Hemodynamic Disorders

Hyperemia, Congestion, Hemorrhage, Edema, Thrombosis & DIC, Embolism, Infarction, & Shock

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Introduction:

**Hemodynamic disorders** are very common & extremely important cause of clinical illnesses.

The health of cells & tissues depends on the circulation of blood, which delivers oxygen & nutrients and removes wastes generated by cellular metabolism.

Under normal conditions, as blood passes through capillary beds, proteins in the plasma are retained within the vasculature and there is little movement of water & electrolytes into the tissues.

This balance is often disturbed by pathologic conditions that alter endothelial cells function, increase vascular pressure, or decrease plasma protein content, all of which promote **edema**, i.e. accumulation of fluid in extra vascular spaces.
Hemostasis is the process of blood clotting that prevents excessive bleeding after blood vessel damage.

Inadequate hemostasis may result in hemorrhage which can affect tissue perfusion & if massive & rapid may lead to hypotension, shock & even death.

Conversely, inappropriate clotting i.e. thrombosis or migration of clot called embolism can obstruct blood vessels causing ischemic cell death i.e. Infarction.

Thrombo-embolism lies at the heart of three major causes of morbidity & death in developed countries, myocardial infarction, pulmonary embolism & cerebro-vascular accidents (CVA) or stroke.
HYPEREMIA & CONGESTION

Both terms, hyperemia & congestion, indicate increased local blood volume in a particular tissue.

But Hyperemia is *an active process*, resulting from increased blood flow due to arteriolar dilation, at sites of inflammation or in skeletal muscle during exercise, & the hyperemic tissue is red.

Congestion is *a passive process*, resulting from impaired venous return from a tissue. The congested tissue is cyanotic, bluish-red in color because congestion leads to accumulation of deoxygenated hemoglobin in the congested tissues.
Figure 1: Diagrammatic view of normal arterio-venous anastomosis, hyperemia & congestion..
Figure 2: Photographic appearance of hyperemia of the inflamed conjunctiva of eye.
Figure 3: Gross view of hyperemia of the brain, brain looks reddish.
Figure 4: Gross view of both kidneys showing hyperemia.
Congestion may be **systemic**, as in Congestive heart failure, or **localised** resulting from an isolated **venous obstruction**.

Congestion & edema commonly occur together.

In long-standing chronic venous congestion (CVC), the stasis of poorly oxygenated blood causes chronic hypoxia, which can result in parenchymal cell degeneration or death, & subsequent tissue fibrosis.

Capillary rupture at sites of CVC may also cause small foci of hemorrhage.
Pulmonary congestion:

**Grossly:** The congested lung is heavy, dark red in color when squeezed, a frothy air-containing fluid or blood-stained fluid will be squeezed out.

**Microscopically:**

*Acute pulmonary congestion* is characterized by alveolar capillaries distension with blood, alveolar septal edema, and/or focal minute intra-alveolar hemorrhage.

*While in chronic pulmonary congestion,* the alveolar septa become thickened & fibrotic, & the alveolar spaces may contain numerous hemosiderin-laden macrophages, so-called *("heart failure cells").*
Figure 5 - Gross view of acute lung congestion, lung tissue is dark red with frothy fluid comes out during cutting.
Figure 6: Normal lung histology.
Figure 7: Microscopic view of acute pulmonary congestion, showing congested capillaries in alveolar septa with intra alveolar edema (arrow).
Figure 8 – Chronic pulmonary congestion showing golden-yellow appearance of hemosiderine–laden macrophages i.e. (Heart-failure cells) & fibrosis of alveolar septa.
Liver Congestion

Grossly: Microscopically

There is centrilobular hepatic cell necrosis & hemorrhage, with hemosiderin-laden macrophages, alternating with a pale peripheral zones of fatty change in peripheral hepatocytes.

In severe & long-standing hepatic central venous congestion (commonly due to heart failure), there may even be grossly evident hepatic fibrosis, so-called "cardiac cirrhosis."

In chronic venous congestion the liver have the nutmeg-like appearance, because the central portions of the hepatic lobule is the last to receive blood from both portal vein & hepatic artery, so they tend to undergo early necrosis due to ischemic injury, whenever there is reduced hepatic blood flow with hemorrhage thus look dark red & peripheral zone look pale, due to fat necrosis.
Figure 9: Normal liver, microscopic view.
Figure 10: Nut meg liver in chronic venous congestion due to heart failure. A- Nut meg grain.
Figure 11: Nut meg liver in CVC, gross view.
Figure 12: Gross & microscopic appearances of liver in CVC.
Figure 13: Microscopic view of liver in CVC (nut meg liver) showing necrotic hepatocytes & hemorrhage around central vein giving red color to this area.
EDEMA

60% of the lean (without fat) body weight is water, with:
- 2/3 intracellular (within cells); &
- 1/3 extracellular (outside the cells), mostly as interstitial fluid.

5% of total body water only is in the intravascular compartment, i.e. in the blood plasma.

The term edema refers increased fluid in the interstitial tissue spaces.

Fluid collections in different body cavities are referred to as:
- Hydrothorax: in pleural cavity.
- Hydropericardium: in pericardial cavity.
- Hydroperitoneum: in peritoneal cavity also called ascites
- Anasarca: Is a severe generalized edema with a profound subcutaneous swelling.
Pathophysiologic causes of edema:

(1) Increased Hydrostatic Pressure.
- Impaired venous return
  - Congestive heart failure,
  - Constrictive pericarditis,
  - Ascites in (liver cirrhosis)

Venous obstruction or compression by
- Thrombosis, External pressure, e.g., tumor
- Lower extremity inactivity with prolonged dependency.

Arteriolar dilation:
- Heat, neurohumoral dysregulation.

(2) Lymphatic Obstruction: caused by
- Inflammatory,
- Neoplastic, Postsurgical & post irradiation causes.
(3) Reduced Plasma Osmotic Pressure (Hypoproteinemia)

Protein-losing glomerulopathies (Nephrotic syndrome),
Protein-losing gastro-enteropathy.
Liver cirrhosis (ascitis).
Malnutrition.

(4) Sodium Retention.

- Excessive salt intake with renal insufficiency.
- Increased tubular reabsorption of Na
  
  (a) Renal hypoperfusion, or
  
  (b) Increased rennin-angiotensin-aldosterone secretion.

(5) Inflammation:

Acute & chronic inflammation, with angiogenesis.
Fluid movement between the vascular & interstitial spaces is governed by two opposing forces, the vascular hydrostatic pressure and the colloid osmotic pressure produced by plasma proteins.

Normally the outflow of fluid produced by hydrostatic pressure at the arteriolar end of the micro circulation is balanced by the inflow due to the slightly elevated osmotic pressure at the venular end, hence, there is only a small net outflow of fluid into the interstitial spaces, which is drained by the lymphatic vessels.

Either increased hydrostatic pressure or decreased osmotic pressure causes increased movement of water into the interstitium.

Excess edema fluid is removed by the lymphatic drainage & returned to the blood stream by the way of the thoracic duct.
Increased hydrostatic pressure:

Local edema: increase in intravascular pressure can result from impaired venous return, for example in deep venous thrombosis in the lower extremities can cause edema in the distal part of the affected limb.

