Causes of thrombosis/embolism:

| Hyperemia | congestion |
|---|---|
| increase in blood volume | increase in blood volume |
| active process | passive process |
| increased blood inflow | impaired outflow |
| inflammation or in exercising | cardiac failure/ venous obstruction |
| redder | blue-red color (cyanosis) |

In long-standing chronic congestion, inadequate tissue perfusion and persistent hypoxia may lead to parenchymal cell death and secondary tissue fibrosis, and the elevated intravascular pressures may cause edema or sometimes rupture capillaries, producing focal hemorrhages.

| Edema |
|---|
| Increase in interstitial fluid |
| …… |
| increased vascular permeability/ increased hydrostatic pressure or diminished colloid osmotic pressure/ Lymphatic Obstruction/ Sodium Retention/ Inflammation |
| Increased Hydrostatic Pressure: impair venous return/ hypoperfusion of the kidneys<br>Reduced Plasma Osmotic Pressure: Reduction of plasma albumin<br>Lymphatic Obstruction: inflammatory or neoplastic condition<br>Sodium and Water Retention: diseases that compromise renal function |
| pitting edema |

edema resulting from cardiac, renal, and hepatic failure

increased salt and water retention by the kidney not only fails to correct the plasma volume deficit but also exacerbates the edema, because the primary defect—low serum protein—persists.

**Hemorrhage** may be external or accumulate within a tissue as a hematoma

Petechiae are minute (1 to 2 mm in diameter) hemorrhages into skin, mucous membranes, or serosal surfaces; causes include low platelet counts (thrombocytopenia), defective platelet function, and loss of vascular wall support, as in vitamin C deficiency • Purpura are slightly larger (3 to 5 mm) hemorrhages. Purpura can result from the same disorders that cause petechiae, as well as trauma, vascular inflammation (vasculitis), and increased vascular fragility. • Ecchymoses are larger (1 to 2 cm) subcutaneous hematomas (colloquially called bruises). Extravasated red cells are phagocytosed and degraded by macrophages; the characteristic color changes of a bruise result from the enzymatic conversion of hemoglobin (red-blue color) to bilirubin (blue-green color) and eventually hemosiderin (golden-brown).

Greater than 20% losses of blood volume can cause hemorrhagic (hypovolemic) shock.

**Hemostasis**:

1.Arteriolar vasoconstriction/ 2.Primary hemostasis: the formation of the platelet plug/ 3. Secondary hemostasis: deposition of fibrin(mainly by tissue factor(tf))/4. Clot stabilization and resorption

Activation of platelets results in a shape change/ degranulation. By: von Willebrand factor (vWF) and collagen

endothelial cells are central regulators of hemostasis

**platelets**:

VWF functions as an adhesion bridge between subendothelial collagen and the glycoprotein Ib (GpIb) platelet receptor

genetic deficiencies of vWF (von Willebrand disease) or GpIb (BernardSoulier syndrome) or GpIIb-IIIa (Glanzmann thrombasthenia) result in bleeding disorders

glycoprotein IIb/IIIa binds to fibrinogen. Phospholipids bind to calcium.

Platelet activation is triggered by coagulation factor thrombin and ADP.

Thrombin activates platelets through protease-activated receptor (PAR).

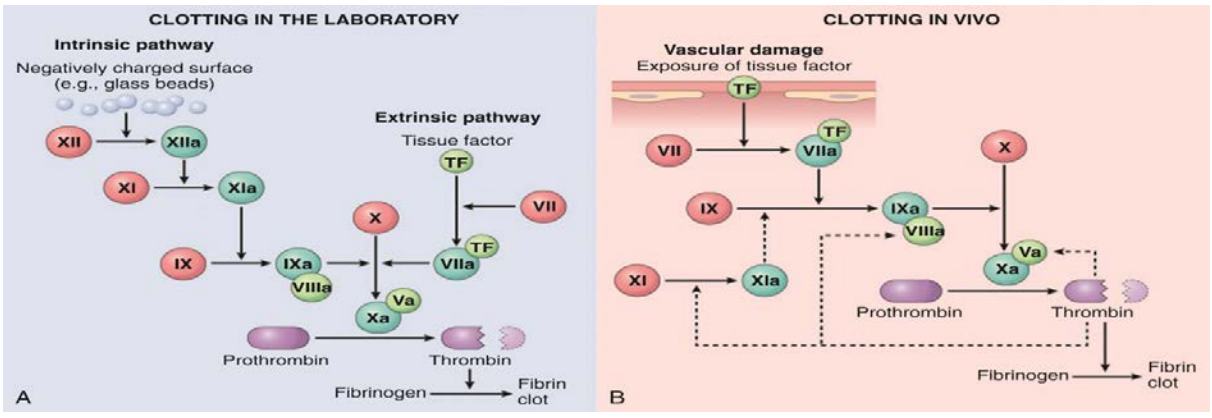
Degranulation of TXA2/ADP lead to recruitment.

