Pathophysiology

Dr. Yasser Mufid

Lecture 8

Disorders of cardiovascular system I

LEARNING OBJECTIVES:

1. Comprehending homeostasis.
2. Comprehending Oedema.
3. Comprehending Hyperemia & Congestion.
4. Know the pathophysiology of edema
5. Comprehending the pathophysiology of thrombosis & embolism.
6. Differentiating thrombosis from embolism.
7. Comprehending the fate of the thrombus
8. Comprehending infarction.

Homeostasis

The mechanism by which constancy of the internal environment is maintained and ensured. Living membranes such as cell wall and vascular endothelium play important role in exchanges of fluid, electrolytes, nutrients and metabolites.

Total body water is about 60% of the body weight and is divided **into intracellular (33%)** and **extracellular compartments (27%).** Intracellular fluid has **low concentration of sodium** and chloride while extracellular compartment has high sodium, chloride and bicarbonate; plasma has high protein content compared from interstitial fluid.

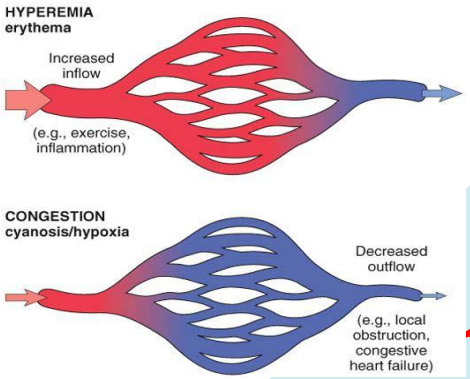
I. Hyperemia & Congestion

Hyperaemia and congestion *are the terms used for localized increase in the* ***volume of blood*** *within dilated vessels of an organ or tissue*.

*Increased volume of blood from arterial and arteriolar dilatation (**i.e. increased inflow**)* is referred to as **hyperemia or active hyperemia.**

*Impaired venous drainage (**i.e. diminished outflow**)* is called venous congestion or passive hyperemia.

If the condition develops rapidly it is called **acute**, while more prolonged and gradual response is known as **chronic**.



Pathophysiology

Hyperemia has two known types:

1- The active hyperemia.

2- The reactive hyperemia.

***Active hyperemia*:** is due to

A. Neurogenic: *hormonal (blushing).*

B. Fever :*heat, chemical substances, UV,… etc.*

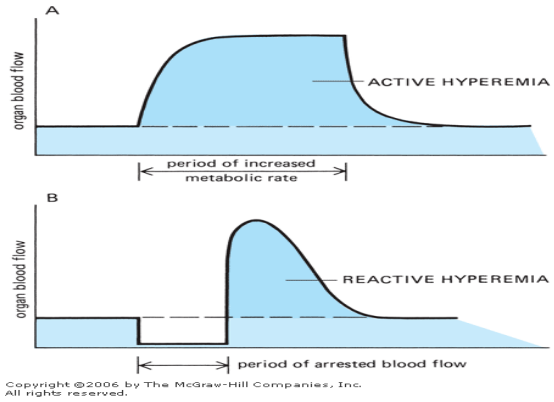
C. **Inflammation:** *("tumor, Rubor, Calor") .*
D. **Blushing:** *i.e. flushing of the skin of face in response to emotions.*
E. Menopausal flush.
F. Muscular exercise: Exercise hyperemia or functional hyperemia. This type of hyperemia occurs due **to increase muscles contraction**. It is produced by the increase in the body's demand to oxygen resulting in vasodilation.
G. Goiter.
H. Arteriovenous malformations.

