Hemodynamic Dysfunction

Part 2
Describe thrombosis: causes, mechanism of formation, types, sites, effects & fate of thrombus.
Describe embolism: types & source, effects, fate & Paradoxical Embolism.
Describe Shock: causes, pathogenesis, compensatory mechanisms & morphological changes.

The pathologic form of hemostasis is thrombosis. It involves blood clot (thrombus) formation in uninjured vessels or thrombotic occlusion of a vessel after relatively minor injury.

Both hemostasis and thrombosis involve three components:

a. the vascular wall
b. platelets
c. the coagulation cascade.

Intact endothelial cells maintain liquid blood flow by
1. actively inhibiting platelet adherence,
2. preventing coagulation factor activation, and
3. lysing blood clots that may form.

Endothelial cells can be stimulated by
1. direct injury or
2. by various cytokines that are produced during inflammation.
Such stimulation results in expression of procoagulant proteins (e.g., tissue factor and vWF) that contribute to local thrombus formation.

Loss of endothelial integrity exposes underlying
1. vWF
2. basement membrane collagen

What is the role of endothelial cells?

It usually limits blood clotting, but can become prothrombotic, with activities that affect platelets, coagulation proteins, and the fibrinolytic system.
What is the relationship between vWF & endothelial cells?

vWF (both circulating and collagen bound) is synthesized largely by normal endothelium.

What is the role of vWF?

*von Willebrand Factor (vWF)*, is an essential cofactor for binding platelets to collagen and other surfaces. Endothelial injury results in platelet adhesion to subendothelial collagen.

**Role of Thrombin in hemostasis and cellular activation:**

1. Thrombin plays a **critical role** in generating cross-linked fibrin via cleavage of fibrinogen to fibrin and activation of factor XIII.
2. Through protease-activated receptors thrombin also modulates several cellular activities.
   a. It directly induces platelet aggregation and TXA₂ secretion
   b. Can activate endothelium to generate leukocyte adhesion molecule and a variety mediators:
      i. fibrinolytic (t-PA)
      ii. vasoactive (NO, PGI₂)
      iii. cytokine (PDGF)
   c. Thrombin also directly activates leukocytes.

**Pathogenesis of thrombus:**

3 primary influences on thrombus formation:

- Endothelial injury
- Stasis or turbulence of blood flow
- Blood hypercoagulability

**Where can a thrombus arise?**

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

NB: ECM, extracellular matrix; NO, nitric oxide; PDGF, platelet-derived growth factor; PGI₂, prostacyclin; TXA₂, thromboxane A₂; t-PA, tissue plasminogen activator.
Endothelial Injury

1. It has a dominant influence on thrombus formation.
2. Endothelial loss by itself can lead to thrombosis.
3. Thrombus formation within
   a. the cardiac chambers (e.g., after endocardial injury due to myocardial infarction)
   b. over ulcerated plaques in atherosclerotic arteries
   c. or at sites of traumatic or inflammatory vascular injury (vasculitis)

Steps:
1. physical loss of endothelium
2. exposure of subendothelial ECM,
3. adhesion of platelets, release of tissue factor
4. local depletion of PGI₂ and plasminogen activators
5. Thrombus

Will thrombus occur even if the endothelium is not physically damaged?

It is important to note that endothelium need not be physically disrupted to contribute to the development of thrombosis.

Any disturbance in the balance of the prothrombotic and antithrombotic activities of endothelium can influence local clotting events

Dysfunctional endothelium may elaborate greater amounts of procoagulant factors (e.g., platelet adhesion molecules, tissue factor, plasminogen activator inhibitors) or may synthesize fewer anticoagulant effectors (e.g., thrombomodulin, PGI₂, t-PA).

What can cause such endothelial dysfunction?

Significant dysfunction (in the absence of endothelial cell loss) occurs in:
1. Hypertension
2. turbulent flow over scarred valves,
3. by the action of bacterial endotoxins.
4. Subtle influences like
   a. Hypercholesterolemia
   b. Radiation
   c. Products absorbed from cigarette smoke
Alteration in normal blood flow: 

Turbulence contributes to arterial and cardiac thrombosis by causing:

1. endothelial injury or dysfunction,
2. forming countercurrents and local pockets of stasis

Stasis is a major contributor to the development of venous thrombi.

