Thrombosis

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Defination:-

- It is the formation of blood clots within the vascular system

→ It is defined as - "Formation of a structured solid mass within the vascular system from the constitue-nts of blood due to inappropriate activation of hemostatic mechanisms.

*It should take place in flowing blood when the person is alive

Post-mortem clotting - blood clotting after death.

Under normal circumstances body prevents thrombosis by;

1. Block plattelet adhesion and aggregation (Anti-platelete effects)
2. Inhibit coagulation (Anti coagulant effect)
3. Lyse clots (Fibrinolytic effect).

① ANTI-PLATELET EFFECT:-

* Endothelial cells often release NO & prostacyclin (PGI2) which inhibit platelet adhesion and aggregation → Preventing thrombosis

*Intact endothelium → Prevents platelet coming in contact with sub endothelium

* Endothelial cells produce Adenosine diphosphatase, an enzyme which degrade ADP, further preventing platelet aggregation

2. Anti-coagulant effects.
- Activation of coagulation cascade after platelet plug formⁿ
* Results in deposition of fibrin over platelet plug.
* Anti-coagulation effects are aimed at inhibiting the coagulation cascade.
* Endothelial cells secrete heparin like molecules, which acts as co-factor for anti thrombin III
* Anti thrombin III - Inhibits factor II, IX, X & inhibits coagulation
* Endothelial cells also secrete molecule called thrombo modulin which binds to thrombin (factor II), Trombin activates protien C
* Activated protien C, inhibits factor V & VIII To inhibit coagulation

3. FIBRINOLYTIC EFFECTS:-
* Aimed at lysing clots after fibrin deposition.
→ Endothelial cells produce tissue type plasminogen activator (t-PA)
→ This induces conversion of inactivated Plasminogen into active form, i.e, Plasmin
→ Plasmin cleaves fibrin to degrade thrombi

PATHOLOGICAL STATE:-

VIRCHOW'S TRIAD.
Three primary abnormalities of the circulation leads to the development of thrombosis, these are

1. Endothelial injury
2. Alteration in normal blood flow (Turbulence/stasis)
3. Hypercoagulability of blood.

These factor can cause thrombosis independently or in combination; also are interconnected.
* Endothelial integrity is the most important factor To maintain normal blood flow

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1. Endothelial Injury:- @biophilicbams.in

Predominant factor for thrombosis in Heart & Arterial circulation.

causes:-

- Ulcerated atherosclerotic plaque
- Hypertension & turbulant blood flow
- Inflammatory condition - Vasculitis
- Hypoxia
- Bacterial toxins.
- IV infection etc.
- cigarette smoking
- Homocysteinemia.
- Radiation.

Mechanism

Endothelial damage → Exposure of the sub endothelium

*Platelets gets adhered to sub-endothelium, followed by aggregation of more and more platelets

*Platelet plug is formed

*Activation of coagulation cascade

*Leads to fibrin deposition over platelet plug

*When blood flows over this primary thrombosis cells like WBC, RBC get entrapped in fibrin meshwork

*causes turbulence with more platelet adhesion

*Results in thrombus of alternating layers of platelets fibrin and RBC.

*Dysfunctional endothelial cells produce mor procoagula -nt factors, & less anti-coagulant factors, which increases the tendency of thrombosis

Alteration in the normal blood flow

*Either due to turbulence or stasis.

*Normal blood has alaminar flow, plasma flows in the periphery, formed elements (RBC, platelets flow centrally, thus laminar flow som prevents platelets coming in contact with the endothelium

*when blood flow becomes turbulant → disturbs laminar flow

* leading to no separation b/w plasma & blood cells
* turbulent flow - contributes to Arterial and cardiac thrombi
* Turbulence produces conter currents (Eddy currents) & causes endothelial injury.
* Turbulence brings platelets in contact with the endothelial layer, which induces endothelial activation, which enhances procoagulant activity → leads to thrombosis

CONDITION FOR PREDISPOSAL OF THROMBOSIS

* Atherosclerotic plaques → Narrowing of lumen → Turbulence
* Ulcerated atherosclerotic plaques → Endothelial injury → Turbulence
* In aneurysmal sacs at the opening
* Heart - valve incompetence.

Stasis :-

* Blood flow is stagnant.
* Major contributor in the development of venous thrombi
* Stasis induces thrombosis by,
  i) Promoting endothelial activation.
  ii) Enhancing pro-coagulant activity.
  iii) Prevents washout & dilution of activated clotting factors.
  iv) Prevents inflow of clotting factor inhibitors.

Stasis induced thrombosis includes.

After MI → Non-contractile areas of the myocardium Leading to thrombosis by stasis of blood.

* Rheumatic mitral valve stenosis → by left atrial dilation & Atrial fibrillation → Leads to stasis. → followed by thrombosis
* within aneurhysmal sacs → contributed by stasis
  - blood inside aneurysmal sacs - stasis
  - blood at the end of the opening of aneurysmal sac = Turbulant flow

conditions where viscosity of blood increases are:-
Hyperviscosity (Polycythemia) → Resistence to blood flow → Small vessel stasis.

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Sickle cell disease → blood cells tend to clump together and obstruct small vessels → stasis of blood.

