HEMOSTASIS AND THROMBOSIS

Normal hemostasis is a precisely orchestrated process involving platelets, clotting factors, and endothelium that occurs at the site of vascular injury and culminates in the formation of a blood clot, which serves to prevent or limit the extent of bleeding .

Thrombosis (the pathologic counterpart of hemostasis):- its a formation of blood clot (*thrombus*) within non-traumatized, intact vessels or formation of solid or semi solid mass from the constituents of blood within the vascular system during life .

Both **hemostasis** and **thrombosis** involve three components :

1- Endothelium.

2- Platelets .

3- Clotting factors.

Pathogenesis of thrombosis

There are three abnormalities lead to thrombus formation (called ***Virchow's triad***):

(1) endothelial injury.

(2) abnormal blood flow (stasis or turbulence) .

(3) blood hypercoagulability .

1- Endothelial Injury

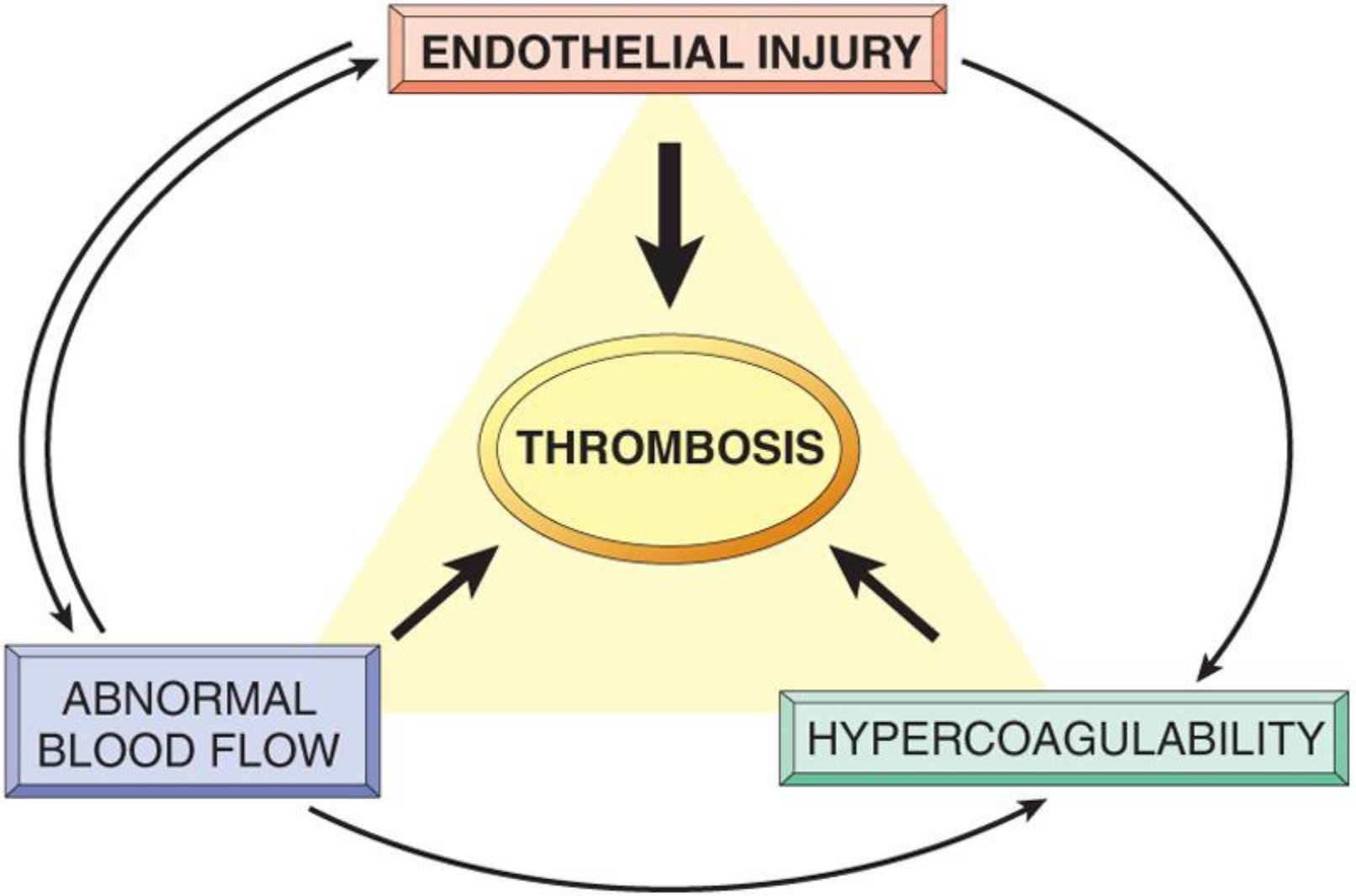
- Endothelial injury leading to platelet activation and is an important cause for thrombus formation particularly in the heart and the arterial circulation .