Stasis and turbulence therefore:

1. Disrupt laminar flow
2. bring platelets into contact with the endothelium
3. Prevent dilution of activated clotting factors by fresh-flowing blood
4. Retard the inflow of clotting factor inhibitors permit the buildup of thrombi
5. Promote endothelial cell activation,
6. resulting in local thrombosis, leukocyte adhesion, etc.

Associated Clinical Conditions:

1. Ulcerated atherosclerotic plaques not only expose subendothelial ECM but also cause turbulence.
2. Abnormal aortic and arterial dilations - aneurysms
3. Acute myocardial infarction results in focally noncontractile myocardium.
4. Mitral valve stenosis (e.g., after rheumatic heart disease) results in left atrial dilation.
5. Atrial fibrillation + a dilated atrium is a site of profound stasis and a prime location for development of thrombi.
6. Hyperviscosity syndromes e.g. polycythemia, increase resistance to flow and cause small vessel stasis;
7. Deformed RBCs in sickle cell anemia cause vascular occlusions, with the resultant stasis also predisposing to thrombosis.
Hypercoagulability:

Hypercoagulability generally contributes less frequently to thrombotic states. It can be divided into

1. primary (genetic)
2. secondary (acquired) disorders

Pathogenesis of acquired thrombotic diatheses is multifactorial

1. Hypercoagulability is associated with oral contraceptive use and the hyperestrogenic state of pregnancy, due to increased hepatic synthesis of coagulation factors and reduced synthesis of antithrombin III.
2. In disseminated cancers, release of procoagulant tumor products predisposes to thrombosis.
3. Smoking and obesity promote hypercoagulability by unknown mechanisms
4. Heparin-induced thrombocytopenia (HIT) syndrome

Morphology:

Size and shape of a thrombus depend on the site of origin and the cause.

Arterial or cardiac thrombi typically begin at sites of endothelial injury or turbulence; Venous thrombi characteristically occur at sites of stasis.

Attachment: Thrombi are focally attached to the underlying vascular surface.

Both tend to propagate toward the heart. The propagating portion of a thrombus tends to be poorly attached and therefore prone to fragmentation, generating an embolus.

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Lines of Zahn: Thrombi can have grossly (and microscopically) apparent laminations which are due to pale platelet and fibrin layers alternating with darker erythrocyte-rich layers. Significance—their presence can distinguish antemortem thrombosis from the bland nonlaminated clots that occur in the postmortem state.

Mural thrombi: Thrombi occurring in heart chambers or in the aortic lumen

Arterial thrombi are frequently occlusive and are produced by platelet and coagulation activation. Friable meshwork of platelets, fibrin, erythrocytes, and degenerating
leukocytes are observed. Arterial thrombi can embolize and cause vascular obstruction at critical sites (e.g., coronary and cerebral vessels) is much more significant clinically.

**Venous thrombosis** (phlebothrombosis) is almost invariably occlusive and the thrombus can create a long cast of the lumen. venous thrombosis is largely the result of activation of the coagulation cascade, and platelets play a secondary role. Venous thrombi can cause congestion and edema in vascular beds distal to an obstruction, but they can embolize to the lungs and cause death.

They are red because these thrombi form in the sluggish venous circulation and they tend to contain more enmeshed erythrocytes. The veins of the lower extremities are most commonly affected.

**Postmortem clots** Postmortem "thrombi" are gelatinous, with a dark red dependent portion where red cells have settled by gravity, and a yellow "chicken fat" supernatant, and they are usually not attached to the underlying wall.

Thrombi on heart valves are called **vegetations**.

**Fate of thrombus:**

1. Propagation. Thrombi accumulate additional platelets and fibrin, eventually causing vessel obstruction.
2. Embolization. Thrombi dislodge or fragment and are transported elsewhere in the vasculature.
3. Dissolution. Thrombi are removed by fibrinolytic activity.
4. Organization and recanalization. Thrombi induce inflammation and fibrosis (organization). These can eventually recanalize.
5. Calcification: If diseased vessels, organization may not occur. Instead thrombus shrinks and calcium salts are deposited and converted into a phlebolith-seen in x rays.

**Embolus:**

**Definition:** An embolus is a detached intravascular

1. Solid
2. liquid or
3. gaseous mass

that is carried by the blood to a site **distant from its point of origin**.

Mostly all emboli represent some part of a dislodged thrombus, hence the term **thromboembolism**.
Where is the final destination of emboli?