Generalized edema: In normal heart, the reduced cardiac output leads to hypoperfusion of the kidneys thus triggering the rennin-angiotensin-aldosterone axis, renin is secreted by specialized cells in renal tubules due to hypoxia. Renin will stimulate angiotensin that enhances tubular reabsorption of Na & water thus inducing Na & water retention, this will increase the intravascular blood volume & improves the cardiac output to restore the renal perfusion and it is called secondary aldosteronism. In congestive heart failure, the heart cannot improve cardiac output and this leads to increased venous hydrostatic pressure and resulting in edema.
Figure 14: Photographic view of swollen edematous right leg due to deep vein thrombosis (local edema).
Reduced plasma osmotic pressure:

Albumin is the serum protein most responsible for maintaining intravascular colloid osmotic pressure.

Reduced osmotic colloid pressure occurs when diffuse albumin is inadequately synthesized as in liver diseases, or in protein deficiency in malnutrition or is lost from circulation through the glomerular capillaries which become leaky as in nephrotic syndrome.
Lymphatic obstruction:

Normally, excess interstitial fluid is removed by lymphatic drainage returning it to the blood stream via thoracic duct.

(Normally 800 to 1000 ml of lymph/per day).

Impaired lymphatic drainage & consequent lymphedema can result from inflammatory or neoplastic obstruction or post-irradiation scarring.

Parasitic infestation by *filariasis* which involves the inguinal lymphatics causing lymphatic obstruction and lymph nodes fibrosis with resultant progressive edema of the external genitalia and the lower limbs can be so massive to be called *elephantiasis*. 
Figure 15 - Filaria Bancrufti. The parasite that causes Elephantiasis due to lymphadenitis, obstructing the lymphatic drainage resulting in extensive edema in lower limbs & the external genitalia.
Figure 16 – Photograph of elephantiasis, severe edema in lower limbs.
Figure 17 – Diagram showing mechanism of edema.
Morphology of edema:

The edema fluid is typically a protein-poor, called transudate, with a specific gravity below 1012.

In inflammatory edema, the increased vascular permeability result in a protein-rich edematous fluid called exudate with a specific gravity over 1020.

Grossly: Edema is most easily recognized, causing swelling and increased weight of the affected organ.

Histologically:

Edema is manifest as clearing & separation of the extracellular matrix elements and cell swelling.

Edema is most commonly encountered in subcutaneous tissues can be diffuse may affect different locations depending on the cause of edema.
Localised edema: can involve any organ or tissue in the body, may be involved the lungs, & brain are especially affected. Glottic or laryngeal edema may be fatal by obstructing the air passages specially in children.

Diffuse systemic edema:

is usually more prominent in certain areas as result of the effect of gravity, which is called dependant edema, involving the legs when standing & sacrum when recumbent.

This is a feature of heart failure especially right ventricular failure.

Edema due to renal failure or nephrotic syndrome is generally more severe than cardiac edema tends to affect many parts of the body equally. However, it may be initially appears in tissues with a loose connective tissue matrix, such as the eyelids, causing periorbital edema.
An important sign of edema is *pitting sign*. If finger pressure is applied over edematous subcutaneous tissue, it displaces the interstitial fluid & leaves a finger-shaped depression so called *pitting edema*.

In breast cancer the skin shows a *Peau d' orange appearance* of the its skin, produced by cutaneous edema causing bulging of the skin (following occlusion of the skin lymphatics by malignant cells around the hair follicles & sweat glands).
Figure 18: Photograph showing pitting edema of skin & subcutaneous tissue.
Figure 19: Photograph of breast showing Peau d' orange appearance of the breast seen in breast cancer.
Pulmonary edema:

Is a common clinical problem seen in left ventricular failure (LVF), renal failure (RF), adult respiratory distress syndrome (ARDS), pulmonary infections, & hypersensitivity reactions.

The edema tends to involve the lower lobes of both lungs.

Grossly: The lungs are heavy (2 to 3 times their normal weight, which is 350g) & on sectioning it reveals frothy, or blood-stained fluid, consisting of air + edema fluid + extravasated RBC mixture.

Clinically:

Pulmonary edema causes dyspnea, interference with normal ventilatory functions of the lung as hypoxia and cyanosis & may be fatal.
Brain edema

May be localized at sites of focal injury as in infarct, abscess or neoplasm.

Or generalized as in encephalitis, hypertensive crises, or obstruction of the venous outflow.

Trauma may result in local or generalized brain edema depending on the nature & extent of the injury.

Grossly: In generalized brain edema, the brain is grossly swollen, flattened against the unyielding skull, heavier than normal weight, showing narrowed sulci & distended gyri.

Clinically:

Brain edema is very serious, & can be rapidly fatal as it causes increased intracranial pressure (ICP) & herniation or extrusion of brain stem through foramen magnum, result in compression of blood supply to medullary vital centres causing sudden death.
Figure 20 - Gross appearance of edema of the brain.
Figure 20 – Gross appearance of lung edema. Lungs are heavy and swollen.
HEMORRHAGE (H)

Is extravasation of blood, due to rupture of blood vessels.

Capillary H can occur

(1) in chronic venous congestion (CVC) &
(2) in hemorrhagic diatheses, as in Hemophilia a disorders characterized by increased tendency to hemorrhage from usually insignificant injury.

Hemorrhage or bleeding from ruptured large artery or vein is almost always due to trauma, other causes include ruptured aneurysms, inflammatory, ulcerative or neoplastic erosion of the vessel wall by tumors.
Hemorrhage is either: 

**External H:** in which bleeding occurs to the outside from:
- Normal cycle uterine bleeding = **menstrual bleeding**
- Excessive or abnormal uterine bleeding = **menorrhagia**.
- Nose = **epistaxis**
- Lung = **hemoptysis**
- Stomach = **hematamesis**
- Urinary tract = **hematuria**
- Colon or rectum = **bleeding per rectum**

**Malena** is a term used to denote a slow bleeding from upper gastro-intestinal tract as in peptic ulcer leading to passage of black stool.

**Internal H.** is enclosed within a
(a) tissue called **hematoma**.
(b) body cavities, as peritoneum, pleura & pericardial sac or joints.
Hematoma

is hemorrhage or blood accumulation in tissue.

Hematomas may be small & insignificant (as in a skin bruise) or may accumulate excessive amount of blood e.g., rupture Atheromatous Abdominal Aortic Aneurysm resulting in massive retroperitoneal hematoma) which is usually usually fatal.
Skin hematomas are of three types:

(1) Petechiae: are minute (1- to 2mm in diameter) hemorrhages into skin, mucous membranes, or serosal surfaces typically associated with:

(1) Locally increased intravascular pressure.
(2) Low platelet counts (thrombocytopenia).
(3) Defective platelet function.
(4) Clotting factor deficiencies.
Figure 21: Petichiae, skin
(II) *Purpuras*: are slightly larger hemorrhagic spots (3- to 5mm in diameter), may be associated with many of the same disorders that cause petechiae, as well as in the settings of trauma, vasculitis, or increased vascular fragility.

