Hemodynamic Disorders, Thromboembolism and Shock

LEC.2 **Dr. Raghad Hanoon**

❖ Hemorrhage

- Hemorrhage; defined as the extravasation of blood from vessels, is most often the result of damage to blood vessels or defective clot formation.

➢ Causes of Hemorrhage:

1. Rupture of a large artery or vein is usually due to vascular injury (e.g., trauma, atherosclerosis, inflammation, or neoplastic erosion of the vessel).
2. Capillary bleeding can occur with chronic congestion.
3. Hemorrhagic diatheses: a tendency to hemorrhage from insignificant injury is seen in a variety of disorders. including inherited or acquired defects in vessel walls, platelets, or coagulation factors, all of which must function properly to ensure homeostasis.

Patterns of hemorrhage with its clinical implications:

- Hemorrhage may be external or Confined within a tissue (hematoma).
- Hematoma: any localized accumulation of blood within a tissue; may be relatively insignificant (e.g., a bruise) or fatal (e.g., a massive retroperitoneal hematoma resulting from rupture of a dissecting aortic aneurysm).
- Large accumulation of blood in the body cavities are described variously according to location— hemothorax, hemopericardium, hemoperitoneum, or hemarthrosis (in joints).
- Extensive hemorrhages can occasionally result in jaundice from the massive breakdown of red cells and hemoglobin.
- **Petechiae:** are minute (1 to 2 mm in diameter) hemorrhages into skin, mucous membranes, or serosal surfaces.

These are most commonly associated with

1. **locally increased intravascular pressure,**
2. low platelet counts (thrombocytopenia),
3. defective platelet function **(as in uremia)** and
4. 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).

Clinical significance of hemorrhage

- **Depends on;**

1. **The volume** of blood loss
2. **The rate of bleeding.** Rapid loss (internal or external) of up to 20% of the blood volume, or slow losses of even larger amounts, may have little impact in healthy adults; greater losses, however, can cause hemorrhagic (hypovolemic) shock (discussed later).

3. **The site of hemorrhage** also is important; bleeding that would be trivial in the subcutaneous tissues can cause death if located in the brain.

- Finally, chronic or recurrent external blood loss (e.g., due to peptic ulcer or menstrual bleeding) frequently culminates in iron deficiency anemia as a consequence of a loss of iron in hemoglobin. By contrast, iron is efficiently recycled from phagocytosed red cells, so internal bleeding (e.g., a hematoma) does not lead to iron deficiency.

Hemostasis & Thrombosis

- **Hemostasis** is a normal physiologic process;

1. Maintaining blood in a fluid, clot-free state within normal vessels
2. Inducing a rapid localized hemostatic plug at sites of vascular injury.

- **Thrombosis** represents a pathologic state; it is the inappropriate activation of hemostatic mechanisms in uninjured vessels or thrombotic occlusion after relatively minor injury.
- Hemostasis and thrombosis are closely related processes that depend upon **three components: endothelium, platelets, and coagulation cascade.**

The general sequence of events leading to hemostasis at a site of vascular injury:
A. Transient arteriolar vasoconstriction due to reflex neurogenic mechanism & local secretion of endothelial derived vasoconstrictors.
B. Platelet adhesion and activation (Platelets **bind** via glycoprotein Ib (GpIb) receptors to von Willebrand factor (VWF) on exposed subendothelial ECM and are **activated,** undergoing a shape change and granule release. Released ADP and thromboxane A2 (TXA2) induce additional platelet aggregation through platelet GpIIb-IIIa receptor binding to fibrinogen, and form the *primary* hemostatic plug).
C. Local activation of the coagulation cascade (involving tissue factor and platelet phospholipids) results in thrombin generation and conversion of circulating fibrinogen to insoluble fibrin, Thrombin also induces additional platelet recruitment and granule release. Polymerized fibrin and platelet aggregates together form a definitive *secondary* hemostatic plug.
D. Activation of counter-regulatory mechanisms, mediated by tissue plasminogen activator (t-PA, a fibrinolytic product) and thrombomodulin, restricts the hemostatic process to the site of injury.

