Thrombosis and Embolism

- What causes thrombosis?
  The primary abnormalities that lead to thrombosis are the so-called **Virchow triad**
  1. endothelial injury
  2. stasis or turbulent blood flow
  3. hypercoagulability of the blood
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- What damages the endothelium?
  Inflammation, toxins (smoking), hypercholesterolemia, hyperhomocyteinemia, physical injury, abnormal blood flow, etc.
- By which mechanism does endothelial injury cause thrombosis?
  Injury to ECs cause them to switch their gene expression to a procoagulant one
  - down-regulation of Thrombomodulin, Protein C, and Tissue Factor Protein inhibitor.
  - secretion of plasminogen activator inhibitors (PAIs), which limit fibrinolysis, and downregulate the expression of t-PA.
- By which mechanism does turbulence cause thrombosis?
  Turbulence contributes to arterial and cardiac thrombosis by causing **endothelial injury** or dysfunction as well as by forming countercurrents that contribute to **local pockets of stasis** (Different from stasis of the venous circulation that is more generalized and a major contributor to the development of venous thrombi)
  Normal blood flow is laminar such that the platelets (and other blood cellular elements) flow centrally in the vessel lumen, separated from the endothelium by a slower moving layer of plasma. Turbulence and stasis therefore:
  - Promote endothelial activation, enhancing procoagulant activity and leukocyte adhesion, in part through flow- induced changes in the expression of adhesion molecules and pro-inflammatory factors
  - Disrupt laminar flow and bring platelets into contact with the endothelium
  - Prevent washout and dilution of activated clotting factors by fresh flowing blood and the inflow of clotting factor inhibitors
- What can cause turbulence or similar blood flow alterations that promote thrombosis?
  - atherosclerotic plaque → turbulence
  - Atrial fibrillation, dilated atrium → stasis (major)
  - Aneurysms→ stasis
  - Sickle cell anemia→ stasis

    - Hyper viscosity→ stasis
- What are the possible causes of hypercoagulability?
  Hypercoagulability refers to an abnormally high tendency of the blood to clot, and is typically caused by alterations in coagulation factors. Hypercoagulability has a particularly important role in venous thrombosis and can be divided into primary (genetic) and secondary (acquired) disorders (Table 4.2). Of the inherited causes of hypercoagulability,

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- **Describe the morphology of different thrombi**
  Arterial or cardiac thrombi usually begin at sites of turbulence or endothelial injury, whereas venous thrombi characteristically occur at sites of stasis.
  Thrombi are focally attached to the underlying vascular surface, particularly at the point of initiation.. The propagating portion of a thrombus is often poorly attached and therefore prone to fragmentation and embolization.
  Mural thrombi:
    - Thrombi in heart chambers or in the aortic lumen
    - Risk factors: abnormal myocardial contraction (arrhythmias, dilated cardiomyopathy, or MI) or endomyocardial injury (myocarditis or catheter trauma)
    - In the **aorta** they frequently develop from ulcerated **atherosclerotic** plaque and **aneurysmal** dilation.
- **Vegetations**
    - thrombi on heart valves
    - may be infected or sterile
        - Blood-borne bacteria or fungi can adhere to previously damaged valves or may cause valve damage directly; in either case, endothelial injury and disturbed blood flow can induce the formation of large thrombotic masses
        - Sterile vegetations can develop on hypercoagulable states (nonbacterial thrombotic endocarditis)
- **Arterial thrombi → WHITE THROMBI**
    - frequently occlusive, most common sites: coronary, cerebral, and femoral arteries.
    - Morphology: meshwork of platelets, fibrin, red cells, and degenerating leukocytes,
    - grow retrograde TOWARDS THE HEART
    - usually superimposed on a ruptured atherosclerotic plaque. Other vascular injuries (vasculitis, trauma) may be the underlying cause.
    - Commonly found in: coronary, cerebral and femoral arteries
- **Venous thrombosis (phlebothrombosis) → RED THROMBI**

    - almost always occlusive.
    - contain **more red cells and relatively few platelets** (red thrombi). They are **firm**, focally attached to the vessel wall, and contain **lines of Zahn** (pale platelet and fibrin deposits alternating with darker red cell–rich layers), Such laminations signify that a thrombus has formed in flowing blood, features that help distinguish them from postmortem clots .
    - 90% of cases happen in veins of lower extremities.
    - extend in the direction of blood flow; thus both propagate toward the heart
    - **Superficial** venous thrombi affect the **saphenous** vein in the presence of varicose veins (varicosities): local pain, congestion, swelling, tenderness varicose ulcers. Rare embolization
    - **DVT** affect the **popliteal, femoral, iliac veins**: asymptomatic in 50% of cases; local pain and edema in the remaining cases. More serious because they can embolize → pulmonary embolism
    - They occur in stasis and hypercoagulability states: bed immobilization, congestive heart failure, tumors, trauma, advanced age.
- **Postmortem clots**
    - gelatinous and have a dark-red dependent portion where red cells have settled by gravity and a yellow “chicken fat” upper portion, and are usually not attached to the underlying vessel wall.
- Describe the evolution of a thrombus
  If a patient survives the initial thrombosis, in the ensuing days to weeks thrombi undergo some combination of the following four events:
    1. **Propagation**: thrombi accumulate additional platelets and fibrin
    2. **Embolization**: thrombi dislodge and travel to other sites in the vasculature
    3. **Dissolution**: the result of fibrinolysis → rapid shrinkage and total disappearance of *recent* thrombi. Extensive fibrin deposition and cross-linking in *older* thrombi render them more resistant to lysis. This distinction explains why therapeutic administration of fibrinolytic agents such as t-PA (e.g., in the setting of acute coronary thrombosis) is generally effective only when given during the first few hours of a thrombotic event.
    4. **Organization and recanalization**: Older thrombi become organized by the ingrowth of endothelial cells, smooth muscle cells, and fibroblasts. Capillary channels eventually form that reestablish the continuity of the original lumen, albeit to a variable degree. Continued recanalization may convert a thrombus into a smaller mass of connective tissue that becomes incorporated into the vessel wall. Eventually, with remodeling and contraction of the mesenchymal elements, only a fibrous lump may remain to mark

