Lecture 1: THROMBOSIS

The "pathological" thrombosis is caused by the presence of at least one of 3 factors (together called Virchow's triad):

1. Endothelial Injury (Heart, Arteries)	2. Stasis (abnormal blood flow)	3. Blood Hypercoagulability
▪ Response of Vascular Wall Cells to Injury: Healing 1. Recruitment of smooth muscles or smooth muscle precursor to the tunica intima 2. Mitosis of smooth muscles 3. Elaboration of ECM ▪ Pathologic effect of vascular healing: Excessive thickening of the intima → luminal stenosis & blockage of vascular flow.	▪ 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: 1. Disrupt normal blood flow. 2. Prevent the dilution of activated clotting factors by fresh blood. 3. Retard the inflow of clotting factor inhibitors 4. Promote endothelial cell injury.	▪ Genetic (primary) most common >> mutations in factor V gene and prothrombin gene. ▪ Acquired (secondary) multifactorial & more complicated

MORPHOLOGY OF THROMBI

Arterial or cardiac thrombi	Venous thrombi
begin at sites of endothelial injury or turbulence, and are usually superimposed on an atherosclerotic plaque	occur at sites of stasis

▪ Thrombi are focally attached to the underlying vascular surface

▪ The propagating portion of a thrombus is poorly attached →fragmentation and embolus formation.

LINES OF ZAHN

* Pale area ➲ platelet and fibrin layers.

* Dark area ➲ erythrocyte-rich layers.

Significance? distinguish antemortem thrombosis from postmortem clots… postmortem blood clots are non-laminated clots (no lines of Zahn).

▪ Mural thrombi ➲ thrombi in heart chambers or in the aortic lumen.

▪ Cardiac vegetation ➲ Thrombi on heart valves. Types:

1. Infectious (Bacterial or fungal blood-borne infections) e.g. infective endocarditis.
2. Non- infectious: e.g. non-bacterial thrombotic endocarditis.

▪ Fate of thrombi:

- Dissolution ⇨ Thrombi are removed by fibrinolytic activity (only in recent thrombi).
- Propagation ⇨ accumulate additional platelets and fibrin, eventually causing vessel obstruction.
- Embolization ⇨ Thrombi dislodge or fragment and are transported elsewhere in the vasculature.

- Organization and recanalization ⇨Thrombi induce inflammation and fibrosis. These can recanalize (re-establishing some degree of flow), or they can be incorporated into a thickened vessel wall.
  Organization refers to the ingrowth of endothelial cells, smooth cells and fibroblasts into the fibrin rich thrombus.
- Superimposed infection (Mycotic aneurysm).

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Lecture 2: EMBOLISM AND INFARCTION

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

▪ Emboli result in partial or complete vascular occlusion ➔ ischemic necrosis (infarction) of downstream tissue.

▪ Types (according to the composition of emboli):

1. Thromboembolism: 99% (from dislodged thrombus)
2. Fat embolism
3. Air /Nitrogen embolism
4. Amniotic fluid embolism

1. Thromboembolism

▪ Types according to the site of origin:

	Arterial emboli	**Venous emboli**
Origin	Most of them from heart chambers (intracardiac mural thrombi)	95% originate from deep veins thrombi of Lower Limbs (DVT)
Target	lower limbs (75%)	Lung (mostly)

▪ **SADDLE EMBOLUS**

large embolus occluding the bifurcation of the pulmonary artery trunk (fatal)

▪ **PARADOXICAL EMBOLUS**

Passage of embolus from venous to the systemic circulation through ASD or VSD

▪ <u>The clinical consequence of pulmonary thromboembolism</u>:

- 60%- 80% of pulmonary emboli are clinically asymptomatic (small) ➔ Organization.
- If it is large ➔ Pulmonary infarction.
- > 60 % of pulmonary vessels are obstructed ➔ RVF, CV collapse ➔ Sudden death.
- Obstruction of medium-sized arteries ➔ Pulmonary hemorrhage.
- If multiple emboli (showers of emboli) over a long time ➔ Pulmonary Hypertension and right ventricular failure.

2. Fat embolism

▪ <u>Causes</u>:

1. Skeletal injury (fractures of long bones)
2. Adipose tissue Injury (massive fat necrosis like acute pancreatitis)

In skeletal injury, fat embolism occurs in 90% of cases, but only 10% or less have clinical findings = Fat embolism Syndrome.

- Fat embolism 'syndrome' is characterized by:

  - Pulmonary Insufficiency (rapid breathing; shortness of breath)
  - Neurologic symptoms (mental confusion; lethargy; coma)
  - Fever
  - petechial rash (pinpoint rash, found on chest, head, and neck area due to bleeding under skin)
  - Anemia
  - Thrombocytopenia
  - Death in 10% of cases.

- Results of fat embolism:

  1. Mechanical obstruction of vessels
  2. free fatty acid release from fat globules ➲ local toxic injury to endothelium.

- Symptoms appear 1-3 days after injury.