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* Prolonged bed rest (After surgery) → Stasis of blood in leg veins (due to ↓ movement) → venous thrombosis

Hypercoagulability :-

* Less frequent contributor of thrombosis.

→ Defined as "Any alteration of the coagulation pathways that predisposes to thrombosis"

Causes :-

a) Genetic (Primary) cause
- → Factor V mutation (Leiden)
- → Prothrombin mutation
- → sticky platelet syndrome
- → Elevated factor VIII, IX, XI or fibrinogen

b) Acquired (2^0) causes
- → Prolonged bed rest or immobilazation
- → Tissue injury (surgery, fracture, burn)
- → MI, cancer
- → Disseminated intra vascular coagulation (DIC)
- → Heparin induced thrombocytopenia
- → Antiphospholipid antibody syndrome.

Characteristic features of Arterial and venous thrombi

Arterial thrombosis

* At the sites of endothelial injury & turbulence.
* In large vessels (Aorta) & heart - Non-occlusive
* In small vessels - often occlusive
* more common in - cerebral, coronary & Femoral arteries.
* Atherosclerosis is the major cause of arterial thrombosis, because it causes both, Turbulence & Endothelial injury.

* shows lines, pale and dark areas, called lines of zohn (alternating light and dark areas)
Pale areas represent platelets and fibrins
Dark area represent RBC.

Venous thrombosis

Thrombophlebitis

* Inflammation of veins leads to thrombosis.
* Thrombus is well attached to the vessel wall
* Inflammation can be,
  a) sterile
  b) Non-sterile
     ↳ Presence of infection causes septic thrombi causing septic emboli

Phlebothrombosis

* No inflammation
* stasis plays a major role

Risk factor
* Immobilization / Prolonged bed rest
* Trauma
* Hypercoagulability
* Surgery (↑ clotting factors)
* Heart failure

→ occurs in superficial & deep leg veins.

Superficial Phlebothrombosis :-

* Occurs in the saphenous vein
* Local oedema & swelling with impaired venous drainage leads to predispose to overlaying skin infec^{n} & varicose ulcers
* Pain & tenderness
* Embolization is rare.

Deep venous thrombosis → lines of zahn are not very prominent
* occurs in popliteal, ~~foss~~ femoral & iliac veins.
* Most often embolize in lungs → Give rise to pulmonary infarction
* Pain & local oedema
* Red in color ∵ of more RBC, less platelete

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Other types of thrombi @ biophilic bams.in

a> Mural thrombi

* Thrombi occurs in heart chambers or in aortic lumen.

→ Cardiac mural thrombosis occurs due to;

* Arrhythmias
* DCM
* MI

→ Aortic mural thrombi is caused by

* Ulcerated atherosclerotic plaques
* Aneurysms.

b> Vegetations:-

Thrombi on heart valves.

* Blood borne bacteria or fungi can adhere to previously damaged heart valves (Rheumatic HD). or,

They can directly damage the healthy valves

↓

Endothelial injury => Turbulence

↓

Thrombosis

Sterile vegetations -

on non infected heart valves

* occurs in people with hypercoagulable state.
* called as non-bacterial thrombotic endocarditis

FATE OF A THROMBUS:-

1. Propogation:-

Thrombi accumulate additional platelets & fibrin & increase in size

* Propogation of thrombus is always towards heart.
  - → venous - Towards the blood flow
  - → Retrograde to blood flow in Arterial thrombi

2. Embolization:-

Thrombi dislodge and travel to other sites.

Dissolution:-

- only smaller thrombi undergo dissolution
- As a result of fibrinolysis
- older thrombi become resistant to fibrinolysis because of extensive fibrin deposition.

Medication:- Administration of fibrinolytic agents (tPA) is effective within first few hours of thrombotic episode

Organisation and Recanalization:-

older thrombi becomes organized by the growth of

a) Endothelial cells
b) Smooth muscle cells } Establish continuity of lumen
c) Fibroblasts.

→ organisation occurs in venous thrombi [blood flow=slow]
→ Recanalization - occurs in Arterial thrombi [↑ blood flow]

* Thrombus undergoes enzymatic digestion to make way for the flowing blood; remaining parts of the thrombus becomes fibrosed and gets attached to the vessel wall

Clinical Manifestation

a) Arterial & cardiac thrombosis
   1. Ischemia & infarction due to obstruction
   2. Thrombo emboli & microemboli generation
   3. Infective endocarditis.
   4. Arterial narrowing after recanalization
   5. weakening of the arterial walls after re canalization (leads to aneurysm formation)
   6. Mycotic aneurysms → infection of aneurysms by bacteria
   7. Predisposed to atheroma formation
b) venous thrombosis
   → Edema, Pulmonary embolism, varicose veins, septic emboli & abcess formation, pyemia

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Difference b/w Antemortem & Postmortem Thrombosis.

Antemortem thrombosis	Post mortem thrombosis
* well attached to vessel wall	* Not attached to vessel wall
* Lines of zahn usually present	* NO lines of zahn (∵ of no platelet component)
* Firm	* Jelly like mass
* Dry and crumble	* RBC settle in lower portion
* can be broken down into small fragments.	* Upper portion is composed of plasma - chicken fat.
	* Moist & soft
	* can be pulled out in one mass

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