(III) *Ecchymoses*: or bruises, are larger (10- to 20mm in diameter) or even larger subcutaneous hematomas.
Figure 22: Purpura.
Figure 23: ecchymoses.
The RBCs in all the above three skin hematomas are degraded & phagocytosed by macrophages, & the hemoglobin (red-blue color) is enzymatically converted into biliverdin (green), then to bilirubin (blue-green color) & eventually into hemosiderin (golden-brown) to yellow color.

The above accounts for the characteristic color changes in hematomas seen, e.g., following improper I.V. puncture.
Figure 24: Ecchymoses.
Figure 25: Ecchymosis caused by improper I.V. puncture.
Figure 2.6  
A- Petechial hemorrhages in colonic mucosa. 
B- Fatal intracerebral hemorrhage.
(b) *Hemothorax, hemopericardium, hemoperitoneum, & hemarthrosis*

are accumulations of blood in the pleural, pericardial, peritoneal & joint cavities respectively.
Figure 27: Hemopericardium, blood in pericardial cavity.
Clinical significance of hemorrhage depends on the:

(I) Rate & volume of blood loss; 
*Rapid removal of up to 20% of blood volume* or, slow losses of even larger amounts may *have little impact in healthy adults*; while greater losses, however, may result in *hypovolemic shock*.

(II) Site of hemorrhage is important; 
Bleeding of about *40 ml of blood*, which is considered *trivial in the subcutaneous tissues*, is *rapidly fatal* if located in the *cerebellum or pons & midbrain*.
Figure 28: Photograph of the hemorrhage in the pons which is rapidly fatal.
(III) Recurrent or chronic external hemorrhages

e.g., menorrhagia or chronic peptic ulcer) cause loss of iron, with subsequent iron deficiency anemia.

In contrast, when RBCs are retained, as in hemorrhage into body cavities or tissues, the iron can be reutilized for hemoglobin synthesis.
Hemostasis & Thrombosis
Normal Hemostasis:

Vascular injury causes transient vasoconstriction through reflex neurogenic mechanism, augmented by local secretion of endothelin by endothelial cells which is a potent endothelial vasoconstrictor causing transient vasoconstriction.

Endothelial cell injury exposes highly thrombogenic subendothelial extracellular matrix (ECM), facilitating platelets adherence, activation & aggregation, leading to the formation of initial platelet plug called primary hemostasis.

Endothelial injury also exposes tissue factor known as Factor III or thromboplastin a protein synthesized by endothelial cells. Exposed tissue factor in conjunction with factor VII is the major in vivo trigger of coagulation cascade & this activate thrombin to promote the formation of an insoluble fibrin clot by cleaving fibrinogen...
Thrombin also activates platelets to aggregate to reinforce the hemostatic plug, this is called secondary hemostasis, resulting in formation of a stable clot capable of preventing further hemorrhage.

As bleeding is controlled, contra regulatory mechanisms i.e. factors that produce fibrinolysis, to dissolve the blood clot are secreted by endothelial cells such as tissue type plasminogen activator, heparin-like molecule & Thrombomodulin are set in motion to ensure blockage of coagulation cascade so that clot formation is limited to the site of injury only.
Figure 29: The classical coagulation cascade.
THROMBOSIS

Definition:

Formation of solid or semi-solid mass, from the blood constituents, within the vascular system, during life.

★ Pathogenesis.

Three primary influences predispose to thrombus formation, the so-called Virchow triad:

(1) Endothelial injury, the single most important factor which can also alter local blood flow & affect coagulability,
(2) Stasis or turbulence of blood flow which in turn, can cause endothelial Cell (EC) injury.
(3) Blood hypercoagulability: These three factors may act independently or may combine to cause thrombus formation.
Figure 30: **Virchow triad** Causes of thrombosis.
(I) ENDOTHELIAL INJURY

Is the dominant influence & by itself can lead to thrombosis.

It is particularly important in thrombus formation in the heart & arterial circulation, for example, within cardiac chambers when there has been endocardial injury (e.g., MI, or valvular endocarditis), over ulcerated plaques in severely atherosclerotic arteries, or at sites of traumatic or inflammatory vascular injury.

Significant EC dysfunction may occur from the hemodynamic stresses of hypertension, turbulent flow over scarred valves, or bacterial endotoxins.

Even other factors as radiation, homocystinuria, hypercholesterolemia, or products absorbed from cigarette smoke may be sources of EC injury.
Endothelial cells have:

I- A prothrombotic properties:

II- Anti-thrombotic properties.

I- Prothrombotic properties: Including:

1- Inhibitory effects on platelets: Endothelial cells prevent adhesion of platelets to the subendothelial collagen or ECM acting as a barrier. By the production of prostacyclin PGI2 & nitric oxide (NO) both are active vasodilators.

2- Inhibitory effects on coagulation factors: By production of Heparin-like molecule, thrombomodulin & tissue factor pathway inhibitor. These are cofactors that enhance the inactivation of thrombin by a plasma protein called anti thrombin III.

3- Fibrinolysis: By production of tissue-type plasminogen activator an enzyme that cleaves fibrin clot.
II- Prothrombotic properties:

1- Activating platelet adhesion: By the presence of Von-Willebrand Factor (vWF) present on endothelial cell membrane which acts as a glue helping the attachment of activated platelets to subendothelial collagen & ECM.

2- Activation of coagulation factors: In response to cytokines like tumor necrosis factor TNF & interleukin-1 IL-1, or bacterial exotoxins. Endothelial cells produce tissue factor which is a major activator to clotting factors.

3- Antifibrinolytic effects: activated endothelial cells secrete plasminogen activator inhibitors (PAIs) which limit fibrinolysis.
(II) ALTERATION IN NORMAL BLOOD FLOW

Normally, blood flow is laminar such that the platelet elements flow centrally in the blood vessel lumen separated from the EC by a slower-moving clear zone of plasma.

★ Turbulence (whorled like movement) contributes to arterial & cardiac thrombosis by causing EC injury or dysfunction, as well as by forming counter currents & local pockets of stasis;

★ Stasis is a major factor in the development of venous thrombi.
Turbulence & stasis therefore

(1) Disrupt laminar flow & bring platelets into contact with the Endothelial Cells.

(2) Prevent dilution of activated clotting factors by fresh-flowing blood,

(3) Retard the inflow of clotting factors inhibitors & permit the build-up of thrombi.

(4) Promote EC activation, predisposing to local thrombosis, WBC adhesion, & a variety of other EC effects.
(III) HYPERCOAGULABILITY

★ generally contributes less frequently to thrombotic states but is nevertheless an important component in the equation.

It is loosely defined as any alteration of the coagulation pathways that predisposes to thrombosis.

It can be

- primary (genetic) OR
- secondary (acquired) disorders
Of the primary inherited causes of hypercoagulability: The most common are mutations in the factor V gene & of the prothrombin gene.

Approximately 2% to 15% of the white population carries a specific factor V mutation (referred to as the Leiden mutation, after the Dutch city in which it was first discovered); among patients with recurrent Deep Vein Thrombosis (DVT), the frequency is much higher.

The (so-called G2021A mutation) of prothrombin gene is associated with an increased level of prothrombin & hence susceptibility to venous thrombosis.
Less common primary hypercoagulability states include inherited deficiencies of natural anticoagulants such as Antithrombin III, protein C, or protein S; affected patients typically present with venous thrombosis & recurrent thromboembolism in adolescence or early adult life.