- Normally high flow rates of blood flow prevent clotting by preventing platelet adhesion or diluting coagulation factors .

Ex. Thrombi in the cardiac chambers due to endothelial injury , ulcerated plaques in atherosclerotic arteries , and traumatic or inflammatory vascular injury (vasculitis) .

- Endothelial injury may trigger thrombosis by exposing VWF, collagen ,and tissue factor .

- inflammation and other noxious stimuli also promote thrombosis.



Virchow's triad in thrombosis. Integrity of endothelium is the most important factor. Injury to endothelial cells can also alter local blood flow and affect coagulability. Abnormal blood flow (stasis or turbulence), in turn, can cause endothelial injury. The factors may act independently or may combine to promote thrombus formation.

2- Abnormal Blood Flow (stasis or turbulence)

Turbulence (chaotic blood flow) 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 .

In Normal laminar blood flow, platelets and other blood cells are flow in the center of vessel lumen, separated from the endothelium by a slower moving layer of plasma.

Stasis and turbulence blood flow have the following deleterious effects:-

1- Stasis allows platelets and leukocytes to come into contact with the endothelium when the flow is sluggish .

2- Stasis also slows the washout of activated clotting factors and impedes the inflow of clotting factor inhibitors .

3- Both Promote endothelial activation, resulting in local thrombosis, leukocyte adhesion, etc .

Turbulent and static blood flow 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 a fertile site for thrombosis .

3- Acute myocardial infarction results in focally noncontractile myocardium. Ventricular remodeling after infarction can lead to aneurysm formation. cause of the local blood stasis .

4- Mitral valve stenosis (e.g., after rheumatic heart disease) results in left atrial dilation which is a site of stasis and a prime location for development of thrombi .

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 also predisposing to thrombosis.

3- Hypercoagulability

its any alteration of the coagulation pathways that predisposes to thrombosis . and it can be divided into *primary* (genetic) and *secondary* (acquired) causes .

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

2- Secondary (acquired) disorders include :-

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

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

- In disseminated cancers, release of procoagulant tumor products predisposes to thrombosis .

- 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 develop any where in the cardiovascular system (e.g., in cardiac chambers, on valves, or in arteries, veins, or capillaries) .

-Arterial or cardiac thrombi typically arise at sites of endothelial injury or turbulence ;

- **Venous thrombi** characteristically occur at sites of stasis . Thrombi are attached to the underlying vascular surface and tend to propagate toward the heart; thus **arterial thrombi** tend to grow in a retrograde direction from the point of attachment, while **venous thrombi** extend in the direction of blood flow . 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. These lines distinguish antemortem thrombosis from nonlaminated postmortem clots .

Types of thrombi

1- Mural thrombi which are thrombi occurring in heart chambers or in the aortic lumen.

Causes

A- Abnormal myocardial contraction (arrhythmias or myocardial infarction) .

B- Endomyocardial injury (caused by myocarditis, catheter trauma) promotes cardiac mural thrombi .

2- Arterial thrombi are frequently occlusive and rich in platelets, as the processes underlying their development (e.g., endothelial injury) lead to platelet activation .

Causes

Arterial thrombi are caused by ruptured atherosclerotic plaque, vasculitis , and trauma .

