Lec 8

General pathology

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HEMODYNAMIC DISORDERS

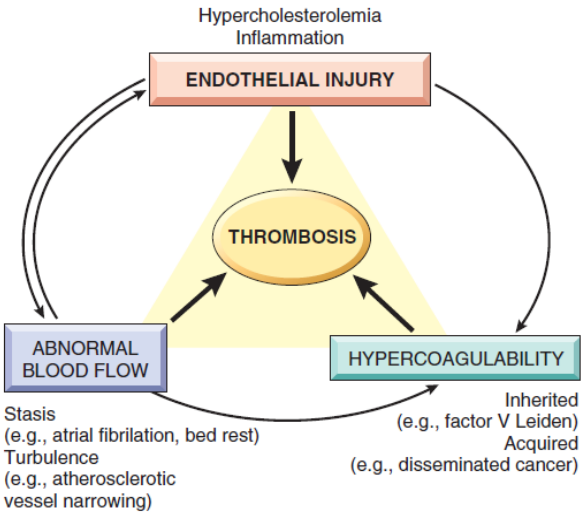
Thrombosis

Thrombosis is a dynamic process in which a thrombus, composed of a solid, tangled mass of fibrin, platelets, erythrocytes and other blood constituent cells, forms within the lumen of a blood vessel in response to disruption of the normal blood flow.

Normal hemostasis comprises a series of regulated processes that suffer in the formation of a blood clot that limits bleeding from an injured vessel. The pathologic counterpart of hemostasis is thrombosis, the formation of blood clot (thrombus) within non-traumatized, intact vessels.

The primary abnormalities that lead to thrombosis the so-called Virchow triad

1) **endothelial injury,**
2) **(2) stasis or turbulent blood flow,**
3) **(3) hypercoagulability of the blood.**



Both hemostasis and thrombosis involve three components:

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

Endothelial Injury

is the main cause of arterial and intracardiac thrombosis: This damage may be either through physical endothelial disruption leads to exposure of subendothelial ECM, adhesion of platelets, release of coagulation factor that help in thrombus formation. or as a consequence of endothelial cell dysfunction. Hence hypertension, turbulent blood flow and bacterial endotoxins may contribute to endothelial dysfunction and thrombus formation.

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 the platelets (and other blood cellular elements) flow centrally in the vessel lumen, separated from the endothelium by a slower moving layer of plasma.

Turbulence and stasis therefore:

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

Causes of turbulence and stasis:

1. **Ulcerated atherosclerotic plaques: not only expose subendothelial and tissue factor.**
2. **Aortic and arterial dilations called aneurysms.**
3. **Acute myocardial infarction results in areas of noncontractile myocardium and sometimes in cardiac aneurysm.**
4. **Rheumatic mitral valve stenosis results in left atrial dilation; in conjunction with atrial fibrillation, a dilated atrium is a site of profound stasis and a prime location for thrombosis.**
5. **Hyperviscosity (such as is seen with polycythemia Vera).**
6. **Deformed red cells in sickle cell anemia**

Hypercoagulability:

Hypercoagulability refers to an abnormally high tendency of the blood to clot, and is typically caused by alterations in coagulation factors.

Hypercoagulability has a particularly important role in venous thrombosis and can be divided into primary (genetic) and secondary (acquired) disorders.

1. **primary (genetic): include Factor V mutation and Prothrombin mutation.**
2. **secondary (acquired): Strong Risk Factors for Thrombosis includes:**

    1. **Prolonged bed rest or immobilization**
    2. **Myocardial infarction**
    3. **Atrial fibrillation**
    4. **Tissue injury (surgery, fracture, burn)**
    5. **Cancer**

6.Prosthetic cardiac valves

7. Disseminated intravascular coagulation

8. Heparin-induced thrombocytopenia

9.Antiphospholipid antibody syndrome

Morphology of thrombus:

Thrombi often have grossly and microscopically apparent laminations called lines of Zahn, which are 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 clots from
the bland nonlaminated clots that occur postmortem.

Types of thrombus:

1. **mural thrombi: Thrombi occurring in heart chambers or in the aortic lumen.**
   Causes:
   a. **Abnormal myocardial contraction (arrhythmias, dilated cardiomyopathy, or myocardial infarction).**
   b. **Ulcerated atherosclerotic plaque and aneurysmal dilation underlie aortic thrombi.**

2.Arterial thrombi: are frequently occlusive; the most common sites in decreasing order of frequency are the coronary, cerebral, and femoral arteries. They typically consist of a friable meshwork of platelets, fibrin, red cells, and degenerating leukocytes. Although these are usually superimposed on a rupture atherosclerotic plaque, other vascular injuries (vasculitis, trauma) may be the underlying cause.

3.Venous thrombosis (phlebothrombosis): is almost invariably occlusive, with the thrombus forming a long luminal cast. Because these thrombi form in the sluggish venous circulation, they tend to contain more enmeshed red cells (and relatively few platelets) and are therefore known as red thrombi or stasis thrombi.

