THROMBOSIS

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THROMBOSIS

- Pathogenesis (called Virchow's triad):
  1. *Endothelial* Injury (Heart, Arteries)
  2. *Stasis*
  3. *Blood Hypercoagulability*

* Endothelial cells are special type of cells that cover the inside surface of blood vessels and heart.
ENDOTHELIAL INJURY → THROMBOSIS → ABNORMAL BLOOD FLOW → HYPERCOAGULABILITY → ENDOTHELIAL INJURY
CONTRIBUTION OF ENDOTHELIAL CELLS TO COAGULATION

- Intact endothelial cells maintain liquid blood flow by:
  1. inhibiting platelet adherence
  2. preventing coagulation factor activation
  3. lysing blood clots that may form.

- Endothelial cells can be stimulated by direct injury or by various cytokines that are produced during inflammation.

- Endothelial injury results in:
  1. expression of procoagulant proteins (tissue factor and vWF) → local thrombus formation.
  2. exposure of underlying vWF and basement membrane collagen → platelet aggregation and thrombus formation.
Endothelial Cell Injury and exposure of subendothelial collagen

Adherence of platelets

Release of tissue factor
1. Recruitment of smooth muscle cells or smooth muscle precursor cells to the intima

2. Smooth muscle cell mitosis

3. Elaboration of extracellular matrix

Endothelium

Internal elastic lamina

Smooth muscle cells

Intima

Media

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Response of Vascular Wall Cells to Injury (Pathologic effect of vascular healing)

- Injury to the vessel wall results in a healing response, involving:
  - Intimal expansion (proliferating SMCs and newly synthesized ECM).
    This involves signals from ECs, platelets, and macrophages; and mediators derived from coagulation and complement cascades.
  - Luminal stenosis & blockage of vascular flow
Causes of Endothelial injury

1. Valvulitis
2. MI
3. Atherosclerosis
4. Traumatic or inflammatory conditions
5. Increased Blood Pressure
6. Endotoxins
7. Hypercholesterolemia
8. Radiation
9. Smoking
- **Stasis**

  - *Stasis is a major factor in venous thrombi*
  - Normal blood flow is *laminar* (*platelets flow centrally in the vessel lumen, separated from the endothelium by a slower moving clear zone of plasma*)
  - Stasis and turbulence cause the followings:

    - Disrupt normal blood flow
    - Prevent dilution of activated clotting factors by fresh flowing blood.
    - Retard the inflow of clotting factor inhibitors
    - Promote endothelial cell injury.
Causes of Stasis

1. Atherosclerosis
2. Aneurysms
3. Myocardial Infarction (Non-cotractile fibers)
4. Mitral valve stenosis (atrial dilation)
5. Hyper viscosity syndromes (PCV and Sickle Cell anemia)
Hypercoagulability

A. Genetic (primary):
- mutations in the factor V gene and the prothrombin gene are the most common

B. Acquired (secondary):
- multifactorial and more complicated
- causes include: Immobilization, MI, AF, surgery, fracture, burns, Cancer, Prosthetic cardiac valves ...etc
MORPHOLOGY OF THROMBI

- Can develop anywhere in the CVS (e.g., in cardiac chambers, valves, arteries, veins, or capillaries).

- **Arterial or cardiac** thrombi → begin at sites of **endothelial injury**; and are usually superimposed on an **atherosclerotic plaque**

- **Venous** thrombi → occur at sites of **stasis**. Most commonly the veins of the lower extremities (90%)

- Thrombi are focally attached to the underlying vascular surface; arterial and venous thrombi both tend to propagate toward the heart.

- The propagating portion of a thrombus is poorly attached → fragmentation and embolus formation
ARTERY WITH AN OLD THROMBUS.

A, H&E-stain.  B, Stain For Elastic Tissue (black).
The original lumen is delineated by the internal elastic lamina (arrows) and is totally filled with organized thrombus.
LINES OF ZAHN

- Thrombi can have grossly (and microscopically) apparent laminations called **lines of Zahn**; these represent pale platelet and fibrin layers alternating with darker erythrocyte-rich layers.
- Such lines are significant in that they represent thrombosis of **flowing** blood (can potentially distinguish antemortem thrombosis from postmortem clots)
- **Postmortem** blood clots are bland non-laminated clots (**no lines of Zahn**)
- **Mural thrombi** = Thrombi occurring in heart chambers or in the aortic lumen.
- **Causes:**
  - Abnormal myocardial contraction (e.g. arrhythmias, dilated cardiomyopathy, or MI)
  - Endomyocardial injury (e.g. myocarditis, catheter trauma)

- **Vegetations** = Thrombi on heart valves
  1. Bacterial or fungal blood-borne infections → (infective endocarditis,).
  2. Non-bacterial thrombotic endocarditis occur on sterile valves.
MURAL THROMBI: A IN HEART; B IN AORTA
RED ARROWS = MURAL THROMBI
BLUE ARROWS = LINES OF ZHAN
Fate of thrombi

1. **Propagation** → Thrombi accumulate additional platelets and fibrin, eventually causing vessel obstruction

2. **Embolization** → Thrombi dislodge or fragment and are transported elsewhere in the vasculature

3. **Dissolution** → Thrombi are removed by fibrinolytic activity (Usually in recent thrombi)

4. **Organization and recanalization** →
   - Thrombi induce inflammation and fibrosis.
   - **recanalization** (re-establishing some degree of flow)
   - Organization = ingrowth of endothelial cells, smooth cells and fibroblasts into the fibrin rich thrombus.

5. **Superimposed infection** *(Mycotic aneurysm)*
Venous thrombi
most common in veins of the legs

a. **Superficial**: e.g. *Saphenous veins.*
- can cause local congestion, swelling, pain, and tenderness along the course of the involved vein, but they rarely embolize

a. **Deep**: e.g. *Popliteal, Femoral and iliac vein.*
- more serious because they may embolize
- can occur with stasis or hypercoagulable states