the original thrombus

- Clinical presentation of thrombosis?
  Thrombi come to clinical attention when they obstruct arteries or veins, or give rise to emboli. The clinical presentation depends on the involved site.
  - Venous thrombi can cause:
    - painful congestion and edema distal to an obstruction
    - **pulmonary embolism**
  - arterial thrombi
    - can embolize and cause downstream infarctions
    - **occlusion** of a critical vessel (e.g., a coronary or cerebral artery)→ **infarction**
- Prevention and Treatment of thrombosis
  Main antithrombotic therapies:
  - Antiplatelet drugs (Aspirin)
  - Anticoagulants (heparin, dicumarolic)
  - Activators of the fibrinolytic system (plasminogen activators)
- Thrombus removal:
  - **Angioplasty** and subsequent placement of a medicated **STENT** (with antiproliferative and antithrombotic factors)
- Thrombotic disease prevention:
  - Risk factor control (diet, hypercholesterolemia, physical activity, lifestyle, smoking, oral contraceptives, etc.)
- What is an embolus?
  An embolus is a **detached intravascular solid, liquid, or gaseous mass** that is carried by the blood from its point of origin to a distant site, until they encounter vessels too small to permit further passage, causing partial or complete vascular occlusion→ tissue dysfunction or infarction.
  The vast majority of emboli are dislodged thrombi, hence the term **thromboembolism**.
  Other rare emboli are composed of fat droplets, nitrogen bubbles, atherosclerotic debris (cholesterol emboli), tumor fragments, bone marrow, or even foreign bodies.
- Describe solid emboli
  99% of solid emboli derive from thrombotic fragmentation and are called thromboemboli.
  The remaining 1%:
  1. fragments of pathological tissues (detaching from neoplasms that have permeated the vessels, from endocarditic or atherosclerotic ulcers, etc.) or even from normal tissues (liver cells, marrow cells, etc.)
  2. micro- and macroscopic parasites (echinococcus, schistosome filarias, ascarids, hookworms, plasmodia, leishmanias,

trypanosomes) or from fungi, etc.
3. foreign bodies of various kinds (needles, bullets, spines, etc.) occasionally penetrated into the heart or vessels

- **Fragmentation of the thrombus is more frequent in the case of white thrombus but it can also occur in red thrombi.**
  Arteries:
  Most systemic emboli (80%) arise from mural thrombi of the heart chambers:
  - 2/3 associated with left ventricular wall infarcts
  - 1/3 associated with left atrial dilatation and fibrillation
- The remaining systemic emboli originate from aortic aneurysms, atherosclerotic plaques (atherosclerotic debris or cholesterol emboli), valvular vegetations, or venous thrombi
  Veins:
  The most common type of thromboembolic disease is **Pulmonary emboli** (PE) which in 95% of cases originates from deep venous thrombosis of lower extremities
  Fragmented thrombi from DVT reach the pulmonary circulation and Depending on the size of the embolus, it can occlude
  - the main pulmonary artery
  - the pulmonary artery bifurcation (saddle embolus)
  - the branching arteries.
- Frequently there are multiple emboli, occurring either sequentially or simultaneously as a shower of smaller emboli from a single large mass; in general, the patient who has had one PE is at high risk for more. Rarely, a venous embolus passes through an interatrial or interventricular defect and gains access to the systemic arterial circulation (paradoxical embolism)
- Describe fat emboli
  Possible causes
  - erroneous i.v. injections of drugs dissolved in oil
  - fat cells escape from adipose tissue or yellow bone marrow
    - fractures of long bones → frequent in elderly
    - tissue trauma (surgeries)
    - burns.
    - It occurs in 90% of individuals with severe skeletal injuries but less then 10% of them have clinical findings
- Risk of occlusion of **pulmonary** and **cerebral** microvasculature. Fatal in 5%-15% of cases
- Describe air emboli
  Air embolism consist of:
  Gas bubbles within the circulation, which can obstruct vascular flow and cause distal ischemic injury A large volume of air (**>100 cc**) in the blood is necessary to produce clinical effects

A form of gas embolism called **decompression sickness**

- Deep sea dive (high pressure) increased amounts of nitrogen dissolved in the blood. When divers ascends (depressurizes) too quickly without compensation stages: nitrogen comes out of solution in the tissue and in the blood (**Hyperbaropathy**).
  - Gas bubbles spread to skeletal muscles and skeletal tissues (around joints): **severe pain.**
  - Gas bubbles in the lung vasculature cause edema, hemorrhage, focal atelectesia or emphysema respiratory distress
- Chronic form: **caisson disease** (pressurized vessels used in bridge construction; workers in these vessels suffered of decompression sickness)
  - persistence of gas emboli in the skeletal system multiple foci of ischemic necrosis (common sites: femoral heads, tibia, and homerus)

- Treatment: hyperbaric chamber