Lecture 13&14 GENERAL PATHOOGY

HEMODYNAMIC DISORDERS

THROMBOSIS

Hemostasis: Normally the blood is kept in a fluid state with rapid formation of a plug at the site of injury. ***Thrombosis: is*** *the formation of a blood clot i*nside the blood vessel.

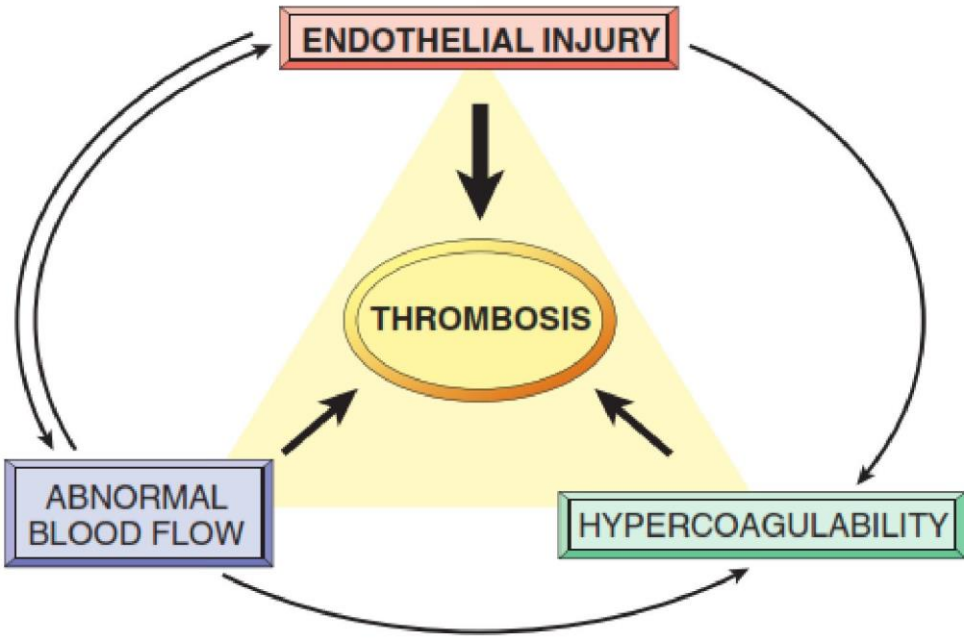
Both hemostasis and thrombosis involve three components:

1. Vascular wall.
2. Platelets.
3. Coagulation cascade.

Pathogenesis of thrombus:

There are three primary abnormalities that lead to thrombus formation called Virchow's triad:

(1) Endothelial injury.
(2) Stasis or turbulence of blood flow.
(3) Blood hypercoagulability.



1-Endothelial Injury

Is an important cause of thrombosis, particularly in the ***heart and the arteries***. Normally high flow rates of blood in the heart or in the arterial circulation prevent clotting by preventing platelet adhesion and diluting coagulation factors.

Physical loss of endothelium leads to exposure of subendothelial ECM, adhesion of platelets, release of coagulation factor that help in thrombus formation**.**

2- Alterations in Normal Blood Flow:

Turbulence contributes to *arterial and cardiac* thrombosis by causing endothelial injury or dysfunction. Stasis is a major contributor to the development of *venous thrombi.*

Normal blood flow is laminar, such that platelets flow centrally in the vessel lumen, separated from the endothelium by a slower moving clear zone of plasma.

Stasis and turbulence (disturbances in blood flow) will: - Disrupt laminar flow and bring platelets into contact with the endothelium.

- Prevent dilution of activated clotting factors by fresh-flowing blood.
-Retard the inflow of clotting factor inhibitors.
- Promote endothelial cell injury, resulting in platelets adhesion.

Causes of turbulence and stasis:)

1- Ulcerated atherosclerotic plaques: not only expose subendothelial ECM but also cause turbulence.
2- Abnormal aortic and arterial dilations, called aneurysms.
3- Acute myocardial infarction results in focally non contractile myocardium.
4- Mitral valve stenosis (e.g., after rheumatic heart disease) results in left atrial dilation which is a site of stasis.
5- Hyperviscosity syndromes (such as polycythemia) increase resistance to flow and cause small vessel stasis.
6- The deformed red cells in sickle cell anemia cause vascular occlusions, with the resultant stasis.

3- Hypercoagulability:

It is any alteration of the coagulation pathways that predisposes to thrombosis. Its contributes infrequently to arterial or intra cardiac thrombosis but important underlying risk factor for **venous thrombosis** and it can be divided into:

1- Primary (genetic) disorders like mutations in the factor V gene and the prothrombin gene.

2- Secondary (acquired) disorders, the pathogenesis of acquired thrombotic disorders are frequently multifactorial and more complicated and include:-

- Cardiac failure or trauma: stasis or vascular injury may be most important causes.

- Hypercoagulability is associated with oral contraceptive use and the hyperestrogenic state of pregnancy, probably related to increased hepatic synthesis of coagulation factors.

- In disseminated cancers, release of procoagulant tumor products predisposes to thrombosis. (mucin from adenocarcinoma)

- The hypercoagulability seen with advancing age has been attributed to increasing platelet aggregation.