Reactive hyperemia:

It *is also called as the* ***passive hyperemia*** *(**Congestion**). The blood collects in a certain organ of the body as a response to the veins being blocked causing the blood not to freely move about.* E.g. *Reactive hyperemia occurs right after a person had an episode of ischemia, removal of a tourniquet.*

The oxygen content in the blood **is reduced** and the presence of metabolic waste in the tissue is **increased,** and build up in an organ and cause some veins to be blocked turning into **blue-red** (**cyanotic**), as worsening congestion leads to accumulation of deoxygenated hemoglobin.

a. ***Normal sclera***
b. Hyperemia associated with allergic conjunctivitis



Pathophysiology of Congestion

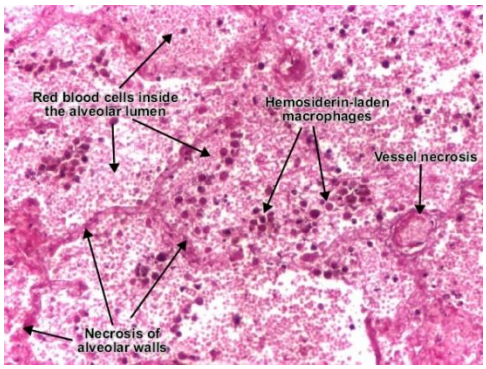
Venous congestion could be:

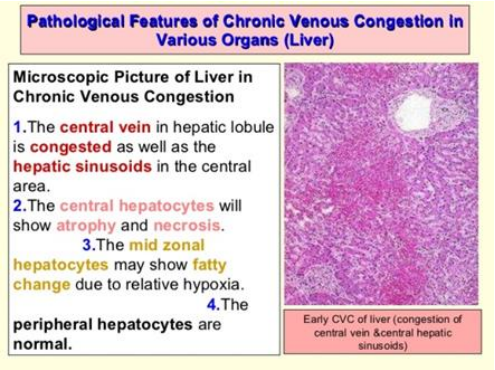
1. **"Local":** This type results from obstruction to the venous outflow from an organ or part of the body e.g. portal venous obstruction in cirrhosis of the liver.
2. **"Systemic" (General) venous congestion:** It is engorgement of veins e.g. in **left-sided and right-sided heart failure and diseases of the lungs** which interfere with pulmonary blood flow like pulmonary fibrosis, emphysema.

Congestion may be **acute or chronic**, the latter being more common and is called **chronic venous congestion (CVC)**.

Long-standing congestion (**chronic passive congestion**) results in:

1. Stasis of poorly oxygenated blood.
2. **Chronic hypoxia which leads to parenchymal cell degeneration, cell death.**
3. Capillary rupture may cause small hemorrhagic foci and breakdown.
4. Phagocytosis of red cell debris may result in **hemosiderin-laden macrophages**.