4.Vegetations: Thrombi on heart valves which may be infected or sterile.

a. **Blood-borne bacteria or fungi can adhere to previously damaged valves (e.g., due to rheumatic heart disease) or may cause valve damage directly; in either case, endothelial injury and disturbed blood flow can induce the formation of large thrombotic masses (infective endocarditis).**
b. **Sterile vegetations can also develop on noninfected valves in persons with hypercoagulable states, so-called nonbacterial thrombotic endocarditis.**

Fate of the Thrombus

1. **Propagation. Thrombi accumulate additional platelets and fibrin.**
2. **Embolization. Thrombi dislodge and travel to other sites in the vasculature.**
3. **Dissolution. Is the result of fibrinolysis, which can lead to the rapid shrinkage and total disappearance of recent thrombi.**
4. **Organization and recanalization. Older thrombi become organized by the ingrowth of endothelial cells, smooth muscle cells, and fibroblasts. Continued recanalization may convert a thrombus into a smaller mass of connective tissue that becomes incorporated into the vessel wall.**

Clinical significance:

1. **they obstruct arteries or veins**
2. **or give rise to emboli.**

Venous thrombi can cause painful congestion and edema distal to an obstruction, but are mainly of concern due to their tendency to embolize to the lungs.

arterial thrombi can also embolize and cause downstream infarctions, the chief clinical problem is more often related to occlusion of a critical vessel (e.g., a coronary or cerebral artery), which can have serious or fatal consequences.

Venous Thrombosis (Phlebothrombosis): Most venous thrombi occur in the superficial or deep veins of the leg.

Superficial venous thrombi typically occur in the saphenous veins in the setting of varicosities. Such thrombi can cause local congestion, swelling, pain, and tenderness, but rarely embolize.

Deep venous thrombi (DVT) involving one of the large leg veins at or above the knee.

is considered serious because such thrombi more often embolize to the lungs and give rise to pulmonary infarction. DVTs may cause local pain and edema due to venous obstruction. Consequently, DVTs are asymptomatic in approximately 50% of affected individuals and are recognized only in retrospect after embolization. Lower extremity DVTs are often associated with hypercoagulable states.

<u>Common predisposing factors:</u>

1. **bed rest and immobilization.**
2. **congestive heart failure**
3. **Trauma**
4. **Surgery**
5. **burns not only immobilize a person but are also associated with vascular insults.**
6. **procoagulant release from injured tissues.**
7. **increased hepatic synthesis of coagulation factors, and decreased t-PA (plasminogen activator; its fibrinolytic activity is largely confined to sites of recent thrombosis) production.**

EMBOLISM

An embolus is a detached intravascular solid, liquid, or gaseous mass that is carried by the blood from its point of origin to a distant site, where it often causes tissue dysfunction or infarction.

Forms of emboli

1.Thromboembolism: The vast majority of emboli are dislodged thrombi.

2. fat droplets: Fat embolism refers to the presence of microscopic fat globules—sometimes with associated hematopoietic bone marrow—in the vasculature after fractures of long bones or, rarely, in the setting of soft-tissue trauma and burns. It is fairly common, occurring in some 90% of individuals

with severe skeletal injuries.

3. air embolism: Gas bubbles within the circulation can coalesce to form frothy masses that obstruct vascular flow and cause distal ischemic injury.

4. atherosclerotic debris (cholesterol emboli)

5. tumor fragments

6. bone marrow

7. foreign bodies

Pulmonary Embolism (PE)

Pulmonary emboli originate from DVT and are the most common form of thromboembolic disease.

In more than 95% of cases, PE originates from leg DVT.

Fragmented thrombi from DVT are carried through progressively larger veins and the right side of the heart before slamming into the pulmonary arterial vasculature.

The major functional consequences of pulmonary emboli:

1. **Most pulmonary emboli (60% to 80%) are clinically silent because they are small.**
2. **Sudden death, acute right heart failure (cor pulmonale), or cardiovascular collapse occurs when emboli obstruct 60% or more of the pulmonary circulation.**

3. **Embolic obstruction of medium-sized arteries with subsequent vascular rupture can result in pulmonary hemorrhage.**
4. **Embolic obstruction of small end-arteriolar pulmonary branches often does produce hemorrhage or infarction.**
5. **Multiple emboli over time may cause pulmonary hypertension and right ventricular failure.**

Systemic Thromboembolism

Most systemic emboli (80%) arise from intracardiac mural thrombi.

***Common arteriolar embolization sites*:**

1. **the lower extremities (75%)**
2. **the brain (10%)**
3. **other tissues, including the intestines, kidneys, spleen.**
4. **upper extremities, may be involved.**

INFARCTION

An infarct is an area of ischemic necrosis caused by occlusion of either the arterial supply or the venous drainage. The vast majority of infarctions result from Arterial thrombosis or arterial embolism.