Congenitally elevated levels of homocysteine contribute to arterial & venous thromboses (& to the development of atherosclerosis). Secondary or acquired thrombotic diatheses pathogenesis in a number of common clinical settings, is more complicated & multifactorial
Predisposing factors for thrombosis:

1. Ulcerated atherosclerotic plaques.
2. Aneurysms which is localized abnormal arterial wall dilations, cause local stasis & are favored sites of thrombosis.
3. Myocardial infarction not only have associated EC injury but also have regions of non-contractile myocardium, adding an element of stasis in the formation of mural (i.e., non-occlusive) cardiac thrombi.
(4) Mitral valve stenosis (e.g., chronic rheumatic heart disease) results in left atrial dilation.

In conjunction with atrial fibrillation, a dilated atrium is a site of profound stasis & a prime location for development of thrombi.

(5) Hyperviscosity syndromes (such as polycythemia) increase resistance to flow & cause small vessel stasis; & the deformed red cells in sickle cell anemia cause vascular occlusions, with the resultant stasis predisposing to thrombosis.
Secondary high risk for thrombosis group include

(1) prolonged bed rest or immobilization.

(2) cancer,

(3) tissue damage (surgery, fracture, burns),

(4) disseminated intravascular coagulation (DIC),

(5) prosthetic cardiac valves.

(6) Heparin-induced thrombocytopenia, affecting 5% of patients treated with un fractionated heparin as anticoagulant, which induces autoantibody against platelets, result in thrombocytopenia.

(7) Anti-phospholipid antibody syndrome, the patients have auto antibody against cardiolipin a plasma protein antigen that are unveiled by binding to such phospholipids like prothrombin.
Secondary low risk for thrombosis group include

(1) oral contraceptive use,
(2) hyperestrogenic states,
(3) cardiomyopathy,
(4) sickle cell anemia,
(5) nephrotic syndrome,
(6) smoking, &
(7) obesity.
Thrombi morphology

Site:

thrombi may develop anywhere in the cardiovascular system:
within the cardiac chambers atria & ventricles, on valve cusps, in arteries, veins or capillaries.

Size & shape:
of thrombi are variable, depending on the

- site of origin & the
- circumstances leading to their development.
• *Arterial or cardiac thrombi* usually begin at a site of endothelial *injury* (e.g., atherosclerotic plaque) or turbulence (vessel bifurcation);
• *venous thrombi* characteristically occur in sites of stasis.

★ Attachment to the underlying vessel or heart wall, firmest at the point of origin, is *characteristic of all thrombi*.
Growth (propagation) of arterial thrombi tend to occur in a retrograde direction from the point of attachment (i.e. toward the heart).

While venous thrombi extend in the direction of blood flow (i.e. that is, toward the heart again) & the propagating tail may not be well attached & particularly in veins, is prone to fragment, creating an embolus (thromboembolism).
Figure 31- Venous thrombosis, propagation directed towards the heart.
Lines of Zhan; are apparent gross & microscopic laminations, produced by pale layers of platelets & fibrin that alternate with darker layers containing more red cells, seen in thrombi formed in the heart or aorta.

Lines of Zhan imply that *thrombosis occur at a site of blood flow*.

**While in veins**, laminations are typically not as apparent, & in fact, thrombi formed in the sluggish venous flow usually resemble statically coagulated blood (*much like blood clotted in a test tube*).
Figure 32 – microscopic view of thrombus showing lines of Zhan, consisting of alternating lines of pale layers of fibrin & platelets, dark layers of RBCs.
Cardiac thrombosis

May follow myocardial infarction, in the Left ventricle. It may occur in the left atrium following mitral valve stenosis and/or atrial fibrillation or both as a complication of chronic rheumatic heart disease.

In all above cases, cardiac thrombi can embolize peripherally.

Virtually any tissue may be affected, but the major sites for arterial embolization are the lower extremities (75%) & the brain (10%), with the intestines, kidneys, & spleen involved to a lesser extent, usually resulting in infarction.
Mural (non-occlusive) thrombi are thrombi attached to the wall of the heart chambers adjacent to an area of diseased endocardium, it may occur following abnormal myocardial contraction (arrhythmias, dilated cardiomyopathy, or MI) or injury to the endomyocardial surface (myocarditis, catheter trauma) usually called ball thrombus, or being attached to the aortic wall overlying an intimal lesion.
Fig. 33: Ball thrombus: left atrium. The dilated, thick-walled left atrium is viewed from above, showing stenosed mitral valve. A globular red thrombus ("ball "thrombus) lies free within the atrial lumen, & obstructing the mitral valve orifice intermittently.
Thrombi may form on heart valves: under special circumstances:

1. **Bacterial or fungal-blood born infections** may lead to valve infection, damage & the development of large thrombotic masses, or vegetations (infective endocarditis).

2. **Sterile vegetations** can develop on noninfective valves in patients with hypercoagulable states, so-called **nonbacterial thrombotic endocarditis**.

3. Less commonly, noninfective, verrucous **(Libman-Sacks) endocarditis** may occur in patients who have systemic lupus erythematosus (SLE).
Fig. 34: Subacute bacterial endocarditis: mitral valve. Large, globular, friable red-brown mass of vegetations on the superior surface of the mitral valve. *Streptococcus viridans* (the most common causative organism of this disease).
Arterial thrombi are usually occlusive.

In arteries, atheroma is a prime initiator of thromboses.

The most common sites, in descending order, are

1. coronary
2. cerebral,
3. femoral arteries,

The thrombus is usually superimposed on an atheromatous plaque & within aortic aneurysm.

Typically the arterial thrombi are firmly adherent to the injured arterial wall, are gray-white & friable, composed of a tangled mesh of platelets, fibrin, RBCs, & degenerated WBCs.
Figure 35 - Gross appearance of coronary artery thrombus.
Figure 36: Complicated atheromatous plaques, most show central ulceration, the **yellow fatty debris** is seen in the plaque at the top right. The brown color of the ulcerated plaques on the left is due to **mural thrombosis**, an important source of **thromboemboli**.
Fig. 37: Saccular aneurysm of the iliac artery.

The lumen is filled with arterial thrombus, which is reddish-brown & shows greyish-white lines of Zhan.
Fig. 38: Large thrombus, (measuring 20X12X12 cm) removed from an atheromatous abdominal aortic aneurysm (AAAA). The laminated structure ([lines of Zahn]) of the thrombus is clearly evident (lower left).
Venous thrombosis or phlebothrombosis

Venous thrombosis or phlebothrombosis is almost always occlusive; creating a long cast of the vein lumen.

As these thrombi form in the slowly moving venous blood, they tend to contain more trapped RBCs & are therefore known as red, or stasis thrombi.

Of which (90%) occurs in either the superficial or the deep veins of the leg:
Superficial venous thrombi

Superficial venous thrombi usually occur in the saphenous system, particularly when there are varicosities.

Such thrombi may cause local congestion, edema, pain & tenderness along the course of the involved vein, but they rarely embolize.
F 39 : Venous Thrombosis. The **inferior vena cava contains** a long pale tapering thrombus. Thrombus is mural & firmly attached to the vein wall.
Deep venous thrombi

In the larger leg veins at or above the knee joint (e.g., popliteal, femoral, & iliac veins DVT) are more serious because they may embolize.