Inevitably, emboli lodge in vessels too small to permit further passage, resulting in partial or complete vascular occlusion.

What are the consequences of emboli?

The clinical picture depends on whether emboli lodge in the pulmonary or systemic circulations.

The final consequences of thromboembolism include ischemic necrosis (infarction) of downstream tissue.

What are the types of embolism?

1. **Pulmonary thromboembolism**
   a. Most pulmonary emboli are clinically silent because they are small. They eventually become organized and become incorporated into the vascular wall.
   b. Many emboli occurring over a period of time may cause pulmonary hypertension with right ventricular failure

2. **Systemic thromboembolism**
   a. Most arise from intracardiac mural thrombi, majorly of which are associated with left ventricular wall infarcts and another quarter with dilated left atria (e.g., secondary to mitral valve disease).
   b. A very small fraction of systemic emboli appear to arise in veins but end up in the arterial circulation, through interventricular defects. These are called *paradoxical emboli*.

3. **Fat embolism**
   a. Fat enters the circulation by rupture of the marrow vascular sinusoids or rupture of venules in injured tissues due to soft tissue trauma as in severe skeletal injuries.
   b. *Fat embolism syndrome* is characterized by pulmonary insufficiency, neurologic symptoms, anemia, and thrombocytopenia.

4. **Air embolism**
   a. Air may enter the circulation during obstetric procedures or as a consequence of chest wall injury. More than 100 mL of air are required to produce clinical effect.
   b. *Decompression sickness*, occurs when individuals are exposed to sudden changes in atmospheric pressure. Scuba and deep-sea divers, and underwater construction workers are at risk.

5. **Amniotic fluid embolism**
   a. It is rare and the underlying cause is entry of amniotic fluid (and its contents) into the maternal circulation via a tear in the placental membranes and rupture of uterine veins.
**Shock**

Synonyms: Circulatory failure, Systemic Hypoperfusion

**Definition:** “Shock” exists when the oxygen delivery ($DO_2$) fails to meet the metabolic requirements of the tissues.

**Introduction: What is Shock?**

Pathophysiology:

- **Large Myocardial Infarction**
- **Massive Pulmonary embolism**
- **Severe hemorrhage due to extensive trauma or burns**
- **Microbial sepsis**
- **Anaphylaxis**
- **Severe hemorrhage due to extensive trauma or burns**
- **Anesthetic accident or a Spinal cord injury**

Important Clinical Emergency

Lethal Clinical Events

Final Common Pathway

Reduced Cardiac Output

*reduced effective circulating blood volume*
What are the types of Shock?

1. Common Types:
   a. Cardiogenic
   b. Hypovolemic
   c. septic

2. Less common Types:
   a. Neurogenic shock due to
      i. spinal cord injury
      ii. Anesthetic accident
   b. Anaphylactic shock (hypersensitivity reaction)
What are the stages of Shock?

Nonprogressive Stage:
- Reflex compensatory mechanisms are activated and perfusion of vital organs is maintained.
- Following neurohumoral mechanisms help maintain cardiac output and blood pressure.
  1. Baroreceptor reflexes,
  2. Release of catecholamines,
  3. Activation of the renin-angiotensin axis,
  4. Antidiuretic hormone release, and
  5. Sympathetic stimulation.

Progressive Stage:
- Start of tissue hypoperfusion and worsening circulatory and metabolic imbalances.
- Severe cellular and tissue injury occurs that even if the hemodynamic defects are corrected, survival is not possible.

Irreversible Stage:
- Tachycardia
- Peripheral vasoconstriction
- Renal conservation of fluid.

Final Destination:
- If uncorrected

In detail:

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Coronary and cerebral vessels are less sensitive to the sympathetic response and thus maintain relatively normal caliber, blood flow, and oxygen delivery to their respective vital organs.
Progressive Stage:
1. Widespread tissue hypoxia.
2. Persistent oxygen deficit
3. Intracellular aerobic respiration replaced by anaerobic glycolysis
4. Excessive production of lactic acid
5. Metabolic lactic acidosis
6. Blunted vasoconstrictor response
7. Arterioles dilate
9. Cardiac output lowers
10. Endothelial cells damaged
11. Predisposed to DIC.
12. Vital organs begin to fail.