- Smoking and obesity promote hypercoagulability by unknown mechanisms.

Morphology of thrombus:

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. These lines distinguish antemortem thrombosis from the bland nonlaminated clots that occur in the postmortem state.

Although thrombi formed in the "low-flow" venous system superficially resemble postmortem clots, careful evaluation generally reveals ill-defined laminations.

Types of thrombus:

1-Mural thrombi:

Thrombi occurring in heart chambers or in the aortic lumen.

Causes:

a- Abnormal myocardial contraction resulting from arrhythmias or myocardial infarction.

b- Endomyocardial injury

2-Arterial thrombi :

are frequently occlusive and are produced by platelet and coagulation activation; they are typically a friable meshwork of platelets, fibrin, erythrocytes, and degenerating leukocytes. **Causes:** Atherosclerotic plaque and vascular injury (vasculitis, trauma).

3- Venous thrombosis (phlebothrombosis)

Is almost occlusive, and it is the result of activation of the coagulation cascade, and platelets play a secondary role. Because these thrombi form in the sluggish venous circulation, they also tend to contain more enmeshed erythrocytes and are therefore called red, or stasis thrombi. The veins of the lower extremities are most commonly affected.

4- Vegetations:

Thrombi on heart valves. Bacterial or fungal blood-born infections can cause valve damage, subsequently leading to large thrombotic masses (infective endocarditis).

Fate of the Thrombus:

If a patient survives the initial thrombosis, in the ensuing days or weeks thrombi undergo some combination of the following four events:

1- **Propagation.** Thrombi accumulate additional platelets and fibrin causing vessel obstruction.

2- **Embolization.** Thrombi dislodged or fragmented and are transported elsewhere in the vasculature.

3- **Dissolution.** Thrombi are removed by fibrinolytic activity which leads to rapid shrinkage and even total lysis of recent thrombi.

4- **Organization and recanalization**. Thrombi induce inflammation and fibrosis, recanalization (re-establishing some degree of flow).

Clinical significance:

Thrombi are significant because they

1. Cause obstruction of arteries and veins

2. Are potential sources of emboli.

Which effect is most important depends on the site of thrombosis. **Venous thrombi** can cause congestion and edema in vascular beds distal to an obstruction, but they are most troublesome for their capacity to embolize to the lungs and cause death.

While arterial thrombi can embolize and even cause downstream tissue infarction, their role in vascular obstruction at critical sites (e.g., coronary and cerebral vessels) is much more significant clinically.

Venous Thrombosis (Phlebothrombosis): Most venous thrombi occur in the superficial or deep veins of the leg. **Superficial thrombi** can cause local congestion, swelling, pain, and tenderness along the course of the involved vein, but they rarely embolize.

Deep thrombi in the larger leg veins at or above the knee joint are more serious because they may embolize. Although they may cause local pain and edema, deep venous thromboses are entirely asymptomatic in approximately 50% of patients.

The risk of deep venous thrombosis increased in:

1-Advanced age, bed rest, and immobilization ,because reduced physical activity diminishes the milking action of muscles in the lower leg and so slows venous return.

2- Cardiac failure.

3-Trauma, surgery, and burns.

4-Peripartum and postpartum states; in addition to the potential for amniotic fluid infusion into the circulation during parturition ,late pregnancy and the postpartum period are associated with hypercoagulability. 5-Hypercoagulable states.

EMBOLISM:

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

Forms of emboli

1- **thromboembolism.** 99% of all emboli represent a dislodged thrombus
Rare forms of emboli include
2- **Fat Embolism:**Microscopic fat globules can be found in the circulation after fractures of long bones (which contain fatty marrow) . Although fat and marrow embolism occurs in some 90% of individuals with severe skeletal injuries, fewer than 10% of such patients show any clinical findings.
3- **Air Embolism:** Gas bubbles within the circulation. Air may enter the circulation during as a consequence of chest wall injury. Air bubbles can coalesce to form frothy masses sufficiently large to occlude major vessels.
4- **Atherosclerotic** emboli (cholesterol emboli): consisting of athermatous debris
5- **Tumor emboli**: made up of fragments of a tumor.
6- **Bone marrow emboli**: consisting of bits of bone marrow.

Emboli lodge in vessels too small to permit further passage, resulting in partial or complete vascular occlusion end in ischemic necrosis (infarction) of downstream tissue.

Pulmonary Thromboembolism

In more than 95% of cases, venous emboli originate from deep leg vein thrombi above the level of the knee such as the femoral, or iliac veins. These emboli are carried through progressively larger channels and pass through the right side of the heart before entering the pulmonary arterial circulation.

Systemic Thromboembolism*:* This refers to emboli in the arterial circulation, (80%)arise from Intracardiac mural thrombi

The major sites for arteriolar embolization are:

1. The lower extremities (75%).
2. The brain (10%).
3. The intestines (mesenteric), kidneys, and spleen.
4. The upper limbs are the least common sites.

INFARCTION:

An infarct is an area of ischemic necrosis caused by occlusion of either the arterial supply or the venous drainage in a particular tissue.