Mural thrombi. **A,** Thrombus in the ventricular apices, overlying white fibrous scar.

3 - Venous thrombosis (phlebothrombosis)

- are almost occlusive ; they propagate some distance toward the heart, forming a long cast within the vessel lumen that is prone to give rise to emboli .

- 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

postmortem clots are gelatinous and due to red cell settling have a dark red lower portion and a yellow "chicken fat" upper portion; not attached to the underlying vessel wall. By contrast, red thrombi firm, focally attached to vessel walls, and contain gray strands of deposited fibrin

4- Vegetations . Are thrombi on heart valves . Bacterial or fungal 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 combination of the following four events :-

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

2- Embolization:- Part or all of the thrombus is dislodged and transported elsewhere in the vasculature .

3- Dissolution:- Thrombi are removed by fibrinolytic activity .

4- Organization and recanalization*:-* Older thrombi become **organized** by the ingrowth of endothelial cells, smooth muscle cells, and fibroblasts into the thrombus. In time, capillary channels are formed along the length of the thrombus, thereby reestablishing the continuity of the original lumen. Further recanalization convert a thrombus into a vascularized mass of connective tissue that is eventually incorporated into the wall of the remodeled vessel .

Clinical significance

Thrombi are significant because:-

1-*Cause obstruction of arteries and veins .*

2- May give rise to emboli .

Which effect is most important and depends on the site of thrombosis.

Venous thrombi can cause congestion and edema in vascular beds distal to an obstruction, they are most worrisome for their capacity to embolize to the lungs and cause death .

Arterial thrombi can embolize and cause tissue infarction , they obstruct vessels (e.g., in coronary and cerebral vessels) is considerably more important .

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- The vast majority of emboli (99% of emboli) derive from a dislodged thrombus term **thromboembolism**

2- Fat embolism :- microscopic fat globules can be found in the circulation after fracture of long bones (which contain fatty morrow).

3- Air embolism :- Air may enter circulation during a chest wall injury . Air bubble can coalesce to form frothy masses sufficiently large to occlude major vessels .

4- Atherosclerotic thrombi (Cholesterol emboli) consisting atheromatous debris .

5- Tumor emboli made up of fragments of a tumor.

6- Bone marrow emboli consisting of bits of bone marrow.