MORPHOLOGY

Infarcts are classified according to color and the presence or absence of infection; they are either red (hemorrhagic) or white (anemic) and may be septic or bland.

1. **Red infarcts occur:**

(1) with venous occlusions (e.g., testicular torsion).

(2) in loose, spongy tissues (e.g., lung) where blood can collect in the infarcted zone.

(3) in tissues with dual circulations (e.g., lung and small intestine) that allow blood to flow from an unobstructed parallel supply into a necrotic zone.

(4) in tissues previously congested by sluggish venous outflow.

(5) when flow is reestablished to a site of previous arterial occlusion and necrosis (e.g., following angioplasty of an arterial obstruction).

2. White infarcts occur with arterial occlusions in solid organs with end-arterial circulation (e.g., heart, spleen, and kidney), and where tissue density limits the leak of blood from adjoining capillary beds into the necrotic area.

3. Septic infarctions occur when infected cardiac valve vegetations embolize or when microbes seed necrotic tissue. In these cases, the infarct is converted to an abscess, with a correspondingly greater inflammatory response.

Histological appearance:

The dominant histologic characteristic of infarction is ischemic coagulative necrosis. Importantly, if the vascular occlusion has occurred shortly (minutes to hours) before the death of the person, histologic changes may be absent; it takes 4 to 12 hours for the dead tissue to show microscopic evidence of necrosis. Acute inflammation is present along the margins of infarcts within a few hours and is usually well defined within 1 to 2 days.

If the tissue harbors tissue stem cells, parenchymal regeneration can occur at the periphery where underlying stromal architecture is preserved. However, most infarcts are ultimately replaced by scar. The brain is an exception to these generalizations, in that central nervous system infarction results in liquefactive necrosis.

Factors That Influence Development of an Infarct

A vascular occlusion can cause effects ranging from virtually nothing to tissue dysfunction and necrosis sufficient to result in death. The variables that influence the outcome of vascular occlusion are as follows:

1. **Anatomy of the vascular supply. The availability of an alternative blood supply is the most important determinant of whether vessel occlusion will cause tissue damage. the lungs have a dual pulmonary and bronchial artery blood supply that protects against thromboembolism-induced infarction. Similarly, the liver, with its dual hepatic artery and portal vein circulation, both are all relatively resistant to infarction. In contrast, renal and splenic circulations are end-arterial, and vascular obstruction generally causes tissue death.**
2. **Rate of occlusion. Slowly developing occlusions are less likely to cause infarction, because they provide time for development of collateral pathways of perfusion.**
3. **Tissue susceptibility to hypoxia. Neurons undergo irreversible damage when deprived of their blood supply for only 3 to 4 minutes. Myocardial cells, although hardier than neurons, are also quite sensitive and die after only 20 to,30 minutes of ischemia. In contrast, fibroblasts within myocardium remain viable even after many hours of ischemia.**
4. **Hypoxemia. Understandably, abnormally low blood oxygen content (regardless of cause) increases both the likelihood and extent of infarction.**

SHOCK:

Shock is a state of circulatory failure that impairs tissue perfusion and leads to cellular hypoxia.

prolonged shock eventually leads to irreversible tissue injury and can be fatal.

Shock may complicate severe hemorrhage, extensive trauma or burns, myocardial infarction, pulmonary embolism, and microbial sepsis. Its causes fall into *three general categories*:

1. **Cardiogenic shock results from low cardiac output due to myocardial pump failure. This can be due to intrinsic myocardial damage (infarction), ventricular arrhythmias, extrinsic compression or outflow obstruction (e.g., pulmonary embolism).**
2. **Hypovolemic shock results from low cardiac output due to low blood volume, such as can occur with massive hemorrhage or fluid loss from severe burns.**
3. **septic shock is most frequently triggered by gram positive bacterial infections, followed by gram-negative bacteria and fungi. Associated with a greater risk of mortality.**

Less commonly, shock can occur in the setting of a spinal cord injury (neurogenic shock), or an IgE-mediated hypersensitivity reaction (anaphylactic shock,). In both of these forms of shock, acute vasodilation leads to hypotension and tissue hypoperfusion.

MORPHOLOGY

The cellular and tissue effects of shock are essentially those of hypoxic injury and are caused by a combination of hypoperfusion and microvascular thrombosis. Although any organ can be affected, the brain, heart, kidneys, adrenals, and gastrointestinal tract are most commonly involved.

Fibrin thrombi can form in any tissue but typically are most readily visualized in kidney glomeruli.

Clinical Features:

In hypovolemic and cardiogenic shock, patients exhibit hypotension, a weak rapid pulse, tachypnea, and cool, clammy, cyanotic skin.

In septic shock, the skin may be warm and flushed owing to peripheral vasodilation. Prognosis varies with the origin of shock and its duration. Thus, more than 90% of young, otherwise healthy patients

with hypovolemic shock survive with appropriate management; by comparison, septic or cardiogenic shock is associated with substantially poorer outcomes, even with appropriate treatment.