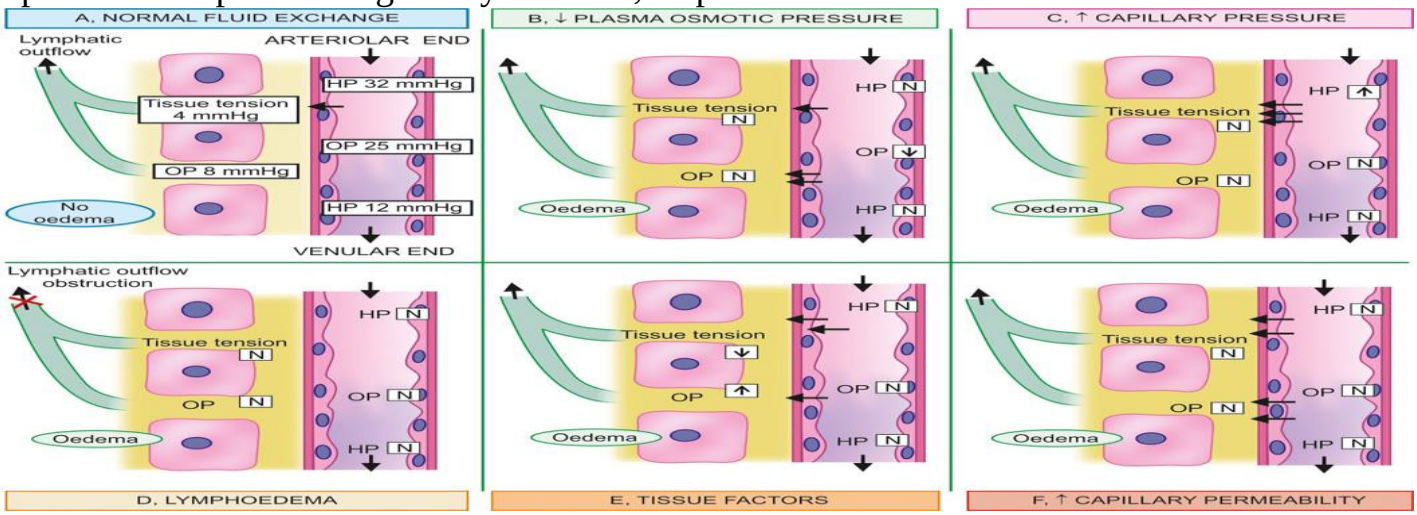


II. Edema

A local or generalized condition in which a*n* ***abnormal and excessive accumulation of "free fluid" in the interstitial tissue spaces and serous cavities***.

Free fluid in body cavities: Commonly called as **effusion**, it is named according to the body cavity in which the fluid accumulates. For example, **ascites** (if in the peritoneal cavity), **hydrothorax** or **pleural effusion** (if in the pleural cavity), and hydropericardium or **pericardial effusion** (if in the pericardial cavity).

Free fluid in interstitial space: Commonly termed as **oedema**, the fluid lies free in the interstitial space between the cells and can be displaced from one place to another. In the case of **oedema in the subcutaneous tissues**, momentary pressure of finger produces a depression known as **pitting oedema**. The other variety is **non-pitting** or solid oedema in which no pitting is produced on pressure e.g. in myxoedema, elephantiasis.



Diagrammatic representation of pathogenesis of oedema **(OP = oncotic pressure; HP = hydrostatic pressure).**
A, Normal pressure gradients and fluid exchanges between plasma, interstitial space and lymphatics.
B, Mechanism of oedema by decreased plasma oncotic pressure and hypoproteinemia.
C, Mechanism of oedema by increased hydrostatic pressure in the capillary.
D, Mechanism of lymphoedema.
E, Mechanism by tissue factors (increased oncotic pressure of interstitial fluid and lowered tissue tension).
F, Mechanism of oedema by increased capillary permeability.

Pathophysiology of Oedema

1- Increased hydrostatic pressure:

a) **Local** e.g., Impaired venous outflow, such as in deep venous thrombosis, or lower extremity inactivity with prolonged dependency.
b) **Generalized** e.g., Congestive heart failure, affecting right ventricular function .

2- Reduced Plasma Oncotic Pressure:

Excessive loss or reduced synthesis of albumin (which is the serum protein most responsible for maintaining colloid osmotic pressure) . In **Nephrotic syndrome**: glomerular capillary wall losses its ability in preventing albumin loss which will lead to generalized edema. While in **Diffuse liver pathology or protein malnutrition** both lead to reduction in albumin synthesis.

Decreased albumin leads to reduced plasma oncotic pressure, with subsequent net movement of fluid into interstitial tissues and resultant plasma volume contraction.

In spite of sodium and water retention, plasma volume deficit cannot be corrected because low serum protein persists.

3. **Lymphatic obstruction**: The interstitial fluid in the tissue spaces escapes by way of lymphatics. Obstruction to outflow of these channels causes localized oedema, known as **lymphoedema**. Example:

a) **Filariasis** – elephantiasis
b) **Carcinoma**: Direct obstruction or Secondary to therapy – e.g., axillary node dissection at time of diagnosis (as with breast carcinoma) or post-irradiation

4. **Sodium and water retention**.

About 80% of **sodium** is reabsorbed by the ***proximal convoluted tubule*** under the influence of either intrinsic renal mechanism or extra-renal mechanism while **retention of water** is affected by release of antidiuretic hormone.

a) ***Intrinsic renal mechanism:*** It is activated in response to sudden reduction in the effective arterial blood volume(hypovolemia) e.g. in severe hemorrhage.
b) ***Extra-renal mechanism***: It involves the secretion of **aldosterone**.
c) **Large amounts of ADH**: It produce highly concentrated urine.