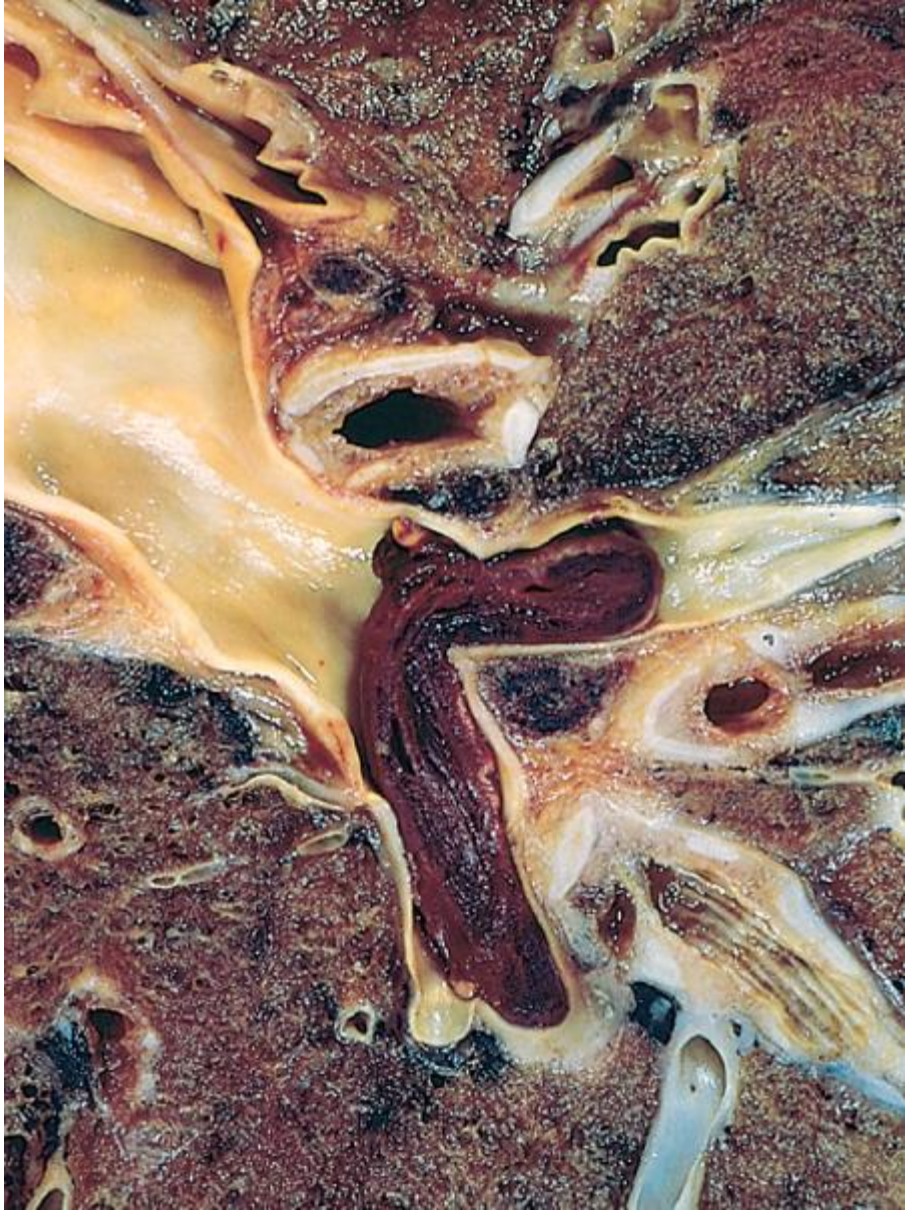
Emboli lodge in vessels too small to permit further passage, resulting in partial or complete vascular occlusion. The consequences of systemic embolization is ischemic necrosis (*infarction*) of downstream tissue. whereas embolization in the pulmonary circulation leads to hypoxia, and right-sided heart failure.

Pulmonary thromboembolism

- Pulmonary emboli originate from deep leg vein thrombi above the level of the knee such as femoral or iliac veins .

-These emboli are carried through larger channels and pass through the right side of the heart before arresting in the pulmonary vasculature .

- Depending on the size of the embolus, it may occlude the main pulmonary artery, lodge at the bifurcation of the right and left pulmonary arteries **(*saddle embolus*) ,** or pass into the smaller, branching arterioles .



Embolus derived from a lower extremity deep venous thrombosis and lodged in a pulmonary artery branch

Systemic Thromboembolism

Systemic thromboembolism refers to emboli in the arterial circulation . Most arise from intracardiac mural thrombi .

Arterial emboli can travel anywhere; their final resting place depends on their point of origin and flow rates of blood to the downstream tissues .

The major sites for arteriolar embolization are :-

- The lower extremities (75%) .
- central nervous system (10%).
- the intestines, kidneys, and spleen are less common sites .

The consequences of embolization in a tissue depend on the caliber of the occluded vessel, the collateral supply, and the affected tissue's vulnerability to anoxia .

Arterial emboli lodge in end arteries and cause infarction .

Amniotic Fluid Embolism

Amniotic fluid embolism is an uncommon, grave complication of labor and the immediate postpartum period occurring in 1in 40,000 deliveries .

- Characterized by sudden severe dyspnea, cyanosis, and hypotensive shock, followed by seizures and coma. If the patient survives the initial crisis, pulmonary edema develops, along with disseminated intravascular coagulation due to release of thrombogenic substances from amniotic fluid .

- Amniotic Fluid Embolism caused by entry of amniotic fluid (and its contents) into the maternal circulation via a tear in the placental membranes and rupture of uterine veins .

- Histologic analysis show squamous cells shed from fetal skin, lanugo hair, fat from vernix caseosa, and mucin derived from the fetal respiratory or gastrointestinal tracts.