Although they may cause local pain & edema, the venous obstruction may be rapidly offset by collateral by-pass channels.

Consequently, DVT are entirely asymptomatic in approximately 50% of patients & are recognized in retrospect only after they have embolized.

DVT may occur with stasis & in a variety of hypercoagulable states.

Less commonly, venous thrombi may develop in the upper extremities, periprostatic plexus, or ovarian & periuterine veins; under special circumstances they may be found in the dural sinuses, portal vein, or hepatic vein.
Postmorten Clots:

At autopsy, postmortem (PM) clots may be mistaken for venous thrombi.

PM clots are:

- gelatinous with a **dark red dependent portion** where RBCs have settled by gravity, & a yellow
- **chicken fat” supernatant**; they are usually
- **not attached** to the underlying wall.

In contrast, red thrombi are firmer, almost always have a point of attachment, & on transaction reveal vague strands of pale gray fibrin.
**F 40 : Post-mortem clot.** Typically, a glistening, semi-translucent, homogeneous pale yellow (chicken-fat) clot which formed a **cast** of the **pulmonary trunk & its branches**, sometimes, they appear deep red (red current jelly clot). Post-mortem clots do **not show lines of Zahn**.
Fate of Thrombus

If a patient survives the immediate effects of a thrombotic vascular obstruction, thrombi undergo combination of the following four events in the following days or weeks:

(1) Dissolution,
(2) Propagation,
(3) Embolization, &
(4) Organization
(1) Dissolution:

Activation of the fibrinolytic pathways resulting in the formation of plasmin {from its inactive circulating precursor plasminogen} either by a factor XII-dependent pathway or by plasminogen activators (PAs), the most important of which is tissue-type PA (t-PA).

Plasmin can lead to rapid shrinkage & even total lysis of recent thrombi.

With older thrombi, extensive fibrin polymerization renders the thrombus substantially more resistant to proteolysis & lysis is ineffectual.
(2) **Propagation:** The thrombus may accumulate more platelets & fibrin (propagate, i.e., grow & enlarge), eventually obstructing some critical vessel.

(3) **Embolization.** Thrombi may dislodge (i.e., separate) & be transported to other sites in the vascular system.
(4) Organization and recanalization.

Thrombi may induce inflammation & (organization) & fibrosis, & may eventually become recanalized (re-established vascular flow), or they may be incorporated into a thickened vascular wall.

Organization refers to the ingrowth of ECs, SMCs, & fibroblasts into the fibrin-rich thrombus.

In time, capillary channels are formed that may anastomose to create connections from one end of the thrombus to the other, re-establishing, to a limited extent, the continuity of the original lumen.

Such recanalization can convert the thrombus into subendothelial mass of connective tissue incorporated as a swelling into the BV wall.
F 41: Artery with an old thrombus. A, H&E stained section. B, Stain for elastic tissue (black). The original lumen is delineated by the internal elastic lamina (3 arrows) & is totally filled with organized thrombus.
Disseminated Intravascular Coagulation (DIC)
DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

**Definition:** A clinical disorder characterized by a sudden or gradual onset of widespread fibrin thrombi in the microcirculation.

DIC is not a primary disease but rather is a *potential complication of any condition associated with widespread activation of thrombin*.

The major causes of which including *obstetric complications, infections, neoplasms, massive tissue injury* & others.

While these thrombi are not visible grossly, they are readily apparent microscopically & can cause widespread & diffuse circulatory insufficiency, especially in the brain, lungs, heart, & kidneys.
DIC is a thrombo-hemorrhagic disorder, characterized by systemic activation of the coagulation cascade by various stimuli, with hundreds of thrombi occluding microcirculation leading to tissue hypoxia or micro infarcts. It is also called consumptive coagulopathy, followed by bleeding due to consumption of platelets & clotting factors in blood.

Mechanism of DIC:

Two major mechanisms can trigger DIC:

1- The release of tissue factor or thromboplastic substances into the circulation.

2- Wide-spread endothelial cell damage.
The release of thromboplastic tissue factor can be due to:

a- The placenta or fetal tissue in obstetric complications.
b- The cytoplasmic granules in acute promyelocytic leukemia cells.
c- Mucin-secreting adenocarcinoma cells
d- Carcinoma cells can secrete pro-coagulant substances such as proteolytic enzymes. Some cancers can express tissue factor on cell membrane.
e- In gram negative & gram positive sepsis.
f- Activated monocytes as well as chemical mediators as TNF & IL-1 both can increase expression of tissue factors on endothelial cell.
g- Widespread endothelial cell injury can be induced by antigen antibody complex as in systemic lupus erythematosus (SLE).
h- Extremes of heat as heat stroke or burn & frostbite.
DIC has two consequences:

1- **Widespread fibrin deposition** within microcirculation leading to ischemia as well as to hemolysis. This is due to destruction of red blood cells (RBCs) which become traumatized during their passage through vessels narrowed by fibrin thrombi. This is called **microangiopathic hemolytic anemia**.

2- **Bleeding diathesis**: this results from depletion of platelets, clotting factors & secondary release of plasminogen activator then plasmin which cleaves fibrin, factor X & factor VIII.

Fibrinolysis creates **fibrin degradation products (FDPs)** which inhibits platelets aggregation & prevent fibrin polymerization thus results in **bleeding**.
Morphology:

Microthrombi are formed principally in the arterioles of the kidneys result in numerous microinfarcts in renal cortex leading to bilateral renal cortical necrosis, then renal failure.

Also microthrombi & numerous micro infarcts in the brain leading to Sheehan’s syndrome which is characterized by postpartum pituitary necrosis.

Lungs, GIT involvement by microinfarcts.

The adrenals involvement leading to extensive bilateral adrenal hemorrhage called Waterhouse-Friedrichsen Syndrome seen in meningococcal septicemia.

In the skin the patient with DIC may present with widespread petichae, and ecchymosis.

Such bleeding manifestations may be seen on serosal surfaces.
Figure 42: Gross appearance of kidney showing renal cortical necrosis in DIC.
Figure 43: DIC in kidney: Microscopic view.
Figure 44 - Microscopic view of renal microthrombi in DIC.
Figure 45: Gross appearance of lung showing features of DIC, numerous hemorrhagic microinfarcts & hemorrhages.
Figure 46: Skin in DIC,
Clinically:

The clinical picture is dominated by bleeding, vascular occlusion & tissue hypoxemia or both.

**Acute DIC**: usually associated with obstetric complications is dominated by bleeding diathesis.

**Chronic DIC**: occurs in individuals with cancer tends to present with thrombosis & infarctions.

Manifestations of acute renal failure, dyspnea, cyanosis, convulsions & coma. Prolonged postpartum hemorrhage.
Laboratory tests reveal:

Thrombocytopenia, prolonged prothrombin time (PT) & partial thromboplastin time (PTT) due to decreased platelets count, clotting factors & fibrinogen.

Fibrin degradation products (FDPs) are increased in plasma.

Treatment of acute DIC by heparin & fresh frozen plasma.

