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PATHOGENESIS OF THROMBOSIS: AN OVERVIEW

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INTRODUCTION

The hemostatic process is a host defense mechanism that preserves the integrity of the closed, high-pressure circulatory system. This process must be rapid. When the process is activated, it remains critical in containing thrombus formation so that it is localized to the site of injury and modulates thrombus size to be proportionate to the injury. Thus, there is a balance between the pathways that initiate thrombus formation and the pathways that regulate or modulate thrombus formation. Physiologically, following vascular injury, a series of delicate, balanced, and dynamic reactions must take place to secure a stable blood clot. This is a preparatory process of normal wound healing to maintain normal circulation.

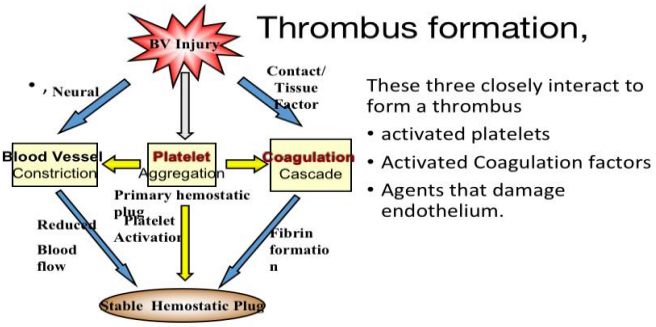

Fig 1: The process of thrombus formation following vascular injury.

1. What is a thrombus?

A thrombus is simply a mechanical intravascular mass that is localized and stable. It is a result of the activation of haemostasis at an inappropriate time and in an inappropriate blood vessel. A thrombus forms when there is a breakdown in balance between thrombogenic

factors and protective mechanisms. It is a pathologic consequence of activated haemostatic mechanism invivo under variable flow conditions.

1.1. Protective factors (Host defense mechanism)

The protective mechanisms are

- Non-thrombogenic properties of the endothelium
- Neutralization of activated coagulation factors by endothelial cell-bound components
- Neutralization of activated coagulation factors by naturally occurring protease inhibitors
- Dilution of activated coagulation factors and disruption of platelet aggregation by blood flow
- Clearance of activated coagulation factors by the liver
- Dissolution of fibrin thrombi by the fibrinolytic system

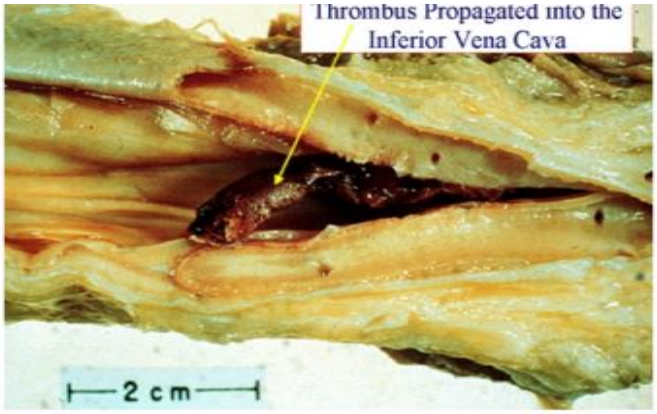

Fig 2: Showing a thrombus propagated in the inferior vena cava.

1.2. Thrombosis

Thrombosis can occur in either the arterial or venous system, but the thrombi differ in their structure and clinical significance. Arterial thrombi usually form at the site of pre-existing vascular lesions, causing platelet reactions and accumulation, leading to the development of a “white” platelet thrombus. In contrast, in veins, thrombus formation is the consequence of increased thrombin formation in areas of retarded blood flow and coagulated blood, leading to the development of a “red” thrombus.

2.2.1 Thrombosis: Sites of occurrence

- Arterial
- Venous
- Chambers of the heart

- Unnatural prosthetic surfaces
- Microcirculation (DIC)

2.2.2 Thrombosis: Notable facts

- Thrombi develop in the cardiovascular system (CVS) whereas clots form outside the CVS; e.g., bleeding into the peritoneal area forms a clot
- Presence of "LINES OF ZAHN" i.e., alternating pale layers of platelets and fibrin with dark layers of red blood cells imply the formation of a thrombus in areas of active blood flow, such as in the heart, aorta, and arteries.
- Venous thrombi often lack Lines of Zahn, implying that they are formed in a more sluggish flow zone.
- Arterial thrombi are usually occlusive, but venous thrombi are almost always occlusive.
- 85-90% of venous thrombi are formed in the lower limbs.