5. **Inflammation**: This is largely related to local increases in vascular permeability.

6. **Increased capillary permeability.**

An intact capillary endothelium is a semipermeable membrane which permits the free flow of water and crystalloids **but** allows minimal passage of plasma proteins normally. However, when the capillary endothelium is injured by various **'capillary poisons'** such as toxins and their products (e.g. **histamine, anoxia, venoms, certain drugs and chemicals**), the capillary permeability to plasma proteins is enhanced due to development of gaps between the endothelial cells, causing leakage of plasma proteins into interstitial fluid. This, in turn, causes **reduced plasma oncotic pressure and elevated oncotic pressure of interstitial fluid**, consequently producing oedema.

Edema occurring in hydrodynamic derangements is usually a transudate: protein-poor, specific gravity < ~1.012 to 1.015, usually with few cells. Edema occurring in inflammatory conditions is usually an exudate: protein-rich, specific gravity >~1.015 to 1.020, often with inflammatory components.

7. Numerous medications can cause edema, including:

a) NSAIDs (ibuprofen, naproxen).
b) Calcium channel blockers.
c) Corticosteroids (prednisone, methylprednisolone).
d) Pioglitazone and rosiglitazone *is an antidiabetic drug*.
e) Pramipexole is a dopamine agonist.

Clinical types of Oedema

1- Localized

a) Involves one organ or part of the body.
b) Clinically important examples: brain edema, lung edema, hydrothorax, ascites.

2- Generalized

Involves the entire body (**anasarca**).

Clinical sign: pitting edema (depression in the skin by pressing on it with a finger) it is due to decreased serum protein, increased systemic venous pressure & increased Capillary permeability.

None pitting edema is caused by abnormalities in the lymphatic drainage (lymphedema).

Characteristics: *Non tender, painless, Does not vary much during the day, Ulceration rare & Hyperkeratosis, thickening of skin.*

0+ No pitting edema
1+ Mild pitting edema. 2 mm depression that disappears rapidly.
2+ Moderate pitting edema. 4 mm depression that disappears in 10–15 seconds.
3+ Moderately severe pitting edema. 6 mm depression that may last more than 1 minute.
4+ Severe pitting edema. 8 mm depression that can last more than 2 minutes.

III. Thrombosis

Is the formation of a blood clot in the intravascular compartment, obstructing the flow of blood through the circulatory system.

A thrombus is a **clot** consisting of fibrin, platelets, red blood cells, and white blood cells that forms in a blood vessel or in a chamber of the heart and can obstruct blood flow.

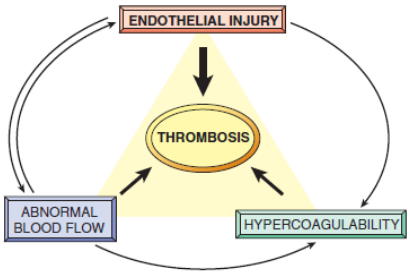
Pathophysiology (**Virchow's triad**)

Any alteration in the:

1- Blood flow (Turbulence/Stasis).

2- Vascular Injury/Inflammation .

3- Hypercoagulability of the blood leads to thrombosis.



1. *Endothelial injury.*

Vascular injury exposes the subendothelial extracellular matrix or ECM (e.g. collagen, elastin, fibronectin, laminin and glycosaminoglycans) **which is thrombogenic** and thus plays an important role in initiating hemostasis as well as thrombosis.

Injury to vessel wall also causes **vasoconstriction** of small blood vessels briefly so as to reduce the blood loss.

Endothelial injury is of major significance in the formation of arterial thrombi and thrombi of the heart, especially of the left ventricle.

