3. Thrombosis, Embolism, DIC, Shock

PATHOLOGY OF VASCULAR OCCLUSION: thrombosis, embolism, disseminated intravascular coagulation (DIC)

Hemostasis ("stopping of hemorrhage")
- Physiological process to maintain blood in a fluid, clot-free state in normal vessels, and to stop bleeding from ruptured vessels (for details see pathophysiology)
- Main components of hemostasis: endothelium, platelets, and coagulation proteins

Endothelial cells have both procoagulant and anticoagulant properties, and according to the needs of the body they may either promote clotting or inhibiting it

Procoagulant functions
Release of
- von Willebrand factor (vWF), which mediates the binding of platelets to endothelial surfaces
- Tissue factor, which promotes the extrinsic pathway of the coagulation cascade
- Inhibitors of plasminogen activator

Anticoagulant functions
- Inhibition of platelet aggregation via prostacyclin secretion
- Dilation of blood vessels via nitric oxide secretion
- Antithrombin activity, accomplished by thrombomodulin, which captures thrombin
- Fibrinolysis, via secreting plasminogen activator, which generates plasmin from plasminogen

Platelets
Upon contact with collagen and/or vWF, platelets become activated and
1) adhere to injured sites
2) release chemical mediators to induce further platelet aggregation, and activation of coagulation proteins
3) aggregate with other platelets and form the primary hemostatic plug
4) contract and create an irreversibly fused mass of platelets constituting the secondary hemostatic plug.
Thrombin converts fibrinogen to fibrin within and about the platelet plug, contributing to the stability of the clot. Both RBCs and leukocytes are also found in hemostatic plugs

Coagulation proteins
Group of plasma proteins that are activated by acting upon each other in a sequence known as the extrinsic and intrinsic pathway. These proteins converge, and finally lead to the polymerization of fibrinogen into fibrin.

Activation of the coagulation in vivo
- Extrinsic pathway - activated by tissue factor released from damaged tissue (TF → VII → VIIa)
- Intrinsic pathway - activated by exposure to intimal collagen or basement membranes denuded of endothelial cells (XII → XIIa → XI → XIa)
- Common pathway – activated by VIIa and Xla in the presence of Ca²⁺ → Xa → V → Va → II (prothrombin) → IIa (thrombin) → fibrinogen → fibrin

THROMBOSIS
A pathologic process, characterized by intravascular clotting in a living person
- Clots formed in circulating blood inside the blood vessels or cardiac chambers are called thrombi
- A thrombus is always a potential source of further complications
- The process of thrombosis depends on the interaction of the endothelial cells, platelets, and the coagulation proteins (similarly to hemostasis)

Factors promoting thrombus formation (Virchow’s triad)
1. Endothelial/endocardial injury
2. Changes in blood flow
3. Changes in the composition of blood

1) Endothelial/endocardial injury
Leading factor in thrombus formation in the arteries and heart
Endothelial injury occurs
- Over atheromatous plaques in aorta and large arteries
- In necrotizing arteritis
- In high blood pressure, hypercholesterolemia, and cigarette smoke (these are subtle influences)
Endocardial injury occurs
- In mural endocardium related to myocardial infarction
- In valvular endocardium in connection with endocarditis

2) Changes in blood flow
Turbulence contributes to arterial and cardiac thrombosis
- by mechanical damage to the endothelial cells
- by forming countercurrents and local pockets of stasis
Stasis is a major factor in the development of venous thrombi.

Normal blood flow is laminar: the cellular elements flow centrally in the vessel lumen, and they are separated from the endothelium by a slower moving clear zone of plasma.

Turbulence and stasis
- 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 build-up of thrombi
3. Thrombosis, Embolism, DIC, Shock

Causes
- Ulcerated atherosclerotic plaques
- Aneurysms (circumscribed dilations of aorta, arteries, or heart); bifurcation of arteries (turbulence)
- Chronic dilation of the left atrium, typically associated with atrial fibrillation, a common type of cardiac arrhythmia (quivering of the heart muscles of the atria, instead of a coordinated contraction)

3) Changes in the composition of blood (hypercoagulability)
- Prolonged bed rest or immobilization of the leg
- Tissue damage (surgery, fracture, myocardial infarction, etc.)
- Disseminated cancer
- Leiden mutation: factor V is resistant to cleavage by activated protein C; 2 to 15% of the white population carry this mutation

Morphology of thrombi
Arterial and cardiac thrombi
- Are gray-red and have laminations (lines of Zahn), produced by pale layers of platelets and fibrin, alternating with darker, RBC-rich layers
- Aortic or cardiac thrombi are typically nonocclusive (mural) as a result of rapid and high-volume flow, but may detach and cause embolism
- Arterial thrombi are frequently occlusive; extend retrograde from the attachment point

