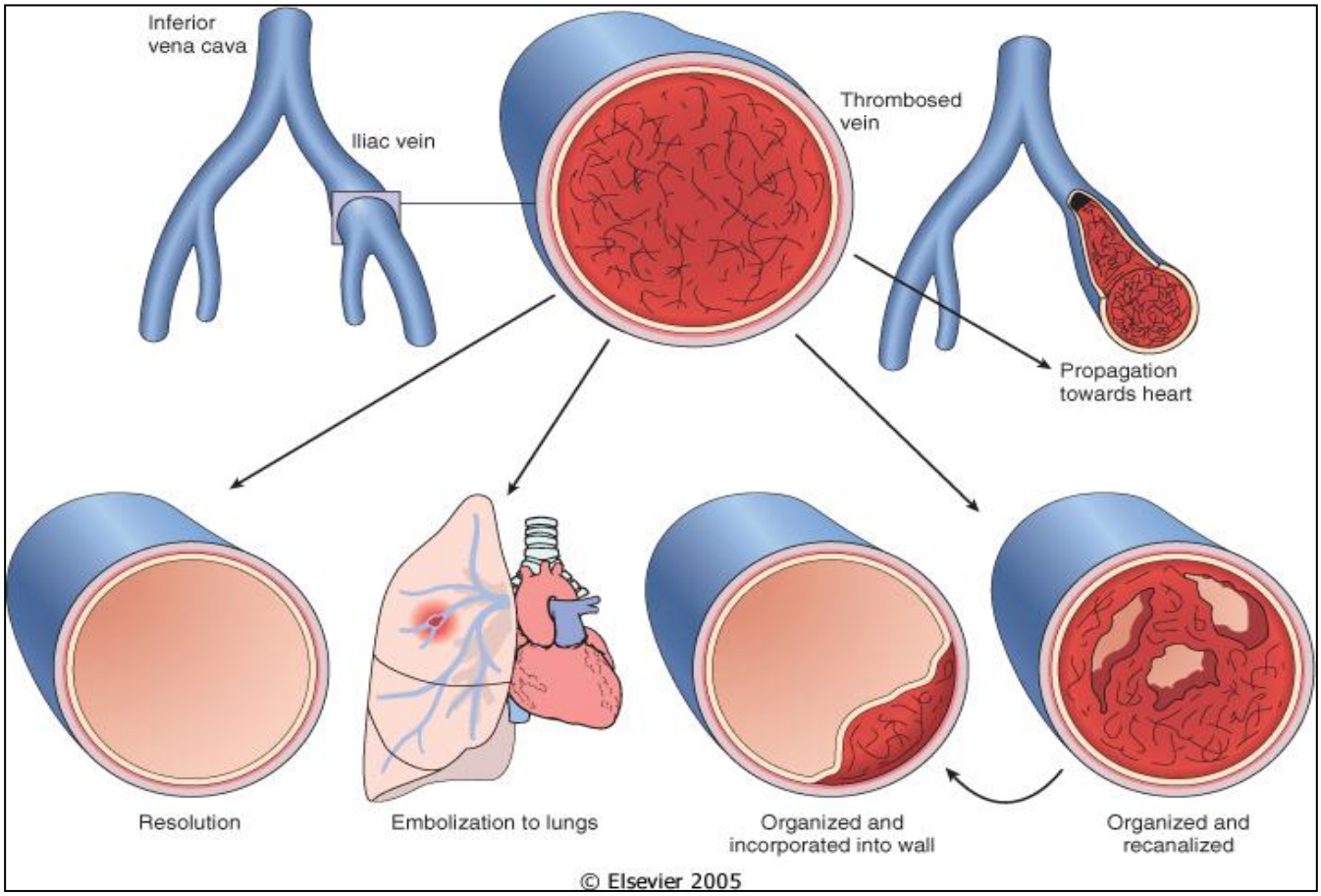
Arterial thrombosis	Venous thrombosis (phlebothrombosis)
Frequently occlusive	almost invariably occlusive
Characteristically associated with **endothelial injury** or **abnormal blood flow**	Characteristically occur at sites of **stasis**
underlying causes include ruptured atherosclerotic plaque, vasculitis, trauma	Also known as red/stasis thrombosis → they contain more RBC's and relatively few platelets.
Most common sites in decreasing order of frequency are : Coronary → cerebral → femoral	Most common site is the **lower extremities (90% of cases)**

- **Deep venous thrombosis (DVT):**
  - *in the larger leg veins—at or above the knee* (e.g., popliteal, femoral, and iliac veins)
  - Such thrombi more often embolize to the lungs and give rise to pulmonary infarction
  - Although they can cause local pain and edema, venous obstructions from DVTs can be rapidly offset by collateral channels.
  - Consequently, DVTs are asymptomatic in -~ 50% cases
    - **Predisposing factors :**
      - **Bed rest and immobilization**
      - **Congestive heart failure**
      - **Trauma, surgery and burns**
      - **Pregnancy**
      - **Tumors**
      - **Advanced age**