Irreversible Stage:

1. Cellular Level:
   a. Widespread cell injury results in lysosomal enzyme leakage
   b. Aggravation of the shock state

2. Organ Level
   a. Myocardial contractile function worsens
   b. Ischemic bowel injury allows intestinal flora to enter the circulation
   c. Endotoxic shock also superimposed.
   d. Complete renal shutdown due to ischemic acute tubular necrosis
   e. Death.

Why do patients with shock appear pale & cool?
Cutaneous vasoconstriction is responsible for the characteristic coolness and pallor of skin in shock.

Is there an exception?
In septic shock there is initially cutaneous vasodilation and thus can present with warm, flushed skin

What are the general features of Shock?

1. CVS
   o Hypotension (systolic BP < 100 mmHg)
   o Tachycardia (> 100/min)
   o Elevated or reduced central venous pressure
2. RS
   o Rapid, shallow respiration
3. Renal System
   o Oliguria (urine output < 30 ml/hr)
4. CNS
   o Drowsiness, confusion, irritability
5. Cold, clammy skin & Multi-organ failure

What is the most dangerous type of Shock?
Septic shock ranks first among the causes of death in intensive care units. Mortality rate is 50%.

What is the most common cause of Septic Shock?
70% are caused by endotoxin-producing gram-negative bacilli - hence the term endotoxic shock. Endotoxins are bacterial wall lipopolysaccharides (LPS)

What is the pathogenesis of Septic Shock?

1. Free LPS attaches to a circulating LPS-binding protein,
2. The complex then binds to a specific receptor (CD14) on
   - monocytes,
   - macrophages
   - neutrophils
3. LPS can directly activate complement also
4. Engagement of CD14 results in profound activation of mononuclear cells
5. Production of potent effector cytokines such as IL-1 and TNF
6. These cytokines act on endothelial cells and have a variety of effects
   - reduced synthesis of anticoagulation factors such as tissue factor pathway inhibitor and thrombomodulin
7. Both TNF and IL-1 act on endothelial cells to produce additional cytokines (e.g., IL-6 and IL-8) and induce adhesion molecules.

At low doses LPS enhances the local acute inflammatory response and improves clearance of the infection.

With moderately severe infections, and therefore with higher levels of LPS

1. Cytokine-induced secondary effectors e.g., nitric oxide and platelet-activating factor; become significant.
2. Systemic effects of TNF and IL-1 appear
   - fever,
   - increased synthesis of acute-phase reactants,
   - increased production of circulating neutrophils
3. Higher LPS levels tip the endothelium toward a net procoagulant phenotype.
1. The same cytokine and secondary mediators, now at high levels, causes
   - Systemic vasodilation (hypotension)
   - Diminished myocardial contractility
   - Widespread endothelial injury and activation
   - Systemic leukocyte adhesion and diffuse alveolar capillary damage in the lung
   - Activation of the coagulation system
   - Ending with disseminated intravascular coagulation (DIC)

Morphology:

The cellular and tissue changes induced by shock = hypoxic injury

Particularly evident in the

1. brain
2. heart
3. kidneys
4. adrenal glands
5. gastrointestinal tract.

Note: Fibrin thrombi common in all affected organs, most readily visualized in kidney glomeruli.

The adrenal changes in shock are those seen in all forms of stress; essentially there is cortical cell lipid depletion.

The kidneys typically reveal acute tubular necrosis resulting in oliguria, anuria, and electrolyte disturbances dominate

The gastrointestinal tract has focal mucosal hemorrhage and necrosis.

The lungs are affected less in pure hypovolemic shock, because they are somewhat resistant to hypoxic injury.

But in shock is caused by bacterial sepsis or trauma, changes of diffuse alveolar damage develop, the so-called shock lung.
Clinical manifestations:

depend on the precipitating insult.

In hypovolemic and cardiogenic shock, there is hypotension; a weak, rapid pulse; tachypnea; and cool, clammy, cyanotic skin.

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

1. The initial threat to life stems from the underlying catastrophe that precipitated the shock state (e.g., a myocardial infarct, severe hemorrhage, or bacterial infection). Later the cardiac, cerebral, and pulmonary changes that occur secondary to the shock state worsen the problem.

2. If patients survive the initial complications, they enter a second phase of:
   a. Renal insufficiency + fall in urine output
   b. Acidosis
   c. Severe fluid and electrolyte imbalances.