A number of factors and conditions may cause vascular injury and predispose to the formation of thrombi. *These are as under:*

i) **Endocardial injury** in myocardial infarction, myocarditis, cardiac surgery, prosthetic valves.

ii) **Ulcerated plaques** in advanced atherosclerosis.

iii) **Hemodynamic stress** in hypertension.

iv) **Arterial diseases**. E.g. Takayaso's arteritis

v) **Diabetes mellitus.**

vi) **Endogenous chemical agents** such as hypercholesterolemia, endotoxins.

vii) **Exogenous chemical** agents such as cigarette smoke.

2. *Altered blood flow.*

Turbulence and stasis occur in thrombosis in which the normal axial flow of blood is disturbed. When blood slows down, the blood cells including platelets marginate to the periphery and form a kind of pavement close to endothelium (margination and pavementing)

While stasis allows a higher release of oxygen from the blood, turbulence may actually injure the endothelium resulting in deposition of platelets and fibrin. Formation of arterial and cardiac thrombi is facilitated by turbulence in the blood flow, while stasis initiates the venous thrombi even without evidence of endothelial injury.

3. ***Hypercoagulability of blood*. (THROMBOPHILIA)**

Thrombophilia or hypercoagulable states are a group of conditions having increased risk or predisposition to develop venous thrombosis. These conditions may be hereditary (or primary) or acquired (or secondary) causes:

Hereditary (Primary) Factors:

i) Deficiency of antithrombin III.
ii) Deficiency of protein C.
iii) Deficiency of protein S.

Acquired (Secondary) Factors

a) Risk factors:

i) Advancing age.
ii) Prolonged bed-rest.
iii) Prolonged immobilization (e.g. in plaster cast, long distance travel).
iv) Cigarette smoking.
v) Obesity.

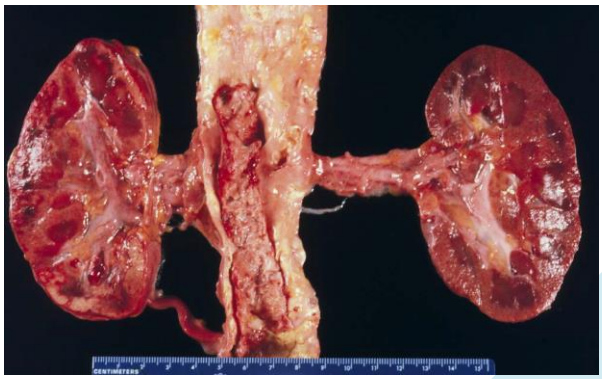
b) Predisposing clinical conditions:

i) Heart diseases (e.g. myocardial infarction, CHF, rheumatic mitral stenosis, cardiomyopathy)
ii) Vascular diseases (e.g. atherosclerosis, aneurysms of the aorta and other vessels, varicosities of leg veins).
iii) Shock.
iv) Tissue damage e.g. trauma, fractures, burns, major surgery on bones, abdomen or brain.
vi) Late pregnancy and puerperium.

Thrombi can develop anywhere in the cardiovascular system (e.g., in cardiac chambers, on valves, or in arteries, veins, or capillaries). **The 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*. Thrombi are focally attached to the underlying vascular surface; arterial thrombi tend to grow in a retrograde direction from the point of attachment, while venous thrombi extend in the direction of blood flow (thus 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.

Thrombi occurring in heart chambers or in the aortic lumen are designated **mural thrombi.** Abnormal myocardial contraction (resulting from arrhythmias, dilated cardiomyopathy, or myocardial infarction) or endomyocardial injury.



Types:

1- Arterial thrombi are frequently **occlusive** and are produced by platelet and coagulation activation; they are typically a friable meshwork of platelets, fibrin, erythrocytes, and degenerating leukocytes. Although arterial thrombi are usually superimposed on an atherosclerotic plaque, other vascular injury (vasculitis, trauma) can be involved.

2- Venous thrombosis (phlebothrombosis) is almost invariably occlusive, and the thrombus can create a long cast of the lumen.