2.2.3 Venous thrombosis

Venous thrombi that form in deep veins (popliteal, femoral, iliac veins) are more likely to embolize. About 50% deep vein thrombosis cases are asymptomatic because of the presence of collaterals. However, it may produce edema, pain, and tenderness. In veins, thrombi seem to be initiated in valve pockets and points of maximal stasis.

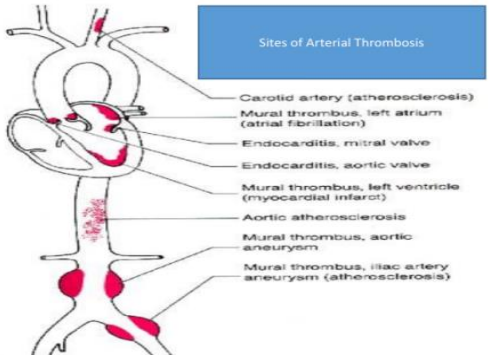

Fig. 3: Sites of arterial thrombosis.

Fate of Thrombi

- Partial or complete lysis by fibrinolysis.
- Organized
- Break free and drift downstream to lodge in pulmonary circulation or other high-flow vascular beds.

2. Pathogenesis: (Virchow Triad)

The complexity of venous thrombosis was already apparent to Virchow, who stated in 1856, that the pathophysiology of thrombosis involved three factors (Fig 4):

1. Damage to the vessel wall
2. Stasis
3. Increase in blood coagulability

None of these factors alone is usually capable of causing thrombosis. It is the coincidence of activation of blood coagulation at the time of surgery, the immobile leg veins, and possibly the damaged vessel wall that cause thrombosis. Whereas the first two components of Virchow's triad represent acquired conditions, blood hypercoagulability is a result of both endogenous (inherited) and exogenous (acquired) factors.

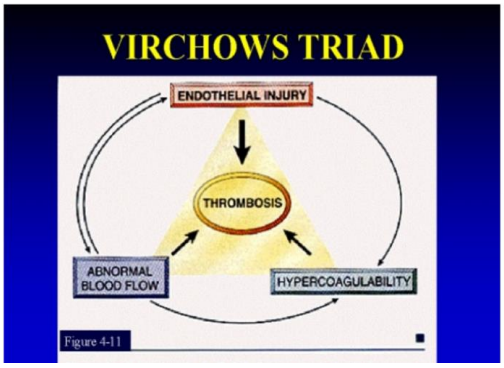

Fig. 4: The Virchow's triad.

Virchow Triad

A modern interpretation of this "Virchow's triad" is that hemodynamic disruption (blood flow), intrinsic hypercoagulability (hypercoagulability), and endothelial damage or dysfunction (endothelial injury); are the three broad categories of events that lead to thrombosis. The risk of thrombosis increases when more than one risk factor is present.

Examples of thrombosis include

- Venous thrombosis, e.g., Deep vein thrombosis (DVT), Pulmonary embolism (PE).
- Arterial thrombosis, e.g., Myocardial infarction (MI), stroke, peripheral occlusive disease.

3.1 Normal blood flow (Laminar flow)/Stasis

Blood flows in concentric cylindrical layers, with the most rapid (RBC) in the center and platelets at the periphery. Naturally, blood cells repel each other and are also repelled by the

endothelium. Normal blood flow ensures the dilution of activated coagulation factors and the disruption of platelet aggregation.

In contrast, in stasis or sluggish blood flow, platelet aggregation and the buildup of activated coagulation factors are enhanced, culminating in thrombosis.