For the chronic DIC by treatment of the cause of DIC.
Embolism

Definition:

Solid, liquid, or gaseous intravascular mass, which is detached & carried by the blood to a site distant from its point of origin.

★ Virtually 99% of all emboli represent part of a dislodged (separated) *thrombus*, hence the commonly used term *thromboembolism*. 
Types of Emboli can be:

1. droplets of fat,
2. bubbles of air or nitrogen,
3. cholesterol emboli from atherosclerotic debris,
4. tumor fragments,
5. bits of bone marrow,
6. foreign bodies such as bullets, or
7. amniotic fluid.
Effects:

Always emboli lodge in vessel too small to permit further passage, resulting in partial or complete vascular occlusion, which may cause necrosis (infarction) of down-stream tissue.

Depending on the site of origin, emboli may lodge either in the :

(I) pulmonary or
(II) systemic circulation
Pulmonary Thromboembolism

★ Incidence: 200 to 250 per million hospitalized patients.

Although the rate of fatal pulmonary emboli (as assessed at autopsy) has declined from **6% to 2%** over the last century. 

pulmonary embolism causes about **200,000 deaths** annually in the USA.
Origin in more than 95% of instances, venous emboli originate from DVT which are carried by inferior vena cava through the right side of the heart into the pulmonary artery.

Depending on the size of the embolus, it may occlude the main pulmonary artery, impact across the bifurcation (saddle embolus) or pass into the smaller, branching arterioles.

Frequently, there are multiple emboli, perhaps sequentially (one new thromboembolism following older one), or as a shower of smaller emboli from a single large mass.

In general the role is that, the patient who has had one pulmonary embolus is at high risk of having more.
Effects of Pulmonary Thromboembolism:

(1) Fatal, Sudden death, acute right heart (ventricular) failure, also called acute cor pulmonale, occur when 60% or more of the pulmonary circulation is obstructed with emboli.

(2) Embolic obstruction of medium- sized arteries may result in:

(A) Pulmonary hemorrhage: but usually does not causes pulmonary infarction (in normal person) because of blood flow into the area from an intact bronchial circulation ( normally there is double pulmonary blood supply from pulmonary & bronchial arterial circulations), however,

(B) A similar embolus in the setting of left-heart failure (& resultant sluggish bronchial artery blood flow) may result in a large pulmonary infarction.
(3) Embolic obstruction of small end-arteriolar pulmonary branches usually does not result in associated infarction.

(4) Multiple emboli over time may cause pulmonary hypertension with chronic right heart failure (cor pulmonale).

(5) Majority (60% to 80%) of pulmonary emboli are clinically silent because they are small.

With time, they undergo organization & become incorporated into the vascular wall may undergo fibrosis leading to pulmonary hypertension.
F 47 : Fatal pulmonary thrombo-embolism (PTE).

A large coiled-up thrombo-embolus. It lies within the Rt.V. outflow tract, filling the pulmonary trunk & the bifurcation of both Rt & Lt pulmonary arteries (saddle embolus).
F 48: Pulmonary Thrombo Embolism: Saddle embolus
F 49 : Recurrent pulmonary Thromboembolism (PTE).
The secondary branches of a pulmonary artery have been opened to reveal two small emboli wedged within the vessels. Both have tapering distal extensions.
Systemic Thromboembolism

**Definition:**

Thromboembolism traveling within the arterial circulation.

★ **Origin:** most *(80%)* arise from intracardiac mural thrombi, 2/3 of which are associated with MI of L.V., & 1/4 with *dilated left atrium* secondary to mitral valve disease.
The remainder (20%) is largely originate from thrombi associated with ulcerated atheromatous plaques or aortic aneurysms, or from fragmentation of a valvular vegetation (of infective endocarditis); only very rarely due to paradoxical emboli (emboli passing from the right heart through atrial or ventricular septal defect into the left heart & then in the aorta).
Effects:

In contrast to venous emboli, which tend to lodge primarily in one vascular bed only (the lung in systemic venous circulation & the liver in the portal circulation), arterial emboli can travel to a wide variety of sites; the site of arrest depends on the point of origin of the thromboembolism.
Major sites for arterial embolization are the
(1) Lower extremities (75%),
(2) Brain (10%), with the intestines, kidneys, & spleen involved to a lesser extent.

The consequences of systemic emboli depend on the:
(1) **Collateral's**, the extent of collateral vascular supply in the affected tissue,
(2) **Tissue's vulnerability to ischemia**, &
(3) **Caliber of the arterial BV occluded**; in general, however, arterial emboli cause infarction of tissues in the distribution of the obstructed vessel.
Fat Embolism

**Source:** microscopic fat globules may be found in the circulation after

1. fractures of long bones (which have fatty marrows) or, rarely, in the setting of
2. soft tissue trauma & burns.

Presumably, the fat is released by marrow or adipose tissue injury & enters the circulation by rupture of the marrow vascular sinusoids or rupture of venules.

Although traumatic fat embolism occurs in some 90% of individuals with severe skeletal injuries, fewer than 10% of such patients show any clinical findings.
Figure 50 - Fat embolism: Brain. Before his death, the patient had a fractured femur. At PM, coronal section of the frontal brain region shows multiple small hemorrhagic foci scattered throughout the white matter.
Clinically, fat embolism syndrome is characterized by pulmonary insufficiency, neurologic symptoms, anemia & thrombocytopenia & is fatal in about 10% of cases.

Typically, the symptoms appear 1 to 3 days after injury with sudden onset of dyspnea, tachypnea & tachycardia, neurologic irritability, progressing to delirium or coma.
Pathogenesis: involves

(1) mechanical obstruction of pulmonary or cerebral microvasculature by neutral fat microemboli,

(2) The fat globules release free fatty acids which cause local toxic injury to Endothelial cells.

(3) A characteristic petichial skin rash is related to rapid onset of thrombocytopenia, presumably caused by platelets adherence to the myriad (tens of thousands) of fat globules & being removed from the circulation.
Air Embolism

★ **Source:** air may enter the circulation (1) during obstetric procedures or (2) as a consequence of chest injury.

Generally, in excess of **100 mL of air** is required to produce a clinical effect; the air bubbles *act like physical obstruction* (just as thromboembolism & causing distal ischemic injury), bubbles may coalesce to form frothy masses sufficiently large to occlude major vessel.
Bone marrow embolus in the pulmonary circulation. The cellular elements on the left side of the embolus are hematopoietic precursors, while the cleared vacuoles represent marrow fat. The relatively uniform red area on the right of the embolus is an early organizing thrombus.
Decompression sickness

Is a particular form of gas embolism, which occurs when individuals are exposed to sudden changes in atmospheric pressure.

**Scuba** (under water breathing apparatus users) deep sea divers, underwater construction workers, & individuals in unpressurized aircraft in rapid ascent are at risk.
Figure 52: Sea diver with scuba.
When air is breathed at high pressure (e.g., during a deep sea dive), increased amounts of gas (particularly nitrogen) become dissolved in the blood & tissues.

If the diver then ascends (depressurizes) too rapidly, the nitrogen expands in the tissues & bubbles out of solution in the blood to form gas emboli.

Clinically, the rapid formation of gas bubbles within skeletal muscles & supporting tissues in & about joints is responsible for the painful arching of the backs, condition called (the bends).
Gas emboli may also induce focal ischemia in a number of tissues, including brain, heart, & in the lungs where it may leads to respiratory distress, called the chokes.