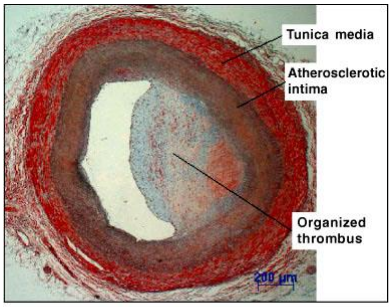


Figure 7 - Cross section photomicrograph of anterior interventricular branch first centimeter (anterior descending) of left coronary artery. Fibrotic atherosclerotic lesion and organized non-occlusive thrombosis are present. (Movat method coloring; objective lens augmentation - 2,5x).

Venous thrombosis is largely the result of activation of the coagulation cascade, and platelets play a secondary role. Because these thrombi form in the sluggish venous circulation, they also tend to contain more **enmeshed erythrocytes and are therefore called red, or stasis, thrombi**.

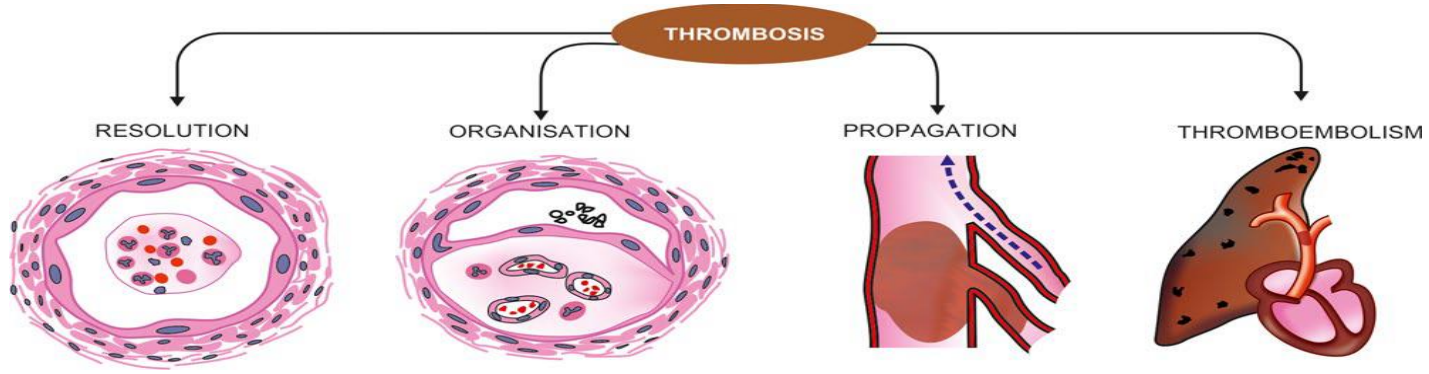
3- Cardiac thrombi are mural (**non-occlusive**) as are the mural thrombi encountered in large vessels such as the aorta in atherosclerosis and in aneurysmal dilatations. Rarely, large round thrombus may form and obstruct the mitral valve and is called ball-valve thrombus.

Thrombi on heart valves are called **vegetations**. Bacterial or fungal blood-borne infections can cause valve damage, subsequently leading to large thrombotic masses (infective endocarditis,).

Fate of the Thrombus :-

If a patient survives the initial thrombosis, in the ensuing days or weeks thrombi undergo some combination of the following four events:

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.
   Fibrinolytic activity can be accentuated by administration of thrombolytic substances (e.g. urokinase, streptokinase), especially in the early stage when fibrin is in monomeric form e.g. thrombolytic therapy in early stage acute myocardial infarction.
4. **Organization and recanalization**: Thrombi induce inflammation and fibrosis (organization). These can eventually recanalize (re-establishing some degree of flow), or they can be incorporated into a thickened vessel wall.