**Coagulation Cascade:**

Each reaction step involves an enzyme, a substrate, and a cofactor. These components are assembled on a negatively charged phospholipid surface, which is provided by activated platelets. factors II, VII, IX, and X needs also calcium because it has γ-carboxylated glutamic acid(wich need vitamin k to pruduce).

The prothrombin time (PT) assay assesses the function of the proteins in the extrinsic pathway (factors VII, X, V, II (prothrombin), and fibrinogen)

The partial thromboplastin time (PTT) assay screens the function of the proteins in the intrinsic pathway (factors XII, XI, IX, VIII, X, V, II, and fibrinogen)



Mild bleeding: XI/ moderate to severe: V,VII,VIII,XI,X/ incompatible with life: prothrombin/ no: XII

Thrombin: Conversion of fibrinogen into crosslinked fibrin (stabilizes the secondary hemostatic plug by activating factor XIII, which covalently crosslinks fibrin) 2.Platelet activation: (PARs)/ 3. Proinflammatory effects: (PARs:  here it will mediate tissue repair and angiogenesis)4. Anti-coagulant effects

Factors That Limit Coagulation: dilution/ the requirement for negatively charged phospholipids/ plasmin (activated by XII–dependent pathway or t-PA/ inhibited by α2-plasmin inhibitor)/ Antithrombotic activity of endothelium.)

An elevated level of breakdown products of fibrinogen (often called fibrin split products), most notably fibrin-derived D-dimers, are a useful clinical markers of several thrombotic states

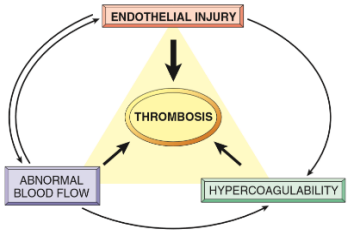
**Antithrombotic of endothelium:**

1. Platelet inhibitory effects: prostacyclin (PGI2), nitric oxide (NO), and adenosine diphosphatase; the latter degrades ADP
2. Anticoagulant effects: thrombomodulin, endothelial protein C receptor, heparin-like molecules, and tissue factor pathway inhibitor. Activated protein C/protein S complex is a potent inhibitor of coagulation factors Va and VIIIa. Heparin-like molecules on the surface of endothelium bind and activate antithrombin III, which then inhibits thrombin and factors IXa, Xa, XIa, and XIIa. Tissue factor pathway inhibitor (TFPI), like protein C, requires protein S as a cofactor and, as the name implies, binds and inhibits tissue factor/factor VIIa complexes
3. Fibrinolytic effects: synthesize t-PA

**** the **vitamin K** - **dependent** coagulation **proteins** are synthesised in the liver and comprise factors II, VII, IX, and X, which have a haemostatic role (i.e., they are procoagulants that arrest and prevent bleeding), and **proteins C** and **S**, which have an anticoagulant role (i.e., they inhibit the clotting process).

## Thrombosis

The primary abnormalities that lead to intravascular thrombosis are (1) endothelial injury, (2) stasis or turbulent blood flow, and (3) hypercoagulability of the blood (the so-called “Virchow triad”)




Endothelial Injury  triggering thrombosis:

By primarily platelet activation.  severe endothelial injury may trigger thrombosis by exposing VWF and tissue factor. However, inflammation and other noxious stimuli also promote thrombosis( endothelial activation or dysfunction)

**prothrombotic alterations:**

1. Procoagulant changes (mostly by inflammation): downregulate of thrombomodulin by cytokines. This will stimulate activation of thrombin, which can in turn stimulate platelets and augment inflammation through PARs expressed on platelets and inflammatory cells. downregulates the expression of other anti- coagulants, such as protein C and tissue factor protein inhibitor.
2. Anti-fibrinolytic effects: Activated Plasminogen activator inhibitors (PAI), which limit fibrinolysis and downregulate the expression of t-PA.

**Abnormal Blood Flow:**

Turbulence (chaotic blood flow) contributes to **arterial and cardiac thrombosis** by causing endothelial injury or dysfunction, as well as by forming countercurrents and local pockets of stasis which is a major factor in the development of **venous thrombi**. platelets are found in the center of the vessel lumen in normal conditions, in contrast to stasis condition.