Venous thrombi (red or stasis thrombi)
- Occur in a stagnating environment, and the thrombi contain more enmeshed RBCs among sparse fibrin strands; appear as long, red-blue cast of the vein lumen
- Are occlusive
- Extend into the direction of blood flow; the propagating tail may fragment to create thromboemboli

Valvular thrombi
- On heart valves, also called vegetations
- May contain bacteria, e.g., in infective endocarditis
- May be sterile, e.g., in endocarditis associated with disseminated cancer

Fate of thrombus
- Propagation, causing complete obstruction → may cause sudden death
- Embolization to other sites in the vasculature
- Dissolution by fibrinolytic activity
- Organization: the thrombus is converted to granulation tissue: ingrowth of endothelial cells, smooth muscle cells, and fibroblasts to create through-and-through capillary channels. Granulation tissue will transform into a fibrous scar.
- Recanalization: the capillaries in the granulation tissue organizing the thrombus may fuse into larger channels, allowing the resumption of blood flow

Complications of thrombosis
- Arterial occlusion: infarction of the tissue supplied by the artery
- Venous occlusion: obstruction of venous flow and edema of the involved extremity
- Embolism (regardless of whether the thrombi are arterial, cardiac, or venous)
- Infection. Thrombi become easily infected with bacteria, particularly those developed at peripheral venous cannula sites → catheter-related bloodstream infection
- Thrombophlebitis. Inflammation of the vein, induced by organization of infected thrombi

Prevention of thrombosis
- Administration of anti-coagulants is essential in the medical practice
- Aspirin prevents thrombosis in the arteries, whereas heparin prevents thrombosis in the veins

EMBOLISM
Emboli are solid, fluid or gaseous material, carried by the bloodstream from the site of their origin or entry into the circulation to other parts of the body, causing obstruction.

Classification according to type of material forming the emboli:
1) Thromboemboli
2) Fat emboli
3) Air emboli
4) Amniotic fluid emboli
5) Other emboli

THROMBOEMBOLISM – most common and most important

Emboli in the pulmonary circulation (pulmonary thromboembolism)
In more than 95%, pulmonary thromboemboli originate from deep leg vein thrombi.
- Occlusion of the main pulmonary artery (PA) or its main branches (saddle embolus) causes sudden death.
- Occlusion of the branches of the PA causes hemorrhagic infarcts (if the patient has left-sided heart failure)
- Occlusion of the small branches of the PA may be clinically unrecognized. Repeated episodes narrow the lumen of PA branches and over time lead to pulmonary hypertension and chronic right ventricular failure

Emboli in the arterial circulation (systemic thromboembolism)
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- Vast majority arise from thrombi within the left chambers of the heart secondary to myocardial infarcts, or from dilated atrium, vegetations on the aortic/mitral valve
- May originate from
  - Aortic aneurysms
  - Ulcerated atherosclerotic plaques
- Small percent of systemic emboli are of unknown origin

**Major targets**
Most frequent: lower extremities → gangrene of toes
Less frequent: brain → infarct(s) in the territory of the middle cerebral artery; viscera → renal infarct, bowel necrosis

**FAT EMBOLISM**
- Caused by entry of fat globules into the circulation, released from bone marrow during fracture(s) of long bones leading to mechanical obstruction of small vessels of lungs, followed by local platelet and erythrocyte aggregation
- The fat globules may cross the pulmonary vascular bed and may enter the systemic circulation, causing multifocal ischemic injury, mainly to the brain
- Fat globules also induce disseminated intravascular coagulation

**Clinical features**
- Most cases remain silent.
- *Fat embolism syndrome* in 10% of cases: in 24-72 hrs after the fracture of bones, progressive pulmonary insufficiency, thrombocytopenia and petechiae develop; with or without mental, sensory or motor disturbances; mortality rate: 10-15%
- Dg.: identification of fat globules in frozen sections in the lungs, brain and other organs

**AIR EMBOLISM**
- Entry of atmospheric air into the venous circulation
- Injection of more than 150 ml air is lethal: blood entering the right ventricle is transformed into a foamy air-fluid mixture that obstructs the blood flow, rapidly causing death
- Air enters the venous circulation as a consequence of
  - Trauma or surgery of the neck accompanied by a tear in the wall of the jugular vein or the superior vena cava, the negative pressure in the thorax sucks the air into the venous blood
  - Childbirth or abortion may allow the entry of air into uterine veins