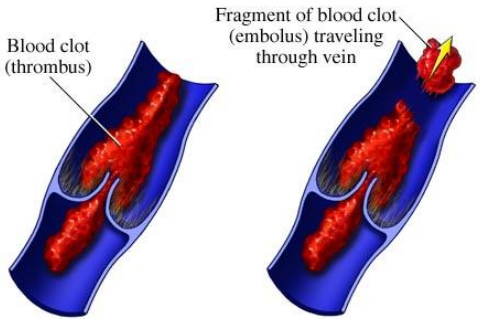


IV. Embolism

Detached intravascular solid, liquid, or gaseous mass that is carried by the blood to a site distant from its point of origin. 99% are dislodged thrombi.

Types

a. Thromboembolism. *Could be arterial or venous.*
b. Fat and marrow embolism.
c. Bacterial embolism.
d. Air embolism (decompression sickness).
e. Amniotic fluid embolism.
f. Tumor cell embolism.
g. Foreign body embolism.



Pathophysiology of Thromboembolism

The pathophysiology and clinical manifestations depend upon four main factors:

a) The extent of occlusion of the vascular tree and the size of the emboli.

b) The patient's pre-existing **cardiopulmonary condition**.

c) Chemical vasoconstriction due to the **release of serotonin and thromboxane from platelets** that adhere to the embolus, as well as to **fibropeptide B**, which is a product of fibrinogen breakdown.

d) The reflex vasoconstriction that is likely to occur as a consequence of artery dilatation.

Fat Embolism Occurs mostly after fractures of long bones, soft tissue trauma or burns. 90% of individuals with severe skeletal injuries, though <10% have any clinical findings.

Fat embolism syndrome is characterized by:

a) Begins 1-3 days after injury.
b) Tachypnea.
c) Dyspnea.
d) Tachycardia.
e) Neurologic symptoms.
f) Diffuse petechial rash (20-50%).
g) Thrombocytopenia.
h) Anemia.

The mechanical obstruction and biochemical injury. **Free fatty acids cause local toxic injury to endothelium, platelet activation**. **Prognosis: The Syndrome is fatal in 10% of the cases.**

Air Embolism

Decompression sickness, "**the bends**" or "**the chokes**", caisson disease**. Clinically needs an excess of 100cc of air to have a clinical effect**.

It is characterized by:

a. Painful muscle cramps.
b. Respiratory insufficiency.
c. Neurological symptoms.
d. Formation of gas bubbles within skeletal muscle, soft tissues and joints causes pain.
e. Focal ischemia to brain and heart.
f. Pulmonary edema and hemorrhage, focal atelectasis or emphysema.
g. Persistence of gas emboli in the skeletal system leads to **multiple foci of ischemic necrosis** (femoral head, tibia and humerus).

Amniotic Fluid Embolism

Clinically it is characterized by:

a. 1 in 50,000 deliveries.
b. 80% mortality rate.
c. Sudden severe dyspnea,
d. Cyanosis.
e. Hypotensive shock, followed by seizures and coma.
f. Pulmonary edema and disseminated intravascular coagulation (DIC).

Pulmonary microcirculation with epithelial squamous cells shed from fetal skin, lanugo hair, fat from vernix, mucin from GI tract are the predominant causes.

Arterial Emboli

may be derived from the following sources:

A. **Causes within the heart (80-85%):** These are **mural thrombi in the left atrium or left ventricle**, vegetations on the mitral or aortic valves, prosthetic heart valves and cardiomyopathy.
B. **Causes within the arteries:** These include emboli developing in relation to atherosclerotic plaques, aortic aneurysms, pulmonary veins and paradoxical arterial emboli from the systemic venous circulation.

Venous Thromboembolism

Venous emboli may arise from the following sources:

i) **Deep vein thrombosis** (DVT) of the lower legs, the most common cause of venous thrombi.
ii) Thrombi in the **pelvic veins**.
iii) Thrombi in the veins of the **upper limbs**.
iv) Thrombosis in **cavernous sinus** of the brain.
v) Thrombi in the **right side of heart**.

The most significant effect of venous embolism is obstruction of pulmonary arterial circulation leading to pulmonary embolism.

