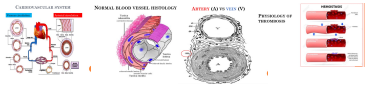
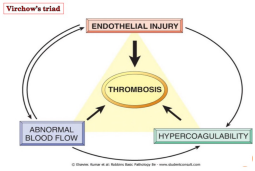
THROMBOSIS- PATHOLOGICAL ASPECTS

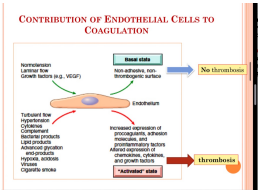


- Blood coagulation is a very important physiological event to protect our hemostasis, and life
- However, at certain points, this process can be pathological that may endorse injury and cause harm to our body
-This happens whenever unnecessary blood clotting is activated
-The "pathological" thrombosis is caused by the presence of at least one of 3 factors (together called Virchow's triad):

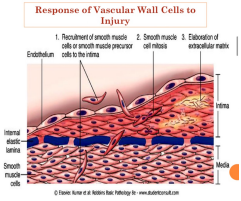


☐ Pathogenesis (called Virchow's triad):
1. Endothelial* Injury (Heart, Arteries)
2. Stasis (abnormal blood flow)
3. Blood Hypercoagulability
* Endothelial cells are special type of cells that cover the inside surface of blood vessels and heart.

1 : endothelial injury



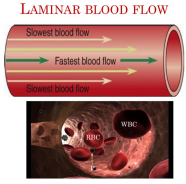
Endothelial Cell Injury and exposure of subendothelial collagen
⬇
Adherence of platelets
⬇
Release of tissue factor
⬇
Progression of coagulation event ...



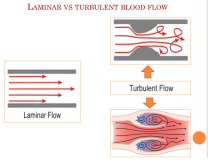
➡ Injury results in a healing response
Pathologic effect of vascular healing:
1. Excessive thickening of the intima : luminal stenosis & blockage of vascular flow

☐ Causes of Endothelial injury :
1. Valvulitis 2. MI 3. Atherosclerosis 4. Traumatic or inflammatory conditions 5. Hypertension 6. Endotoxins 7. Hypercholesterolemia 8. Radiation 9. Smoking

2 : Abnormal blood flow



- 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 :
- Stasis is a major factor in venous thrombi
-Causes of Stasis
1. Atherosclerosis
2. Aneurysms
3. Myocardial Infarction (Non-cotractile fibers)
4. Mitral valve stenosis (atrial dilation)
5. Hyper viscosity syndrome (PCV and Sickle Cell anemia)

- 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.

3 : Hyper-coagulability

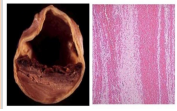
Hypercoagulability
A. Genetic (primary):
- most common >> mutations in factor V gene and prothrombin gene

B. Acquired (secondary):
- multifactorial & more complicated
- causes include: Immobilization, MI, AF, surgery, fractures, burns, Cancer, Prosthetic cardiac valves ...etc

MORPHOLOGY OF THROMBI :
1.Can develop anywhere in the CVS (e.g., in cardiac chambers, valves, arteries, veins, or capillaries).
2.Arterial or cardiac thrombi —> begin at sites of endothelial injury or turbulence; and are usually superimposed on an atherosclerotic plaque
3.Venous thrombi —> occur at sites of stasis. Most commonly the veins of the lower extremities (90%)
4.Thrombi are focally attached to the underlying vascular surface.
5.The propagating portion of a thrombus is poorly attached—> fragmentation and embolus formation

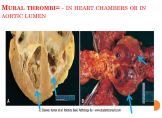
Terms to remember

1



LINES OF ZAHN
-gross and microscopically apparent laminations
-represent pale platelet and fibrin layers alternating with darker erythrocyte-rich layers
-Significance? distinguish antemortem thrombosis from postmortem clots
-postmortem blood clots are non-laminated clots (no lines of Zahn)

2



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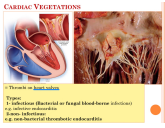
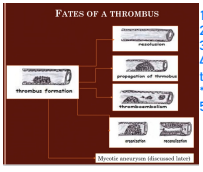
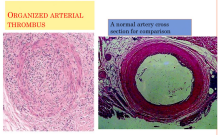


FATES OF A THROMBUS



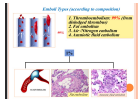
1. Propagation —> accumulate additional platelets and fibrin, eventually causing vessel obstruction
2. Embolization —> Thrombi dislodge or fragment and are transported elsewhere in the vasculature
3. Dissolution —> Thrombi are removed by fibrinolytic activity (only in recent thrombi)
4. Organization* 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.
5. Superimposed infection (Mycotic aneurysm)

