Thrombosis

Pathogenesis :

There are three primary influences on thrombus formation (called Virchow's triad):

(1) endothelial injury, (2) stasis or turbulence of blood flow, and (3) blood hypercoagulability.

1- Endothelial Injury:

This is a dominant influence, since endothelial loss by itself can lead to thrombosis. It is particularly important for thrombus formation occurring in the heart or in the arterial circulation, where the normally high flow rates might otherwise hamper clotting by preventing platelet adhesion or diluting coagulation factors. Thus, thrombus formation within the cardiac chambers (e.g., after endocardial injury due to myocardial infarction), over ulcerated plaques in atherosclerotic arteries, or at sites of traumatic or inflammatory vascular injury (vasculitis) is largely a function of endothelial injury. Clearly, physical loss of endothelium leads to exposure of subendothelial ECM, adhesion of platelets, release of tissue factor, and local depletion of PGI₂ and plasminogen activators. However, it is important to note that endothelium need not be denuded or physically disrupted to contribute to the development of thrombosis; any perturbation in the dynamic balance of the prothrombotic and antithrombotic activities of endothelium can influence local clotting events. Thus, dysfunctional endothelium may elaborate greater amounts of procoagulant factors (e.g., platelet adhesion molecules, tissue factor, plasminogen activator inhibitors) or may synthesize fewer anticoagulant effectors (e.g., thrombomodulin, PGI₂, t-PA). Significant endothelial dysfunction (in the absence of endothelial cell loss) may occur with hypertension, turbulent flow over scarred valves, or by the action of bacterial endotoxins. Even relatively subtle influences, such as homocystinuria, hypercholesterolemia, radiation, or products absorbed from cigarette smoke, may be sources of endothelial dysfunction.

2 - Alterations in Normal Blood Flow :

Turbulence contributes to arterial and cardiac thrombosis by causing endothelial injury or dysfunction, as well as by forming countercurrents and local pockets of stasis; 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 therefore:
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 and permit the buildup of thrombi
Promote endothelial cell activation, resulting in local thrombosis, leukocyte adhesion,

Turbulence and stasis contribute to thrombosis in several clinical settings. Ulcerated atherosclerotic plaques not only expose subendothelial ECM but also cause turbulence. Abnormal aortic and arterial dilations, called aneurysms, create local stasis and consequently a fertile site for thrombosis. Acute myocardial infarction results in focally noncontractile myocardium; ventricular remodeling after more remote infarction can lead to aneurysm formation. In both cases cardiac mural thrombi form more easily because of the local blood stasis. Mitral valve stenosis (e.g., after rheumatic heart disease) results in left atrial dilation. In conjunction with atrial fibrillation, a dilated atrium is a site of profound stasis and a prime location for development of thrombi. Hyperviscosity syndromes (such as polycythemia) increase resistance to flow and cause small vessel stasis; the deformed red cells in sickle cell anemia cause vascular occlusions, with the resultant stasis also predisposing to thrombosis.

**Hypercoagulability :-**
Hypercoagulability generally contributes less frequently to thrombotic states but is nevertheless an important component in the equation. It is loosely defined as any alteration of the coagulation pathways that predisposes to thrombosis, and it can be divided into *primary* (genetic) and *secondary* (acquired) disorders.

Hypercoaguable States

**Primary (Genetic)**
Common
- Mutation in factor V gene (factor V Leiden)
- Mutation in prothrombin gene
- Mutation in methyltetrahydrofolate gene

Rare
- Antithrombin III deficiency
- Protein C deficiency
- Protein S deficiency

Very rare
- Fibrinolysis defects

**Secondary (Acquired)**
High risk for thrombosis
- Prolonged bedrest or immobilization
- Myocardial infarction
- Atrial fibrillation
- Tissue damage (surgery, fracture, burns)
- Cancer
- Prosthetic cardiac valves
Disseminated intravascular coagulation
Heparin-induced thrombocytopenia
Antiphospholipid antibody syndrome (lupus anticoagulant syndrome)
Lower risk for thrombosis
Cardiomyopathy
Nephrotic syndrome
Hyperestrogenic states (pregnancy)
Oral contraceptive use
Sickle cell anemia
Smoking

**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:

2. *Embolization.* Thrombi dislodge or fragment and are transported elsewhere in the vasculature.
3. *Dissolution.* Thrombi are removed by fibrinolytic activity.
4. *Organization and recanalization.* Thrombi induce inflammation and fibrosis (organization). These can eventually recanalize (re-establishing some degree of flow), or they can be incorporated into a thickened vessel wall.

**Morphology**
Thrombi can develop anywhere in the cardiovascular system (e.g., in cardiac chambers, on valves, or in arteries, veins, or capillaries). The size and shape of a thrombus depend on the site of origin and the cause. Arterial or cardiac thrombi typically begin at sites of endothelial injury or turbulence; venous thrombi characteristically occur at sites of stasis. Thrombi are focally attached to the underlying vascular surface; arterial thrombi tend to grow in a retrograde direction from the point of attachment, while venous thrombi extend in the direction of blood flow (thus both tend to propagate toward the heart). The propagating portion of a thrombus tends to be poorly attached and therefore prone to fragmentation, generating an *embolus.*

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. Such lines are significant only in that they represent thrombosis in the setting of flowing blood; their presence can therefore potentially distinguish antemortem thrombosis from the bland nonlaminated clots that occur in the postmortem state (see also below). Although such lines are typically not as apparent in veins or smaller arteries (thrombi formed in sluggish venous flow usually resemble statically coagulated blood), careful evaluation generally reveals ill-defined laminations.
Thrombi occurring in heart chambers or in the aortic lumen are designated mural thrombi. Abnormal myocardial contraction (resulting from arrhythmias, dilated cardiomyopathy, or myocardial infarction) or endomyocardial injury (caused by myocarditis, catheter trauma) promotes cardiac mural thrombi. While ulcerated atherosclerotic plaques and aneurysmal dilation promote aortic thrombosis.

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. Although arterial thrombi are usually superimposed on an atherosclerotic plaque, other vascular injury (vasculitis, trauma) can be involved.

Venous thrombosis (phlebothrombosis) is almost invariably occlusive, and the thrombus can create a long cast of the lumen; venous thrombosis is largely 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 (90% of venous thromboses); however, venous thrombi can occur in the upper extremities, periprostatic plexus, or ovarian and periuterine veins; under special circumstances they may be found in the dural sinuses, portal vein, or hepatic vein.

Postmortem clots can sometimes be mistaken at autopsy for venous thrombi. However, postmortem "thrombi" are gelatinous, with a dark red dependent portion where red cells have settled by gravity, and a yellow "chicken fat" supernatant, and they are usually not attached to the underlying wall. In contrast, red thrombi are firmer and are focally attached, and sectioning reveals strands of gray fibrin.

Thrombi on heart valves are called vegetations. Bacterial or fungal blood-borne infections can cause valve damage, subsequently leading to large thrombotic masses (infective endocarditis). Sterile vegetations can also develop on noninfected valves in hypercoagulable states, so-called nonbacterial thrombotic endocarditis. Less commonly, sterile, verrucous endocarditis (Libman-Sacks endocarditis) can occur in the setting of systemic lupus erythematosus.