3.2 Roles of Endothelium and Endothelial Disruption

Endothelial disruption results to rapid platelet adhesion, platelet degranulation, and the enlargement of thrombi mass. The endothelium has both anti-thrombotic and pro-coagulant properties, as shown in Figure 5

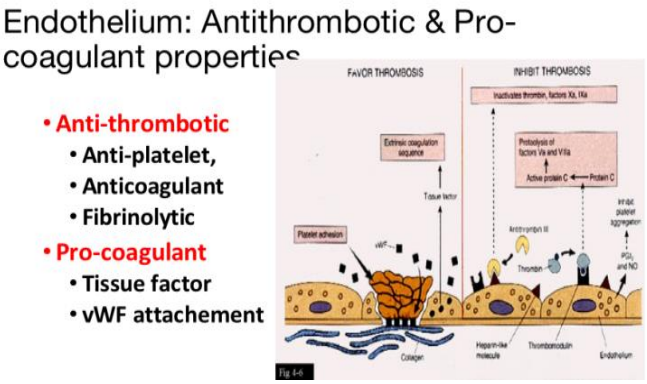

Fig. 5: Showing antithrombotic and pro-coagulant properties of the endothelium.

3.2.1 Anticoagulant roles of the endothelium.

Endothelial anti-platelet effect: The endothelium serves as a physical barrier that prevents platelet contact with the extracellular matrix (ECM). Endothelial production of prostacyclin and nitric oxide inhibits platelet adhesion to normal endothelium.

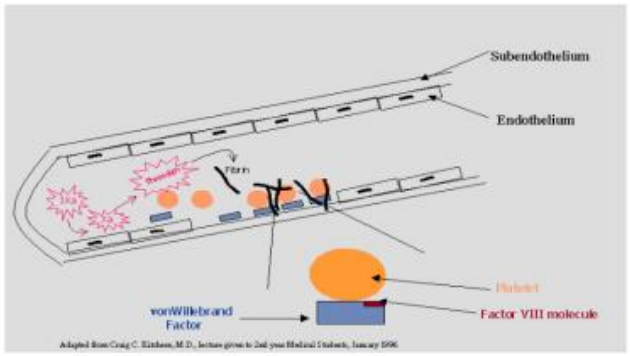

Fig.6: Showing sequence of events upon endothelial disruption.

In the event of blood vessel injury (as shown in Fig. 6), the disruption of the vessel causes, in sequence, alterations in blood flow, reflex vasoconstriction, endothelial stripping, collagen exposure, and platelet activation. Platelet aggregates become available and release their granule contents, including ADP, thromboxane A2, serotonin, which lead to the formation of a primary platelet plug that is fixed by the presence of collagen, endothelium, platelets, plasma vWF, and platelet glycoprotein binding sites.

3.2.3. Endothelial fibrinolytic effects: To initiate fibrinolytic activity, the endothelium synthesizes tissue-type plasminogen activator (t-PA) which promotes fibrinolytic activity.

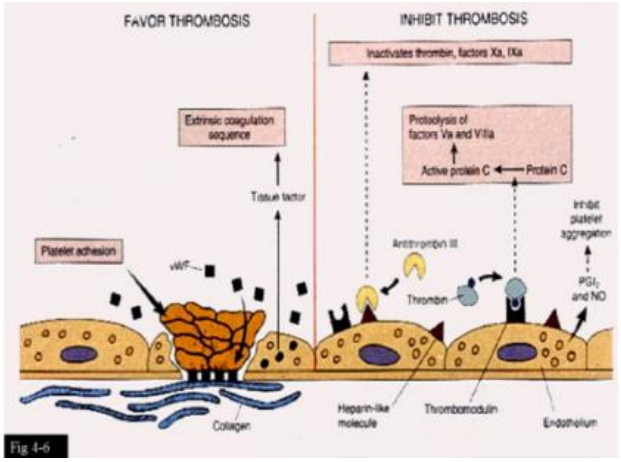

Fig. 7: Endothelial functions that favor and inhibit thrombosis.

3.3. Hypercoagulability

Hypercoagulability refers to any alteration of the coagulation pathways that predisposes individuals to thrombosis. This can be due to primary (genetic) or secondary (acquired) disorders.

Thrombophilia (hypercoagulability): refers to patients with a tendency to thrombosis. The term “inherited thrombophilia” should be used for individuals with predisposing genetic defects. Hypercoagulability and thrombophilia are synonymous.

Thrombophilia is usually suspected in patients with one or more of the following clinical features:

- idiopathic thrombosis
- thrombosis at a young age
- recurrent thrombosis

- thrombosis at an unusual site.