Stasis allows platelets and leukocytes to come into contact with the endothelium

Stasis also slows the washout of activated clotting factors

Both Turbulence and stasis promote endothelial cell activation and enhanced procoagulant activity.

Ulcerated atherosclerotic plaques causes Turbulence. Abnormal aortic and arterial dilations called aneurysms cause stasis. cardiac mural thrombi cause because of stasis, this stasis is caused by Acute myocardial infarction or Ventricular remodeling after more remote infarction. Mitral valve stenosis cause stasis (dilated atrium). Hyperviscosity (stasis). sickle cell anemia(stasis).

**Hypercoagulability:**

high tendency of the blood to clot by alterations in coagulation factors. Usually causes **venous thrombosis**.

Primary (inherited) hypercoagulability is most often caused by mutations in the factor V Leiden mutation (The mutation alters an amino acid residue in factor V and renders it) and prothrombin genes G2021A (increased prothrombin transcription)

Less common primary hypercoagulable states include inherited deficiencies of anti-coagulants such as antithrombin III, protein C, or protein S.

Secondary {high risk} for thrombosis: (1)Prolonged bed restor immobilization(even  inactivity for the duration of an overseas plane flight may be sufficient to induce DVT in the leg), (2)Tissuedamage(surgery, fracture, burns), (3)Prosthetic cardiac valves, (4)MI,(5)Cancer, (6)DIC.

Secondary {low risk} for thrombosis groupinclude: (1)Oral contraceptive use (2)Hyperestrogenic states (3)Atrial fibrillation (4)Cardiomyopathy (5)Sickle cell anemia, (6)Nephrotic syndrome (7) Smoking& (8)Obesity.

Arterial thrombi grow in a retrograde direction from the point of attachment, whereas venous thrombi extend in the direction of blood flow

lines of Zahn: they are only found in thrombi that form in flowing blood; their presence can therefore usually distinguish antemortem thrombosis from the bland nonlaminated clots that form in the postmortem state

Thrombi occurring in heart chambers or in the aortic lumen are designated as mural thrombi(non-occlusive)

Abnormal myocardial contraction (arrhythmias, dilated cardiomyopathy, or myocardial infarction) or endomyocardial injury (myocarditis, catheter trauma) promote cardiac mural thrombi, whereas ulcerated atherosclerotic plaques and aneurysmal dilation promote aortic thrombosis

| Arterial thrombi | Venous thrombi |
|---|---|
| Frequently occlusive | Almost occlusive |
| rich in platelets | Rise to emboli/ contain more enmeshed red cells(red, or stasis, thrombi) |
| in ruptured atherosclerotic plaque/ vascular injuries (vasculitis, trauma) | Lower extremities 90%/ upper extremities, periprostatic plexus, ovarian and periuterine veins, dural sinuses, portal vein, or hepatic vein |

| postmortem clots | venous thrombi |
|---|---|
| Gelatinous/ have dark red dependent portion and a yellow “chicken fat” upper portion | Red and firm/ they contain gray strands of deposited fibrin. |
| not attached to the underlying vessel wall | attached to vessel walls |

Thrombi on heart valves are called vegetations

infective endocarditis: Bacterial or fungal bloodborne infections can cause valve damage

nonbacterial thrombotic endocarditis: noninfected vegetations in hypercoagulable

verrucous endocarditis (Libman-Sacks endocarditis) can occur in the setting of systemic lupus erythematosus

**Fate of the Thrombus:**If a patient survives an initial thrombotic event, four processes will occur:

Propagation: thrombus enlarges lead to increase the odds of vascular occlusion or embolization.

Embolization: thrombus is dislodged and transported elsewhere in the vasculature

Dissolution: activation of fibrinolytic factors (if a thrombus is newly formed)

older thrombi, extensive fibrin polymerization lead to thrombus resistant to plasmin-induced proteolysis, and lysis is ineffectual.

Organization and recanalization: Older thrombi become organized by the ingrowth of endothelial cells, smooth muscle cells, and fibroblasts. In time, capillary channels are formed in thrombus. Or it incorporated into the wall of the remodeled vessel.