Nearly 99% of all infarcts result from thrombotic or embolic events, and almost all result from arterial occlusion.

Morphology:

Infarcts are classified on the basis of their color (reflecting the amount of hemorrhage) and the presence or absence of microbial infection. Therefore, infarcts may be either red (hemorrhagic) or white (anemic) and may be either septic or nonseptic.

Red infarcts: Occur in these situations:

(1) With venous occlusions.

(2) In loose tissues (such as lung) that allow blood to collect in the infarcted zone.

(3) In tissues with double circulations such as lung and small intestine, permitting flow of blood from an unobstructed parallel supply into a necrotic area (such perfusion not being sufficient to rescue the ischemic tissues).

(4) In tissues that were previously congested because of sluggish venous outflow.

(5) When flow is re-established to a site of previous arterial occlusion and necrosis e.g., fragmentation of an occlusive embolus.

White infarcts:

Occur with arterial occlusions or in solid organs (such as heart, spleen, and kidney), where the solidity of the tissue limits the amount of hemorrhage that can seep into the area of ischemic necrosis from adjoining capillary beds.

Septic infarctions

Occur when bacterial vegetations from a heart valve embolize or when microbes infect an area of necrotic tissue. In these cases the infarct is converted into an abscess, with a correspondingly greater inflammatory

response.

Histological appearance:

The dominant histologic characteristic of infarction is ischemic coagulative necrosis. In stable or labile tissues, parenchymal regeneration can occur at the periphery. However, most infarcts are ultimately replaced by scar. The brain is an exception to these generalizations; ischemic tissue injury in the central nervous system results in liquefactive necrosis.

Factors That Influence Development of an Infarct

Vascular occlusion can have no or minimal effect, or can cause death of a tissue or even the individual. The major determinants of the eventual outcome include:-

1- Nature of the Vascular Supply:

The presence of an alternative blood supply is the most important determinant of whether occlusion of a vessel will cause damage.

Lungs, liver, hand and forearm have a double artery blood supply; are all resistant to infarction. Thus, obstruction of small arterioles does not cause infarction in healthy individual with an intact bronchial circulation. Renal and splenic circulations have end-arterial blood supply so obstruction of such vessels generally causes infarction.

2- Rate of Development of Occlusion:

Slowly developing occlusions are less likely to cause infarction because they provide time for the development of alternative perfusion pathways.

3- Tissues susceptibility to Hypoxia:

The susceptibility of a tissue to hypoxia affects the occurrence of infarction. **Neurons** undergo irreversible damage when deprived of their blood supply for only 3 to 4 minutes. **Myocardial cells** are also quite sensitive and die after only 20 to 30 minutes of ischemia.

In contrast, **fibroblasts** within myocardium remain viable after many hours of ischemia.

4- Oxygen Content of Blood:

Partial flow obstruction of a small vessel in an anemic or cyanotic patient might lead to tissue infarction, whereas it would be without effect under conditions of normal oxygen tension.

SHOCK:

Shock is the final step for a number of potentially lethal clinical events including: Severe hemorrhage .Extensive trauma or burns. Large myocardial infarction. Large pulmonary embolism. Microbial sepsis.

Regardless of the underlying pathology, shock gives rise to systemic hypoperfusion caused either by reduced cardiac output or by reduced circulating blood volume. The end results are hypotension, impaired tissue perfusion, and cellular hypoxia resulting in the death of the patient.

Types of shock:

1- **Cardiogenic shock**: Results from failure of the cardiac pump. This may be caused by myocardial infarction, ventricular arrhythmias, extrinsic compression to the heart, or outflow obstruction (e.g., pulmonary embolism).

2- Hypovolemic shock: Results from loss of blood. This may be caused by hemorrhage, fluid loss from severe burns, or trauma.

3- Septic shock: Caused by microbial infection. Most commonly this occurs in the setting of gram-negative infections but it can also occur with gram-positive and fungal infections.

4- Neurogenic shock: Less common shock may occur in the setting of an anesthetic accident or a spinal cord injury as a result of loss of vascular tone and peripheral pooling of blood.

5- Anaphylactic shock: Represents systemic vasodilation and increased vascular permeability caused by an immunoglobulin E hypersensitivity reaction. In these situations, acute severe widespread vasodilation results in tissue hypoperfusion and cellular anoxia (Absence of oxygen).

Morphology:

Shock will induce cellular and tissue necrosis due to hypoxia or combination of decrease blood supply and fibrin thrombi which may be identified in any tissue, mostly visualized in kidney glomeruli.

Clinical manifestations: In hypovolemic and cardiogenic shock, the patient presents with hypotension; a weak, rapid pulse; tachypnea; and cool, clammy , cyanotic skin.

In septic shock, the skin may be warm and flushed as a result of peripheral vasodilation. The prognosis varies with the type of shock, its duration, age and general health of the patients.

Thus, 80% to 90% of young, healthy patients with hypovolemic shock survive with appropriate management, whereas cardiogenic shock associated with extensive myocardial infarction, or gram-negative sepsis carries a mortality rate of 75%, even with appropriate treatment.