**AMNIOTIC FLUID EMBOLISM**
- Uncommon but serious complication of labor and the immediate postpartum period; mortality rate 80%
- The shed skin cells of the infant, moreover lanugo hairs, and meconium particles can be recognized in the pulmonary vessels of the mother
- If the patient survives the initial crisis, DIC may ensue owing to the release of thrombogenic substances from the amniotic fluid

**OTHER EMBOLI**
- Tumor emboli: major route of dissemination of malignancies – metastasis
- Cholesterol emboli: frequently seen in the lower limbs of atherosclerotic patients – cigar shaped clefts
- Foreign body emboli: most commonly talc or starch in drug abusers → granulomatous reaction in the lungs → pulmonary hypertension

**DISSEMINATED INTRAVASCULAR COAGULATION (DIC)**
- A thrombohemorrhagic disorder characterized by the formation of microthrombi in arterioles, capillaries, and venules.
- Formation of these microthrombi consumes the platelets → thrombocytopenia, and leads to the depletion of fibrinogen and other coagulation proteins → severe diffuse bleeding

**Causes of DIC**
- Infections – Gram-negative sepsis, Neisseria bacteria in the blood; fungal infections
- Neoplasms – carcinomas of the gastrointestinal tract, and promyelocytic leukemia
- Massive tissue injury – trauma, burns, and extensive surgery
- Shock – any form
- Obstetric complications – amniotic fluid embolism, eclampsia, and abruptio placenta (premature separation of the placenta from the uterus)

**Pathogenesis**
Intravascular coagulation can be initiated by three often interrelated pathways:
- Activation of Hageman factor initiating the intrinsic coagulation cascade
- Tissue factor activating the extrinsic coagulation pathway
- Endothelial cell injury

**Pathologic findings**
- Gross: hemorrhages of skin, mucous membranes, serosal surfaces, and viscera
- LM: numerous fibrin microthrombi in small vessels, particularly in the heart, brain, glomeruli of the kidneys, and other sites + microinfarcts
- Most patients die before such foci of ischemic necrosis become histologically apparent

**Laboratory findings**
- Bleeding tests (prothrombin [PT] and activated partial thromboplastin time [aPTT]) are prolonged
- Thrombocytopenia
- Fibrin degradation products in the urine
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Waterhouse-Friderichsen syndrome
- Represents a DIC caused by Neisseria meningitidis (meningococcus) infection
- Presents with bilateral massive hemorrhages of adrenals, purpura of skin, DIC, low blood pressure, and shock
- High mortality rate

SHOCK
A condition resulting from hypoperfusion of tissues with blood. Ensuing hypoxia or anoxia leads to multiorgan failure.

Classification
- **Cardiogenic**, due to pump failure (ejection fraction < 20%), which develops most frequently in association with coronary occlusion
- **Hypovolemic**, due to loss of blood owing to an arterial wound, rupture of aortic aneurysm, etc., or loss of plasma fluid due to severe burns, diarrhea, etc.
- **Septic**, caused by endotoxin-producing gram-negative bacilli
- **Anaphylactic**, due to systemic vasodilation and increased vascular permeability elicited by an IgE hypersensitivity reaction

Stages of shock
Shock is a progressive disorder that, if uncorrected, leads to death. Shock tends to evolve through three phases.
- **An initial nonprogressive phase** during which reflex compensatory mechanisms are activated and perfusion of vital organs is maintained
- **A progressive phase** characterized by tissue hypoperfusion and onset of worsening circulatory and metabolic imbalances including acidosis
- **An irreversible phase** that sets in after the body has incurred cellular and tissue injuries so severe that even if the hemodynamic defects are corrected, survival is not possible

Clinicopathology of shock
Fibrin thrombi in microvessels and hypoxic injury to cells and tissues can be observed in any tissue

The most severe lesions are seen in the brain, heart, lungs, kidneys, GI tract, and liver
- **Brain**: ischemic encephalopathy → loss of consciousness
- **Heart**: focal or widespread coagulation necrosis of myofibers → diminished myocardial contractility
- **Kidneys**: acute tubular necrosis → oligoanuria
- **Lungs**: seldom affected in hypovolemic shock. In septic shock, diffuse alveolar damage may develop → arterial hypoxemia
- **GI tract**: patchy mucosal hemorrhages → paralytic ileus (absence of bowel sounds)
- **Liver**: fatty change + central hemorrhagic necrosis → plasma total bilirubin > 70 mmol/l, elevated liver enzymes

Outcome
All tissue changes may revert to normal if the patient survives (with the exception of neuronal and myocyte loss)