Thrombosis

- Thrombosis is inappropriate activation of blood clotting in uninjured vasculature or thrombotic occlusion of a vessel after relatively minor injury.
- **Thrombus: solid or semisolid mass from blood constituents within the cardiovascular system during life.**
- **Pathogenesis:**
- There are three primary **abnormalities that lead to** thrombus formation, called **Virchow's triad:**

1. Endothelial injury
2. Stasis or turbulent blood flow
3. Hypercoagulability of the blood

1- Endothelial injury:

- Endothelial injury may be either physical damage or endothelial dysfunction (or activation).
- **Physical Endothelial Injury**

- It is particularly important for thrombus formation in the heart or arterial circulation (where the high rates of blood flow impede clot formation).
- **Causes:**

1. Chambers of heart: For example, endocardial injury due to myocardial infarction with damage to the adjacent endocardium, catheter trauma.
2. Valves: Small thrombi on the valves are called as vegetations. (e.g. Infective endocarditis, Libman-Sacks endocarditis)
3. **Arteries:** For examples, ulcerated **atherosclerotic plaques**, traumatic or inflammatory vascular injury **(vasculitis)**.
4. **Capillaries:** Causes include **acute inflammatory lesions**, vasculitis and disseminated intravascular coagulation

(DIC).

Mechanism:

- Endothelial injury lead to exposure of subendothelial ECM, increased platelet adhesion, procoagulant production (i.e., tissue factor, PAI) and reduced anticoagulant activity (i.e., PGI2, thrombomodulin, t-PA).

➢ **Endothelial Dysfunction**

- any disturbance in the balance of the prothrombotic and antithrombotic activities of endothelium. Thus, thrombus can develop without any denudation or physical disruption of endothelium.
- **Causes:**

1. Hypertension.
2. Turbulent blood flow.
3. Toxins (e.g. bacterial endotoxins, toxins from cigarette smoke).
4. Metabolic abnormalities (e.g. homocystinemia or hypercholesterolemia).
5. Radiation injury

2- Abnormal blood flow:

- Normal blood flow is laminar (i.e. platelets (and other blood cells are found mainly in the center of the vessel lumen, separated from the endothelium by a slower-moving layer of plasma.
- **Abnormal blood flow: either** Stasis or turbulence have the following deleterious effects:

1.Disrupt laminar flow and bring platelets into contact with the endothelium.
2. Prevent dilution of activated clotting factors by flowing blood.
3. Retard the inflow of clotting inhibitors.
4.Promote endothelial cell activation.

- Stasis causes thrombosis in the venous circulation, cardiac chambers, and arterial aneurysms;
- turbulence causes thrombosis in the arterial circulation as well as endothelial injury.
- **Turbulence & stasis** contributes to thrombosis in a number of clinical settings:

1. **Ulcerated atherosclerotic plaques;** not only expose subendothelial ECM but also cause turbulence.
2. Abnormal aortic and arterial dilations called **aneurysms** create local stasis and consequently are fertile sites for thrombosis.
3. **Acute myocardial infarction** results in focally noncontractile

myocardium and ventricular remodeling after more remote infarction can lead to aneurysm formation. In both cases, cardiac mural thrombi are more easily formed because of the local blood stasis.

4. Mitral valve stenosis (e.g., after rheumatic heart disease) results in left atrial dilation. In conjunction with atrial fibrillation, a dilated atrium also produces stasis and is a prime location for the development of thrombi.

5. Hyperviscosity syndromes (such as polycythemia vera) increase resistance to flow and cause small vessel stasis.

6. the deformed red cells in **sickle cell anemia** cause vascular occlusions, and the resultant stasis also predisposes to thrombosis.

3- Hypercoagulablity:

- Refers to an abnormally high tendency of the blood to clot, and is typically caused by alterations in coagulation factors.
- Divided into primary (genetic) and secondary (acquired) disorders.

➢ **Primary (genetic) disorders**

As in mutation in factor V and Inherited mutation of antithrombin III, protein C&S leading to venous thrombosis & recurrent thromboembolism in adolescent& early adult life.