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.

Causes

1-Arterial thrombosis or arterial embolism

2- vasospasm

3-expansion of an atheroma

4-extrinsic compression of a vessel, such as by tumor .

5-vessel twisting (e.g., in testicular torsion or bowel volvulus),

Morphology

Infarcts are classified on the basis of their color (reflecting the amount of hemorrhage) to :-

1-red (hemorrhagic) infarcts .

2- white (anemic) infarcts.

and the presence or absence of microbial infection.

1-septic infarcts

2- bland (non septic) infarcts.

Red infarcts :- occur

(1) with **venous occlusions** (such as in ovarian torsion).

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

(3) in tissues with **dual circulations** such as lung and small intestine, permitting flow of blood from an unobstructed parallel supply into a necrotic area .

(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) .

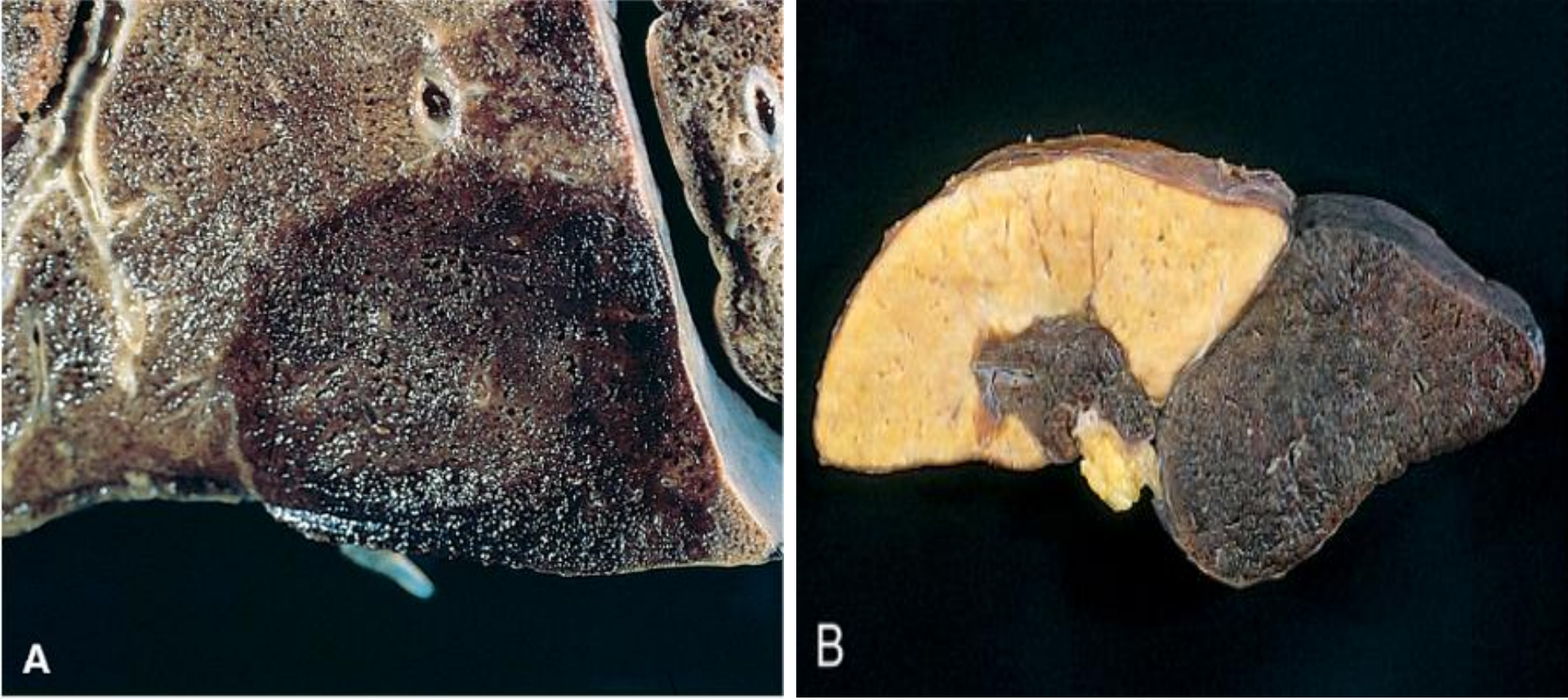
White infarcts

occur

-with arterial occlusions in organ with single arterial blood supply.