**Treatment of gas embolism** consist of placing the individual in a compression chamber, where the barometric pressure may be raised, thus forcing the gas bubbles back into solution.

Subsequent, slow decompression, theoretically permits gradual resorption & exhalation of the gases so that obstructive bubbles do not reform.

★ A more chronic form of decompression sickness is called Caisson disease,

in which persistence of gas emboli in the bones leads to multiple foci of ischemic necrosis; the commonest sites are the heads of the femur, tibia, & humeri.
Figure 53: Compression chamber.
Amniotic Fluid Embolism

**Source:** infusion of amniotic fluid & its contents into the maternal circulation via a tear in the placental membranes & rupture of uterine veins.

**Effects:** impaction in the pulmonary microcirculation of squamous cells shed from fetal skin, lanugo hair, & mucin derived from the fetal respiratory or GIT, causing DIC & pulmonary edema
Incidence:

A grave, but fortunately uncommon fatal complication of labor & the immediate postpartum period (20 per million deliveries), with a mortality rate in excess of 80%, & as other obstetric complications (e.g., eclampsia, pulmonary embolism) have been better controlled, amniotic fluid embolism has become an important cause of maternal mortality.
Clinically:

The onset is characterized by sudden severe dyspnea, cyanosis, & hypotensive shock, followed by seizures & coma.

If the patient survives the initial crisis, pulmonary edema typically develops, along with DIC (in half the patients), due to release of thrombogenic substances from the amniotic fluid.
INFARCTION

Definition

Infarction is an area of ischemic necrosis caused by occlusion of either the arterial supply or the venous drainage in a particular tissue.
Infarction is a common & extremely important cause of clinical illness.

More than 50% of all deaths in the USA are caused by cardiovascular disease, & most of these are attributable to myocardial or cerebral infarction.

Pulmonary infarction is a common complication in a number of clinical settings, bowel infarction is frequently fatal, & ischemic necrosis of the extremities, i.e., (gangrene) is a serious problem in the diabetic population.
INFARCT ETIOLOGY

★Nearly 99% of all infarcts result from thrombotic or embolic event & almost all result from arterial occlusion.

Occasionally, infarction may also be caused by other ★ mechanisms, such as

(1) local vasospasm,
(2) extrinsic compression of a BV (e.g., by tumor, surgical tourniquet or band, entrapment in a hernial sac),
(3) torsion, i.e., twisting of the BV (e.g., of testis, bowel volvulus, ovarian cysts & tumors),
(4) traumatic rupture of the blood supply.
Although venous thrombosis may cause infarction, it more often only induces venous obstruction & congestion.

Usually, bypass channels then rapidly open, providing some outflow from the area, which in turn improves the arterial inflow.

★ Infarcts caused by venous thrombosis are more likely in organs with a single venous outflow channel, such as the testis & ovary.
**Morphology of infarcts:**

GROSSLY, Infarcts can be either *white or red* (reflecting the amount of hemorrhage).

**RED INFARCTS** occurs:

1. In venous occlusion (such as ovarian torsion);
2. In loose tissues (e.g., lung) that allow blood to collect in the infarcted zones;
3. In tissues with dual blood circulations such as lung, liver, & small intestine, permitting flow of blood from the unobstructed vascular channel in to the necrotic area (obviously such perfusion is not sufficient to rescue the ischemic tissues);
4. In previously congested tissue because of sluggish venous outflow;
5. When blood flow is re-established to a site of previous arterial occlusion & infarction (e.g., fragmentation of an occlusive embolus or angioplasty of a thrombotic lesion).
Figure 54 - Lung infarction. There is lower lobe, sub-pleura, pale pink, wedge-shaped infarct. The infarct is swollen, with raised pleural surface over it, & is surrounded by a dark-red congested border.
**WHITE INFARCTS** occurs:

1. In arterial occlusion, or
2. In solid organs (such as heart, kidney, & spleen), where the solidity of the tissue limits the amount of hemorrhage that can seep into the area of ischemic necrosis from the adjoining capillary beds.
Fig. 55: A, Hemorrhagic wedge-shaped pulmonary (red infarct).

B, Sharply demarcated pale infarct in the spleen (white infarct).
INFARCTS SHAPE:

All infarcts tend to be **wedge shaped (Δ)**, with the occluded vessel at apex & the periphery of the organ forming the base; when the base is a serosal surface, there is often an overlying **fibrinous exudate**.

The lateral margins may be irregular, reflecting the pattern of vascular supply from adjacent vessels. *At the beginning all infarcts are poorly defined & slightly hemorrhagic*. *With time*, the margins of both red & white infarcts tend to become **better defined** by a narrow rim of hyperemia attributable to inflammation at the edge of the lesion.
F 56 : Infarction: Brain. The patient had tentorial herniation obstructing the posterior cerebral arteries, which results in recent hemorrhagic infarction of the infero-medial aspects of both occipital lobes.
★ In solid organs, infarcts resulting from arterial occlusion typically become progressively more pale & sharply defined with time, by contrast, infarcts

★ In spongy organs are associated with extensive hemorrhage & therefore it is red, & after few days, it become firmer & browner, reflecting the development of hemosiderin pigment.
Histologically, ischemic coagulative necrosis is the characteristic feature of infarction except in the brain, in which liquefactive necrosis occurs.

If the patient survive (e.g., MI), coagulative necrosis can be demonstrated about 12 hours after arterial occlusion.

Necrotic tissue incite (stimulate) inflammatory responses along the margins of infarct within a few hours & is usually well defined within 1 to 2 days. Infiltration of the necrotic tissues by neutrophils first, followed by monocytes result in degradation of the dead tissue with phagocytosis of the tissue debris.

Eventually, repair begins from the viable preserved margins:
In labile or stable tissues, some parenchymal regeneration may occur at the periphery where the underlying stromal architecture has been spared.

However, in most of the infarcts, & permanent tissue infarcts (myocardial & skeletal muscles) are ultimately replaced by scar tissue.
The brain is an exception to these generalization; like other causes of necrosis, ischemic necrosis in the CNS results in liquefactive necrosis.

Septic infarction may arise when embolization occurs by fragment of bacterial vegetation from a heart valve, or when microbes seed an area of necrotic tissue. In these cases, the infarct is converted into an abscess, with eventual organization.
Factors Influencing the Development of an Infarct

The consequences of a vascular occlusion can range from no or minimal effect, all the way up to death of a tissue or organ.

The major determinants are:

(I) Alternative blood supply or the vascular supply nature is the most important factor in determining whether occlusion of a BV will cause damage.

For example, the liver has a dual hepatic artery & portal vein circulation. The lungs have a dual pulmonary & bronchial artery blood supply, and the hand and forearm have dual radial & ulnar arterial blood supply, are all relatively resistant to infarction.

In contrast, renal & splenic circulations are end-arterial, & obstruction of such arteries causes infarction.
(2) Rate of development of occlusion:

*Slowly developing occlusion is less likely to cause infarction because they provide time for the development of alternative pathways of flow.*

For example, small interarteriolar anastomoses, normally with minimal functional flow, interconnect the three major coronary arteries in the heart.