3. Air embolism

- Cases:

  1. Surgical and obstetric procedures
  2. Vascular catheterization
  3. Traumatic chest wall injury
  4. Decompression sickness: in Scuba deep-sea divers [nitrogen]

- Clinical consequence:

  1. Painful joints: rapid formation of gas bubbles within Skeletal Muscles and supporting tissues.
  2. Respiratory distress (chokes): Lung edema, hemorrhage, atelectasis, emphysema.
  3. Focal ischemia in brain and heart.
  4. Caisson disease: in scuba divers; gas emboli in the bones leads to multiple foci of ischemic necrosis, usually the heads of the femurs, tibias, and humeri

4. Amniotic fluid embolism

infusion of amniotic fluid into maternal circulation via tears in placental membranes and rupture of uterine veins.

- Symptoms:

Sudden severe dyspnea, cyanosis, ARDS, and hypotensive shock, followed by seizures, DIC and coma

- Microscopic Findings upon autopsy:

fetal squamous cells, lanugo hair, fat, mucin, keratin within the maternal pulmonary microcirculation (arterioles).

- High Mortality Rate, very rare complication of labor.

INFARCTION

an area of ischemic necrosis caused by occlusion of arterial supply or venous drainage in a tissue.

- Causes: thrombi/emboli (99%) - Vasospasm - extrinsic compression (e.g., by tumor) - vessel twisting (e.g.testicular torsion, volvulus) - traumatic vessel rupture

- Histologic hallmark of infarction is ischemic coagulative necrosis; the brain is an exception (liquefactive necrosis).

- Most infarcts are ultimately replaced by scar.

- infarcts may be:

1. **red (hemorrhagic) infarcts**, the causes:

   a. venous occlusions (e.g. ovarian torsion)
   b. loose tissues (e.g. lung) that allow blood to collect in the infarcted zone
   c. tissues with dual circulations (e.g. lung and small intestine)
   d. previously congested tissues because of sluggish venous outflow
   e. when flow is re-established to a site of previous arterial occlusion and necrosis

2. **White infarcts**, occur with:

   a. arterial occlusions
   b. Solid organs

3. **Septic infracts**:

Infraction + Infection → infarct is converted into abscess with a greater inflammatory response.

4. **Bland infarcts**

- Factor that influence the development of an infarcts:

   1. nature of vascular supply
   2. oxygen content of blood
   3. rate of occlusion development (collateral circulation)
   4. tissue vulnerability to hypoxia
      - Neurons undergo irreversible damage → 3 to 4 minutes of ischemia
      - Myocardial cells die after only 20 to 30 minutes of ischemia

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Lecture 3: VEINS AND LYMPHATICS

Pathology of veins	
Varicose Veins	▪ Abnormally dilated, tortuous veins produced by prolonged increase in intra-luminal pressure and loss of vessel wall support. ▪ The superficial veins of the leg are most typically involved. ▪ Symptoms: venous stasis and edema (simple orthostatic edema) + cosmetic effect ▪ Risk factors: Obesity, Pregnancy, Female gender, Familial tendency (premature varicosities result from imperfect venous wall development) ▪ Microscopic Morphology: 1. Vein wall thinning 2. Intimal fibrosis in adjacent segments 3. Spotty medial calcifications (phlebosclerosis) 4. Focal intraluminal thrombosis 5. Venous valve deformities ▪ Complication: 1. stasis, congestion, edema, pain, and thrombosis 2. chronic varicose ulcers 3. embolism is very rare
Thrombophlebitis & Phlebothrombosis (Interchangeable terms)	▪ Inflammation + thrombosis of veins ▪ Most common site: deep leg veins (90% of all) ▪ Predispositions: congestive heart failure, neoplasia, pregnancy, obesity, the postoperative state, and prolonged bed rest or immobilization ▪ local manifestations: distal edema, cyanosis, superficial vein dilation, heat, tenderness, redness, swelling, and pain ▪ Thrombophlebitis of upper limb veins are usually associated with local risk factors like: catheter or canula site or systemic hypocoagulabilities.
Special thrombophlebitis types	**1. Migratory thrombophlebitis (Trousseau sign)** hypercoagulability occurs as a paraneoplastic syndrome related to tumor elaboration of pro-coagulant factors. **2. Superior vena caval syndrome** - neoplasms that compress or invade the superior vena cava (Most common is lung cancer). - marked dilation of veins of head, neck, and arms with cyanosis. **3. Inferior vena caval syndrome** - caused by neoplasms compressing or invading inferior vena cava (m/c: hepatocellular carcinoma and renal cell carcinoma) - marked lower extremity edema, distention of the superficial collateral veins of the lower abdomen (medusa)
Pathology of Lymphatics	
Lymphedema	1. Primary (congenital) lymphedema → lymphatic agenesis or hypoplasia 2. Secondary (obstructive) lymphedema → blockage of a previously normal lymphatic
Lymphangitis	- Acute inflammation due to bacterial infections spreading into lymphatics (m/c are group A β-hemolytic streptococci) - Red, painful subcutaneous streaks - Lymphatics are dilated and filled with an exudate of neutrophils and monocytes - Subsequent passage into the venous circulation can result in bacteremia or sepsis
Chylous	- Milky accumulations of lymph in various body cavities - Caused by rupture of dilated lymphatics, typically obstructed secondary to an infiltrating tumor mass - Types: chylous ascites (abdomen)/ Chylothorax (chest)/ Chylopericardium(pericardium)

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