- **Thrombi on heart valves** → *it could be due to **infection** where a large thrombotic masses develop on the heart called vegetations **(infective endocarditis)** or it could be **sterile** vegetations in patients with **hypercoagulability** states **(nonbacterial thrombotic endocarditis)** and less commonly, it can occur in patients with **SLE** due to elevated levels of circulating immune complexes **(non infective, verrucous "Libman sacks" endocarditis)***



- **Fate of thrombosis :**

Platelet plug + fibrin mesh → RBCs and other cells entrapped → the thrombus may →

- **Grow in layers (PROPAGATION)**
- **Be removed by fibrinolysis**
- **Be organized and re-canalized**
- **Embolize**

Embolism :

- **Embolus definition:**

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

- **Embolism can be caused by any obstruction of a blood vessel such as**
  - Fat droplets
  - Bubbles of air or nitrogen
  - Atherosclerotic debris (cholesterol emboli)
  - Tumor fragments
  - Bits of bone marrow
  - Foreign bodies (such as bullets)

But all these are ***rare*** causes **whereas 99% of all emboli represent part of dislodged thrombus (thrombo-embolism)**

- **Pulmonary thromboembolism :**

- In more than 95% of cases, venous emboli originate from **deep leg vein thrombi** above the level of the **knee** → progressively larger channels and pass through the right side of the heart → entering the pulmonary vasculature
- Depending on the size of the embolus, it may:
  - occlude the main pulmonary artery
  - impact across the bifurcation (*saddle embolus*)
  - pass out into the smaller, branching arterioles

In general, *the patient who has had one pulmonary embolus is at high risk of having more*

- 60%-80% of cases are clinically silent because they are small. These eventually become organized and incorporated into vascular wall.

- **When 60% or more of the pulmonary circulation** is obstructed with emboli →
  - sudden death
  - right ventricular failure (*cor pulmonale*)
  - cardiovascular collapse
- **embolic obstruction of pulmonary arteries** :
  → if the arteries are **medium sized** → **No infarction** → because the lung has **dual blood supply** and the intact bronchial arterial circulation continues to supply blood to the area
  ➔ if they are **small end arterioles** → there is **infarction**
- Many emboli occurring over a period of time may cause pulmonary hypertension → right ventricular failure

***Paradoxical embolism*:**

Rarely, an embolus can pass through an interatrial or interventricular defect, thereby entering the systemic circulation.

- **Systemic thromboembolism :**

- Emboli in the ***arterial*** circulation
- Most (80%) arise from **intra-cardiac mural thrombi**
- Major sites are :
  - Lower extremities
  - Brain
  - Intestines, kidneys, and spleen affected to a lesser extent.

Mural thrombi → thrombi in heart champers or aortic thrombi

Other forms of emboli :

- **Fat embolism :**

Microscopic fat globules can be found in the circulation after **fractures of long bones** (which contain fatty marrow), burns or after soft-tissue trauma.

Characterized by :

- **pulmonary insufficiency**
- **neurologic symptoms**
- **anemia**
- **Thrombocytopenia**

- **Air embolism :**
  - Gas bubbles within the circulation can obstruct vascular flow .
  - Air may enter the circulation during obstetric procedures or as a consequence of chest wall injury
  - Generally, more than 100 mL of air are required to produce a clinical effect

- ***Decompression sickness***

  Occurs when individuals are exposed to **sudden changes** in atmospheric pressure. Ex.scuba and deep sea divers are at risk
  Can induce **focal ischemia** in an number of tissues :
  - Brain and heart
  - Skeletal muscle causing pain (the bends)
  - In the lung causing respiratory distress (the chokes)

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 → gas emboli

- **Amniotic embolism :**

- A grave but fortunately uncommon → 1 in 40,000 deliveries but when it happens there is 80% chance it will be fatal
- **Complication of labour** and the immediate postpartum period
- The underlying cause is **entry of amniotic fluid** (and its contents ex. Squamous cell from the fetal skin, mucin from fetal GIT or respiratory tract) into the maternal circulation via a tear in the placental membranes and rupture of uterine veins
- The onset is characterized by sudden severe dyspnea, cyanosis, and hypotensive shock, followed by seizures and coma
- If the patient survives the initial crisis, the patient may develop:
    - pulmonary edema and diffuse alveolar damage
    - disseminated intravascular coagulation (DIC), due to release of thrombogenic substances from amniotic fluid

Good luck