Individuals who have laboratory abnormalities or clinical disorders that are known to predispose them to thrombosis but have not had an episode of thrombosis are potentially thrombophilic. Previous studies showed that the diagnosis of a hereditary disorder could be established in only 10– 15% of younger patients presenting with venous thromboembolism (VTE). (Ref). it is currently possible to define genetic risk factors in many younger patients with idiopathic venous thrombosis.

3.3.1 Inherited and acquired hypercoagulable states

a) Inherited

- Activated protein C resistance due to factor V Leiden mutation
- Prothrombin gene mutation
- Antithrombin deficiency
- Protein C deficiency
- Protein S deficiency
- Elevated factor VIII level
- Dysfibrinogenemia (rare)
- Hyperhomocysteinemia

b) Acquired

- Acquired hypercoagulable states
- Antiphospholipid syndrome (lupus anticoagulant)
- Malignancy
- Nephrotic syndrome
- Myeloproliferative disorders (MPD)
- Paroxysmal nocturnal hemoglobinuria
- Postoperative state
- Immobilization
- Old age
- Pregnancy
- Oral contraceptives or other estrogen use

3.3.2 Hypercoagulable State and Anti-Phospholipid Syndrome (APS)

APS Endothelial cell expression of adhesion molecules and upregulation of tissue factor production leads to thrombosis.

In APS, there is monocyte upregulation of tissue factor production leading to a thrombogenic state and thrombosis formation.

Also in APS, there is upregulation of platelet expression of glycoprotein IIb-IIIa, thereby promoting thrombus formation.

3.3.3 Primary (Genetic) Causes of Hypercoagulability

Hypercoagulable state: Mutation of factor V Leiden (MFVL) is the most common inherited cause of hypercoagulability. Mutant factor V is resistant to the anticoagulant effect of activated protein C; thus, there is a functional deficiency of protein C.

Hypercoagulability secondary to inherited lack of other anticoagulants, e.g., Lack of protein S, protein C and antithrombin III, may be accountable for venous thrombosis and recurrent thromboembolism in adolescence and early adulthood.

3.3.4: Hypercoagulability: other associations This include Smoking, Obesity, Oral contraceptives (BCP), Lupus anticoagulant with Lupus erythematosus associated with Arterial and Venous thrombosis. It is called an anticoagulant because it interferes with coagulation tests, artificially prolonging them, but it is not an anticoagulant; it is a procoagulant.

3. Clinical Risk Factors Predisposing to Thrombosis

4.1 VENOUS

- Immobilization
- Pregnancy
- Congestive heart failure
- Varicosities
- Previous thrombosis
- Obesity
- Increasing Age
- Coagulation activation

- Trauma
- Surgery
- Malignancies
- Factor IX concentrate
- Lupus inhibitor
- Myocardial infarction
- MPD
- Pregnancy

Inadequate regulation

- Genetic disorder
- Nephrotic syndrome
- Oral contraceptives

Others

- Lack of physical Exercise
- ?Personality

4.2 Arterial thrombosis

Pathophysiology of atherosclerosis

In the arteries, endothelial injury causes increased vascular permeability, leukocyte adhesion, and thrombosis. This is followed by the accumulation of lipoproteins in the vessel wall, mainly LDL and its oxidized forms. Also, monocyte adhesion to the endothelium, followed by migration into the intima and transformation into macrophages and foam cells, culminates in the formation of atherosclerotic plaque. Platelet adhesion factors released from activated platelets, macrophages, and activated wall cells induce smooth muscle cell recruitment.

Lipid accumulation both extracellularly and within cells (macrophages and smooth muscle cells)

Clinical events in arterial thrombosis include

- Unstable angina
- Myocardial infarction (MI)
- Coronary death
- Stroke

- Critical leg ischemia

These processes increase with increasing age.

4.2.1 Arterial thrombosis

a) Vascular occlusive

- Hyperviscosity
- Sickle Cell Disease
- Polycythaemia
- Plasma cell dyscrasia –macroglobulinemia

b) Abnormal surface

- Arteriosclerosis
- Hyperlipidemia
- Diabetes
- Homocystinuria
- Hypertension
- Cigarette smoking
- Estrogen therapy
- Prosthetic cardiovascular device

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