If one of the coronaries is only slowly occluded (e.g., by an atheromatous plaque), flow within this collateral circulation may increase sufficiently to prevent infarction, even though the major coronary artery is eventually occluded.
(3) **Vulnerability (susceptibility) to hypoxia:**

Neurons die when deprived of their blood supply for only 3 to 4 minutes; myocardial cells die after 20 to 30 minutes. In contrast, fibroblasts within myocardium remain viable after many hours of ischemia.

(4) **Oxygen content of blood:**

Partial flow obstruction of a small BV in an anemic or cyanotic patient might lead to tissue infarction, whereas it would be without effect under conditions of normal oxygen tension. In this way, congestive heart failure (CHF), with compromised flow & ventilation, could cause infarction.
SHOCK

Definition:

Shock constitutes systemic hypoperfusion due to a reduction either in cardiac output or in the effective circulating blood volume, resulting in hypotension, impaired tissue perfusion & cellular hypoxia.

Types of shock

The three major types of shock are:

I. Cardiogenic shock results from myocardial pump failure.

   The most common causes are:
   (1) intrinsic myocardial damage (infarction, MI).
   (2) ventricular arrhythmias (fibrillation).
   (3) outflow obstruction (massive pulmonary thromboembolism) or
   (4) extrinsic compression (cardiac tamponade, e.g., hemopericardium resulting from rupture MI, or aortic aneurysm).
(II) Hypovolemic shock:

Results from loss of blood or plasma volume. This may be caused by hemorrhage, fluid loss from severe burns, vomiting, diarrhea or trauma.

(III) Septic shock:

Is caused by systemic infection. Most commonly, this occurs in the setting of gram-negative infections (*endotoxic shock*), but it can also occur with gram-positive & fungal infections.
Less commonly, shock may occur in two other settings:

(a) **Anesthetic accident or a spinal cord injury (neurogenic shock)** due to loss of vascular tone & peripheral pooling of blood, &

(b) **Anaphylactic shock**, initiated by a generalized immunoglobulin E-mediated hypersensitivity response, is associated with systemic vasodilation & increased vascular permeability.

In the above two instances, **widespread vasodilation** causes a sudden increase in the capacity of the vascular bed, which cannot be filled adequately by the normal circulating blood volume. Thus, tissue hypoperfusion & cellular anoxia result.
Septic Shock

**Incidence:**

Septic shock is the first and most common cause of death in intensive care units, and with a 25% to 50% mortality rate.

Moreover, the reported incidence is increasing dramatically, in part due to increasing invasive procedures, & the growing numbers of immunocompromised hosts (secondary to immunosuppression, chemotherapy, or HIV infection).

Septic shock results from spread of an initially localized infection (e.g., abscess, peritonitis, pneumonia) into the blood.
Pathogenesis of Septic Shock

Endotoxins:

Are bacterial wall lipopolysaccharides (LPSs) released when the bacteria die & their cell wall are degraded (e.g., in an inflammatory response).

LPS consists of a toxic fatty acid core common to all gram-negative bacteria (lipid A), & a complex polysaccharide coat that is unique for each species (O antigens).

★ Analogous molecules in the walls of gram-positive bacteria & fungi can also elicit septic shock.
At low doses,

(1) LPS can directly activate complement which contributes to local bacterial eradication,

(2) More important, *free LPS attaches to a circulating LPS-binding protein* & the complex then bind to a specific receptor on neutrophils, monocytes, & macrophages.

   *This result in profound mononuclear cell activation (enhance phagocytosis), & their production of cytokine TNF, which in turn induces IL-1 synthesis.*

   Both IL-1 & TNF act on EC (& other cell types) to produce further cytokines (e.g., IL-6 & IL-8), & induce adhesion molecules & further chemotaxis.
In summary:

The initial release of LPS results in a circumscribed cytokine cascade, that enhances local acute inflammatory response & improves clearance of the infection.

With a moderately severe infections, & therefore, with higher levels of LPS, secondary effectors (e.g., nitric oxide (NO) & platelet-activating factor (PAF)) become significant.

So in addition to local inflammatory effect, systemic effects of TNF & IL-1 may begin to be seen, including fever, leukocytosis, & increased synthesis of acute-phase reactants. The combined effects of the above result in hypoperfusion causing multiorgan system failure that affects the liver, kidneys, & CNS, & others. Unless the underlying infection is rapidly brought under control, the patient usually dies...
Finally, at still higher levels of LPS, septic shock supervenes; the same cytokine & secondary mediators now at higher levels result in the following serious effects:

1. **Hypotension** (due to systemic widespread vasodilation)
2. Diminished myocardial contractility (pump failure)
3. Activation of the coagulation system, culminating in DIC.
4. Widespread EC injury & activation, causing systemic leukocyte adhesion & diffuse alveolar capillary damage in the lung, so-called **Adult respiratory Distress Syndrome (ARDS)**.
Figure 57: Effects of lipopolysaccharides (LPS) & secondarily induced effector molecules.
Stages of shock

Shock is a progressive disorder that if uncorrected leads to death. Unless the insult is massive & rapidly lethal, shock tends to evolve (pass) through three general stages.

These stages have been documented most clearly in hypovolemic shock but are common to other forms.

An initial nonprogressive stage:

During which reflex compensatory mechanisms are activated & perfusion of vital organs is maintained.

A progressive stage:

characterized by tissue hypoperfusion & onset of worsening circulatory & metabolic imbalances.

An irreversible stage:

that sets in after the body has incurred cellular & tissue injury so severe that even if the hemodynamic defects are corrected, survival is not possible.
MORPHOLOGICAL CHANGES OF SHOCK

The cellular & tissue changes induced by shock are essentially those of hypoxic injury.

Changes are particularly evident in the brain, heart, lungs, kidneys, adrenal, & GIT.

- **Brain** may develop so-called ischemic encephalopathy.
- **Heart** may develop extensive focal & widespread coagulation necrosis, or it may exhibit subendocardial hemorrhage and/or contraction band necrosis.
• **Kidneys** typically exhibit extensive acute tubular necrosis, so that oliguria, anuria, & electrolyte disturbances constitute major clinical problems.

• **Lungs** are seldom affected in pure hypovolemic shock as they are somewhat resistant to hypoxic injury. However, when shock is caused by bacterial sepsis or trauma, changes of diffuse alveolar damage may appear the so-called shock lung or Adult respiratory Distress Syndrome (ARDS).
Adrenal: non-specific changes seen in all forms of stress; essentially there is cortical cell lipid depletion.

Gastrointestinal tract: may suffer patchy mucosal hemorrhage & necrosis, referred to as hemorrhagic enteropathy.

Liver: may develop fatty change & central hemorrhagic necrosis.

Clinically, the manifestations depend on the precipitating insult.

In hypovolemic & cardiogenic shock, the patient present with hypotension, weak rapid pulse, rapid respiration, & cool, clammy (moist), pale or cyanosed skin. The prognosis varies with the origin of shock & its duration.

Thus, 80% of young, otherwise healthy patients with hypovolemic shock survive with urgent appropriate management; whereas extensive M.I. associated with cardiogenic shock or gram-negative septic shock carry mortality rates of 75%.