- 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 nearby capillaries .

Septic infarctions:- occur when bacterial vegetations from a heart valve embolize or when microbes seed an area of necrotic tissue. In these cases the infarct is converted into an abscess, with a greater inflammatory response .



Red and white infarcts. **A,** Hemorrhagic, roughly wedge-shaped pulmonary infarct (*red infarct*). **B,** Sharply demarcated pale infarct in the spleen (*white infarct*).

Factors That Influence Development of an Infarct

***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. For example,, **lungs** have a dual pulmonary and bronchial blood supply; thus, obstruction of small pulmonary arterioles does not cause infarction in healthy individual with an intact bronchial circulation. Similarly, the **liver,** with its dual hepatic artery and portal vein circulation, and **the hand and forearm**, with their dual radial and ulnar arterial supply, are all resistant to infarction. In contrast, **renal and spleenic** circulations are end-arterial blood supply , and obstruction of such vessels generally causes infarction.

2- Rate of Occlusion Slowly developing occlusions are less likely to cause infarction because they provide time for the development of alternative perfusion pathways. For example, the three major coronary arteries in the heart. If one of the coronaries is slowly occluded (e.g., by atherosclerotic plaque), flow within this collateral circulation may increase sufficiently to prevent infarction, even if the the major coronary artery is eventually occluded.

3- Tissue susceptiblity to Hypoxia The susceptibility of a tissue to hypoxia influences the likelihood of infarction. Neurons undergo irreversible damage when deprived of their blood supply for only 3 to 4 minutes. Myocardial cells, though hardier than neurons, are die after only 20 to 30 minutes of ischemia. In contrast, fibroblasts within myocardium remain viable after many hours of ischemia.

4-Hypoxemia (low oxygen Content of Blood) abnormally low blood O2 content (regardless of cause) increases both the likelihood and extent of infarction.

Shock

Shock is a state in which diminished cardiac output or reduced effective circulating blood volume impairs tissue perfusion and leads to cellular hypoxia.

At the outset of shock , the cellular injury is reversible. prolonged shock leads to irreversible tissue injury that often fatal

Shock is a complication of **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 as a result failure of cardiac pump . This may be caused by myocardial infarction , ventricular arrhythmias, extrinsic compression on the heart (cardiac temponade) , or outflow obstruction (e.g., pulmonary embolism) .

2- Hypovolemic shock results from low cardiac output due to loss of blood or plasma volume (e.g. due to hemorrhage, fluid loss from severe burns).

3- Septic shock is caused by microbial infection. Most commonly this occurs in gram-negative infections (*endotoxic shock*), but it can also occur with gram-positive and fungal infections .

Less commonly

4- *Neurogenic* shock :- shock can result from a loss of vascular tone associated with anesthesia or secondary to a spinal cord injury

5- Anaphylactic shock results from systemic vasodilation and increased vascular permeability caused by an immunoglobulin E hypersensitivity reaction .

Morphology

Shock induce cellular and tissue necrosis by hypoxic injury or combination of decrease blood flow and microvascular thrombosis . Although any organ can be affected but brain, heart, kidneys, adrenals, and gastrointestinal tract are most commonly involved .

Clinical manifestations

In hypovolemic and cardiogenic shock, the patient exhibit *hypotension;* a weak and rapid pulse; tachypnea; and cool, clammy, cyanotic skin.

In septic shock the skin may be warm and flushed as a result of peripheral vasodilation .

prognosis

The prognosis varies with the type of shock and its duration ,age , and general health of patients .

Thus, more than 90% of young, patients with hypovolemic shock survive with appropriate management, whereas septic or cardiogenic shock is associated with worse outcomes, even with appropriate management .