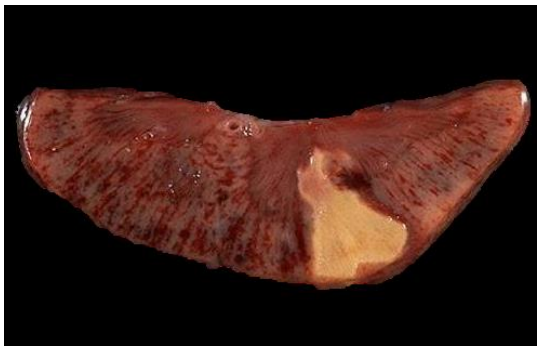
1. Pulmonary embolism *is the most common and fatal form of venous thromboembolism in which there is occlusion of pulmonary arterial tree by thromboemboli.*

2. Systemic thromboembolism *is emboli travelling within arterial circulation & impacting in the systemic arteries.*

V. Infarction :

An area of ***ischemic necrosis*** *caused by occlusion of either arterial supply or venous drainage.*

a. 99% from thrombotic or embolic events.
b. Remainder:
   i. Local vasospasm.
   ii. Extrinsic compression.
   iii. Hemorrhage within a plaque.
   iv. Torsion, traumatic rupture.



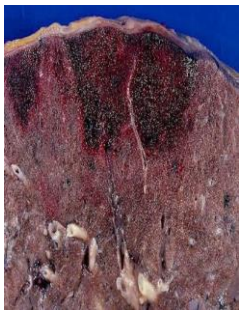
Infarcts caused by venous thrombosis are more common in **organs with single venous outflows**: e.g. testis, ovary.

Types of infarction

1- White Infarct.
2- Red infarction.
3- Septic infarctions.

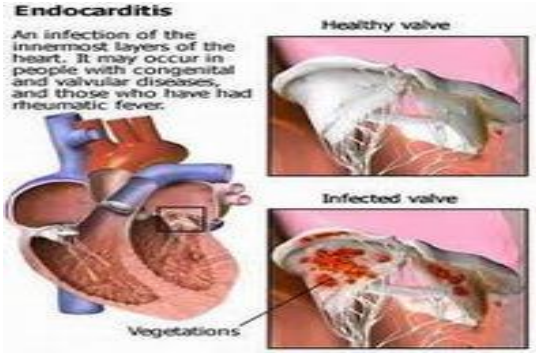
White Infarct: This type of infarction is due to **arterial occlusion**. It is referred as white due to **lack of erythrocytes accumulation**, it shows a Pyramid shape necrosis the apex of the pyramid points to the occluded artery while the base is at periphery it is a **coagulative necrosis** and can become red infarct when reperfusion occurs. It occurs in solid organs with no dual arterial blood supply such as the heart, Spleen and Kidneys. This is because solid organ may limit the amount of hemorrhage that can seep into the area of ischemic necrosis from adjoining capillary beds.

Red infarction is due to **venous occlusion**. Referred as red due to **massive erythrocytes accumulation**, it consist of numerous fibrin strands and often with **irregular shape necrosis**. It involves loose organs with dual circulation such as the lungs, kidneys, GIT and brain. The loose tissue enables erythrocytes to seep during injury and accumulate inside the tissue.



SEPTIC INFARCTIONS may develop due to:

a. Bacterial vegetation fragments.
b. Microbes seed in a necrotic tissue.
c. An infarct converting into an abscess.



Factors That Influence Development of an Infarct:

1. **Vascular supply**: The duel blood supply organs are less vulnerable than single blood supply organs.
2. **Rate of development of occlusion** (time for development of alternate perfusion pathways).
3. **Vulnerability of the tissue to hypoxia** (neurons 3-4 minutes, myocardium 20-30 minutes).
4. **The blood oxygen** content (e.g. ventilation).

Reference:

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2. Kathryn McCance , Sue E. Huether, Valentina L., Neal S. Pathophysiology - The Biologic Basis for Disease in Adults and Children, 7th Edition- 2014.

Thank You