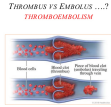


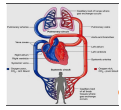
EMBOLISM : An embolus is a detached intravascular solid, liquid, or gaseous mass that is carried by the blood to a site distant from its point of origin

Types :1- (according to composition of emboli):
1. Thromboembolism: 99% (from dislodged thrombus)
2. Fat embolism
3. Air /Nitrogen embolism
4. Amniotic fluid embolism

→ 1%



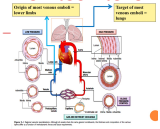


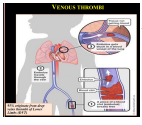


2-TYPES /SIDES OF CIRCULATION(types according to site of origin : VENOUS & ARTERIAL (SYSTEMIC) emboli

Clinical significance?
-Emboli result in partial or complete vascular occlusion.
-The consequences of thromboembolism: ischemic necrosis (infarction) of downstream tissue

Thromboembolism

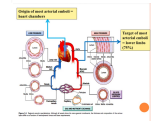


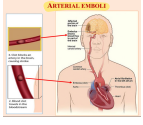


Special terms

CLINICAL CONSEQUENCE OF PULMONARY THROMBOEMBOLISM :

- Asymptomatic (60%- 80%; small)
- Pulmonary infarction (large)
- Pulmonary hemorrhage
- Pulmonary Hypertension and right ventricular failure: (showers of emboli over a long time)
- Sudden death (RVF, CV collapse): > 60 % of pulmonary vessels are obstructed





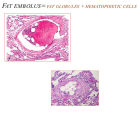
Systemic (arterial) thromboembolism
- Emboli traveling within the arterial circulation
- 80% due to intracardiac mural thrombi (origin)
- causes: -2/3 Lt. ventricular failure - 1/4 Lt. atrial dilatation- Ulcerated atherosclerotic plaque - Aortic aneurysm- valve vegetation ....etc
- The major targets are:

Lower limbs; Brain; Intestine; Kidneys; Spleen; etc... (any organ that has arterial supply!)

Fat embolism

- Causes:
1. Skeletal injury: (long bones fractures)
2. Adipose tissue Injury :(e.g. fat necrosis in acute pancreatitis)

-Results:
1- Mechanical obstruction of vessels
2- free fatty acid release —> toxic injury to endothelium + systemic immune response
- In skeletal injury, fat embolism occurs in 90% of cases, but only 10% or less have clinical findings = Fat embolism syndrome

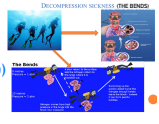


is characterized by:
- Pulmonary Insufficiency (rapid breathing; shortness of breath)
- Neurologic symptoms (mental confusion; lethargy; coma)
- petechial rash (pinpoint rash, found on chest, head, and neck area due to bleeding under skin) • Fever • Anemia • Thrombocytopenia • Death in 10% of the case
- Symptoms appear 1-3 days after injury

THERAPY FOR FAT EMBOLISM SYNDROME
no specific treatment
prevention, early diagnosis, and adequate symptomatic treatment are of paramount importance.
Supportive care is the mainstay of therapy
Includes. maintenance of adequate oxygenation and ventilation, stable haemodynamics, blood products as clinically indicated, hydration, prophylaxis of deep venous thrombosis and stress-related gastrointestinal bleeding, and nutrition.

Air Embolism

causes:
1. Surgical and obstetric procedures
2. Traumatic chest wall injury
3. Decompression sickness: in Scuba deep-sea divers ((nitrogen))

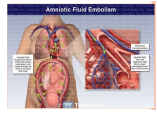


CLINICAL CONSEQUENCE
1. Painful joints: rapid formation of gas bubbles within Skeletal Muscles and supporting tissues.
2. Focal ischemia in brain and heart
3. Respiratory distress (chokes) —> Lung edema, hemorrhage, atelectasis, emphysema
4. Caisson disease. in scuba divers; gas emboli in the bones leads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

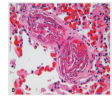
Amniotic fluid embolism

- High Mortality Rate = 20%-40%
- Very rare complication of labor
- 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 .....etc within the maternal pulmonary microcirculation



AMNIOTIC FLUID EMBOLUS: KERATIN AND FETAL SQUAMOUS CELLS IN PULMONARY ARTERIOLES



INFARCTION

- infarct = an area of ischemic necrosis caused by occlusion of arterial supply or venous drainage in a tissue
- 99% of infarcts result from thromboi/emboli events
- other mechanisms:

Local Vasospasm
expansion of atheroma,
extrinsic compression of vessel (e.g., by tumor)
vessel twisting (e.g.testicular torsion, bowel volvulus) and traumatic vessel rupture

Infarcts

RED INFARCTS:
- occur in any of the following scenarios:

(1) venous occlusions (e.g. ovarian torsion)
(2) loose tissues (e.g. lung)
(3) tissues with dual circulations (e.g.lung and small intestine)
(4) previously congested tissues because of sluggish venous outflow
(5) when flow is re-established to a site of previous arterial occlusion and necrosis

WHITE INFARCTS
- occur with:

1) arterial occlusions
2) solid organs (such as heart, spleen, and kidney)

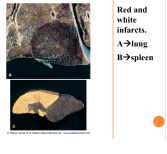
MORPHOLOGY OF INFARCTS :

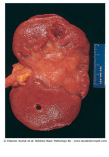
- infarcts may be either red (hemorrhagic) or white (anemic) and may be either septic or bland
- tend to be wedge shaped (occluded vessel at the apex and the periphery of the organ forming the base)
- margins of infarcts tend to become better defined with time
- histologic hallmark of infarction is ischemic coagulative necrosis (ultimately replaced by scar)
- note: The brain is an exception (liquefactive necrosis)

Septic infarctions:

- occur when infarct is superimposed by infection; - examples:

1- infected vegetations
2- microbes seed an area of necrotic tissue
- infarct is converted into abscess with a greater inflammatory response





KIDNEY WHITE INFARCT
kidney infarct replaced by a large fibrotic scar

FACTORS THAT INFLUENCE DEVELOPMENT OF AN INFARCT

- nature of vascular supply
- rate of occlusion development (collateral circulation)
- tissue vulnerability to hypoxia and irreversible damage

- Neurons ——> only 3 minutes
- Myocardial cells ——> 20 to 30 minutes
- oxygen content of blood

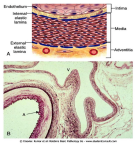
Q: If we have an embolus in the pulmonary artery will the embolus be considered of venous or arterial origin and will its final target be the lungs ?

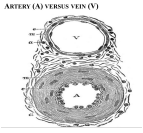
A: Embolism in the pulmonary arteries belongs to venous embolism and the main target is the lung itself. It is a bit confusing but remember that pulmonary artery carries venous blood from the right side of the heart to the lungs, so it's quite the opposite to what do arteries do.

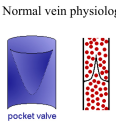
Q: Can pulmonary embolism be of an arterial origin?

A: Yes, the lung can be a target of both venous and arterial embolism types. It depends on the side of the circulation it originated from. So if the embolus is coming from venous circulation and is reaching the lung through the right side of the heart it is a venous embolus. On the other hand, if the embolus is coming out of the left side of the heart and reaching the lung through bronchial circulation, then it is an arterial embolus.

Veins and Lymphatics







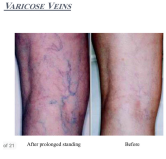
PATHOLOGY OF VEINS

1-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

- 10% to 20% of adult males and > 30% of adult females develop lower extremity varicose veins



RISK FACTORS

- Obesity
- Female gender
- Pregnancy
- Familial tendency (premature varicosities results from imperfect venous wall development)

Microscopic Morphology

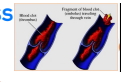
- Vein wall thinning
- intimal fibrosis in adjacent segments
- spotty medial calcifications (phlebosclerosis)
- Focal intraluminal thrombosis
- venous valve deformities(rollingand shortening)

COMPLICATIONS

- stasis, congestion, edema, pain, and thrombosis
- chronic varicose ulcers
- embolism is very rare

2-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 in some cases can be associated with systemic hypercoagulabilities.

Special thrombophlebitis types:

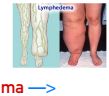
1- Migratory thrombophlebitis (Trousseau sign):
- hypercoagulability occurs as a paraneoplastic syndrome related to tumor elaboration of pro- coagulant factors (e.g. colon cancer; pancreatic ca; etc...)

2- THE SUPERIOR VENA CAVAL SYNDROME
- caused by 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) —> striking tendency to grow within veins
- marked lower extremity edema, distention of the superficial collateral veins of the lower abdomen (medusa)

Pathology of Lymphatics

1• LYMPHEDEMA



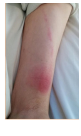
Can occur as :

1- Primary (congenital) lymphedema —> lymphatic agenesis or hypoplasia.

2- Secondary (obstructive) lymphedema —> blockage of a previously normal lymphatic examples:
- Malignant tumors
- Surgical procedures removing lymph nodes
- Post-irradiation
- Fibrosis
- Filariasis
- Postinflammatory thrombosis and scarring

2• LYMPHANGITIS

- acute inflammation due to bacterial infections spreading into lymphatics
- m/c are group A β-hemolytic streptococci.
- lymphatics are dilated and filled with an exudate of neutrophils and monocytes.
- red, painful subcutaneous streaks (inflamed lymphatics), with painful enlargement of the draining lymph nodes (acute lymphadenitis).
- Sometimes, subsequent passage into the venous circulation can result in bacteremia or sepsis.



3• 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)