**Venous Thrombosis (Phlebothrombosis):**

| Superficial venous | Deep venous thromboses (DVTs) |
|---|---|
| in the saphenous system (varicosities) | in the larger leg veins at or above the knee joint (e.g., popliteal, femoral, and iliac veins |
| rarely embolize | prone to embolize |
| painful and can cause local congestion and swelling from impaired venous outflow | Asymptomatic approximately 50%(may cause local pain and edema) |
| predisposing the overlying skin to the development of infections and varicose ulcers. | Predisposing congestive heart failure, bed rest, and immobilization ( because it associated with stasis and hypercoagulable states) |

Trauma, surgery, burns: immobilize/ vascular injury/ procoagulant release/ synthesis of coagulation factors/ reduced t-PA production

late pregnancy and the postpartum period are associated with hypercoagulability

Tumor associated procoagulant: increased risk of thromboembolic (migratory thrombophlebitis)

Arterial and Cardiac Thrombosis

Atherosclerosis is a major cause of arterial thromboses

Myocardial infarction/ rheumatic heart disease can cause mural thrombi

Both cardiac and aortic mural thrombi are prone to embolization

brain, kidneys, and spleen is the most effected organs because of their rich blood supply.

Disseminated Intravascular Coagulation (DIC)

DIC is widespread thrombosis

consumes platelets and coagulation proteins (synonym consumptive coagulopathy) and fibrinolytic mechanisms are activated

The net result is excessive clotting and bleeding.

DIC is not a primary disease but rather is a potential complication of any condition associated with widespread activation of thrombin, major causes includes: obstetric complications, infections, neoplasms, & massive tissue injury.

**EMBOLISM**

solid, liquid, or gaseous mass

causes tissue dysfunction or infarction

resulting in partial or complete vascular occlusion after lodge

consequence of systemic embolization: ischemic necrosis (infarction) of downstream tissues

pulmonary circulation embolization: hypoxia, hypotension, and right-sided heart failure.

**Pulmonary Thromboembolism**

Most commonly from DVT

Fragmented thrombi from DVTs are carried through progressively larger channels and usually pass through the right side of the heart before arresting in the pulmonary vasculature

Its place Depending on its size (main pulmonary artery/ bifurcation of the right and left pulmonary arteries (saddle embolus)/ branching arterioles)

Most pulmonary emboli (60%–80%) are small and clinically silent/ they organized & become incorporated into the vascular wall.

Fatal PTE with Sudden death from anoxia or acute RVF occur when 60% or more of the pulmonary circulation is obstructed by PTE.

PTE obstruction of medium-sized arteries may result in pulmonary hemorrhage, but usually does not cause pulmonary infarction in normal person (area receives blood through an intact bronchial circulation (dual circulation). However, a similar embolus in the setting of left-sided cardiac failure (and diminished bronchial artery perfusion) can lead to a pulmonary infarct).

PTE obstruction of small end-arteriolar pulmonary branches usually does not result in infarction.

Multiple PTE over time may cause pulmonary hypertension with chronic RHF & cor pulmonale.

**Systemic Thromboembolism**: Most systemic emboli (80%) arise from intracardiac mural thrombi (left ventricular infarcts/ dilated left atria)

venous emboli, which lodge primarily in the lung

arterial emboli can travel virtually anywhere; their final resting place understandably depends on their point of origin and the relative flow rates of blood to the downstream tissues. Common arteriolar embolization sites include the lower extremities (75%) and central nervous system (10%)

The consequences of systemic emboli depend on: (1) collateral vascular supply, (2) the tissue's vulnerability to ischemia, & (3) the caliber of the vessel occluded.

arterial emboli often lodge in end arteries and cause infarction.

**Fat Embolism:** Soft tissue crush injury or rupture of marrow vascular sinusoids (eg, due to a long bone fracture) release microscopic fat globules into the circulation

symptomatic fat embolism syndrome characterized by pulmonary insufficiency, neurologic symptoms, anemia, thrombocytopenia. Clinical signs and symptoms appear 1 to 3 days after injury as the sudden onset of tachypnea, dyspnea, tachycardia, irritability, and restlessness, which can progress to delirium or coma

The pathogenesis syndrome involves mechanical obstruction (occlude pulmonary and cerebral microvasculature directly or by triggering platelet aggregation )/ biochemical injury(fatty acid release from lipid globules, which causes local toxic endothelial injury)

petechial skin rash is related to rapid onset of thrombocytopenia, caused by platelets adherence to the fat globules & being removed from the circulation.

**Amniotic Fluid Embolism:** Caused by the entry of amniotic fluid into the maternal circulation via tears in the placental membranes and/or uterine vein rupture

Histologic analysis shows squamous cells shed from fetal skin, lanugo hair, fat from vernix caseosa, and mucin derived from the fetal respiratory or gastrointestinal tracts in the maternal pulmonary microcirculation (causes DIC & pulmonary edema)

Onset is characterized by sudden severe dyspnea, cyanosis, and hypotensive shock, followed by seizures and coma

If the patient survives the initial crisis, pulmonary edema & DIC typically develops

اعداد: محمود الفريحات
**#بصمة_طبيب**