➢ **Secondary disorders:**

1. **1. Prolonged bed rest or immobilization**
2. **Oral contraceptives or the hyperestrogenic state of pregnancy;** may cause hypercoagulability by increasing hepatic synthesis of coagulation factors and reduced synthesis of antithrombin III.
3. **Certain malignancies;** can release procoagulant tumor products.
4. **Heparin-induced thrombocytopenia syndrome;** occurs when heparin products (unfractionated more commonly than low molecular weight heparin) induces circulating antibodies that activate platelets and injure ECs.
5. **Antiphospholipid antibody syndrome** occurs in patients with antibodies against anionic phospholipids that activate platelets or interfere with protein C activity.

Morphology of thrombi

- Thrombi can develop anywhere in the cardiovascular system (in cardiac chambers, on valves, or in arteries, veins, or capillaries).

➢ Thrombi occurring in **heart chambers or in the aortic lumen** are designated **mural thrombi**.

- Causes of mural cardiac thrombi: Abnormal myocardial contraction (arrhythmias, myocardial infarction) or endomyocardial injury (myocarditis or catheter trauma).
- Thrombi on heart valves are called **vegetations**. Blood-borne bacteria or fungi can adhere to previously damaged valves (e.g. due to rheumatic heart disease) or can directly cause valve damage; in both cases, endothelial injury and disturbed blood flow can induce the formation of large thrombotic masses (**infective endocarditis**).
- Sterile vegetations can also develop on no infected valves in persons with hypercoagulable states, so-called **nonbacterial thrombotic endocarditis**.
- Less commonly, sterile, verrucous endocarditis (**Libman-Sacks endocarditis**) can occur in the setting of systemic lupus erythematosus.

➢ Arterial thrombi: (white thrombi)

- Usually begin at sites of turbulence or endothelial injury.
- Most common sites are coronary, cerebral & femoral arteries, superimposed on atherosclerotic plaques.
- Pale thrombus, composed of platelets, fibrin, RBCs &degenerated WBCs (lines of Zhan).
- Firmly adheres to arterial wall.
- Are frequently occlusive.

➢ Venous thrombi: (red thrombi)

- Occur at sites of stasis.
- 90% affect veins of lower limbs.
- They contain more RBCs, known as Red or stasis thrombi.
- Loosely attached to vessel wall.
- Almost invariably occlusive.

➢ Grossly and microscopically

- Thrombi often have laminated appearance called **lines of Zahn**; these represent pale platelet and fibrin deposits alternating with darker red cell–rich layers.
- Such laminations signify that a thrombus has formed in **flowing blood;** their presence can therefore distinguish **antemortem** thrombosis from the bland non laminated clots that occur **postmortem.**
- Although thrombi formed in the "low-flow" venous system superficially resemble postmortem clots, careful evaluation generally shows ill-defined laminations.

➢ Postmortem clots:

- Confused with venous (red) thrombus.
- They are gelatinous with dark red dependent portion where RBCs settled by gravity with yellow fat "chicken fat" supernatant.
- Not attached to arterial wall.
- While red thrombi are: more firm, almost always have point of attachment & transaction reveals vague strands of pale gray fibrin.

• Fate of thrombus

1. **Propagation:** Thrombus accumulates more platelets & fibrin &lead to obstruction.
2. **Embolization:** Part or all of the thrombus is dislodged and transported elsewhere in the vasculature.
3. **Dissolution:** Activation of fibrinolytic pathway will lead to shrinkage & total lysis of recent thrombus while older ones undergo fibrin polymerization & become more resistant to proteolysis.
4. **Organization & recanalization:** Ingrowth of endothelial cells, smooth muscle cells & fibroblasts to create conduits along the length of the thrombus, and reestablishing the continuity of the original lumen into fibrin rich thrombus will create conduits from one end of thrombus to other & re-establish continuity of original lumen or incorporate the thrombus into the vessel wall.

➢ Rarely, microbial seeding of a thrombus may weaken the vessel wall, leading to the formation of **a mycotic aneurysm.**