Cardiovascular system block

Pathology team 431

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Thromboembolism (5th lecture)

Hemostasis Vs. Thrombosis

Physiological balance in the flowing state of the blood.

> maintenance of the blood in a fluid, clot-free state in normal vessels.

+ with the ability to induce rapid formation of a localized hemostatic plug (clot) when needed at a site of vascular injury

Pathological form of hemostasis, where a thrombus (clot) may be formed in an uninjured or relatively minor-injured vessel.

Note: [imp for forensics]
Thrombosis can only occur during life
Clotting can also occur after death or in a test tube

Hypercoagulability:

A pathological thickening of the blood due to an alteration in the coagulation pathways

Predisposes or promotes thrombus formation

Causes:

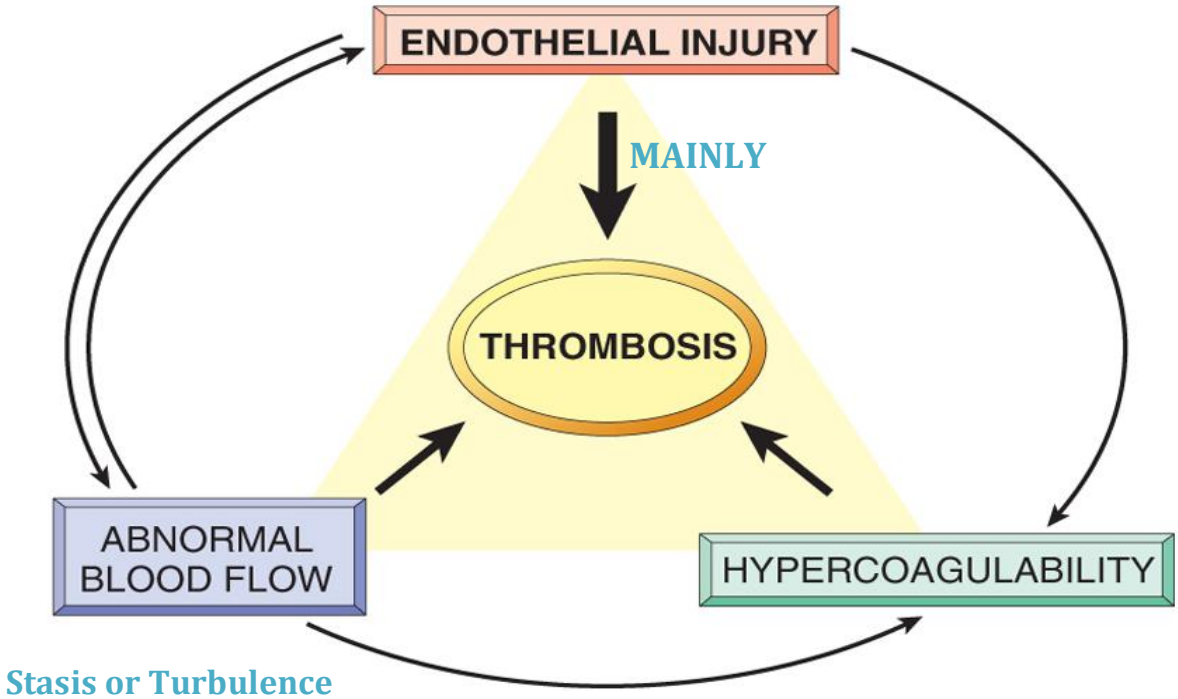
1. Primary (Genetic)
   – Common
   Mutation in factor V gene (factor V Leiden)
   Mutation in prothrombin gene
   – Rare
   Protein C deficiency (Protein C is a major component in anticoagulation)
   Protein S deficiency (it functions as a cofactor to Protein C)
   – Very rare
   Fibrinolysis defects

2. Secondary (Acquired)

–High risk for thrombosis
Prolonged bed rest or immobilization
Myocardial infarction
Atrial fibrillation
Tissue damage (surgery, fracture,burns)
Cancer
Prosthetic cardiac valves
Disseminated intravascular coagulation
Heparin-induced thrombocytopenia
Anti-phospholipid antibody syndrome

– Lower risk for thrombosis
Cardiomyopathy
Nephrotic syndrome
Hyperestrogenic states (pregnancy)
Oral contraceptive use
Sickle cell anemia
Smoking

Causes of Thrombus Formation:
Virchow's Triad: may occur collectively or individually



Both hemostasis and thrombosis involve three **Structural and Molecular Components:**

–vascular wall
–platelets a defect in any will predispose to thrombus formation
–coagulation cascade

The Vascular Wall:

Physiological: {balance between procoagulant and anti-coagulant molecules}

Intact endothelial cells maintain liquid blood flow by actively:

- inhibiting platelet adherence
- preventing coagulation factor activation
- lysing blood clots that often form

Loss of endothelial integrity exposes underlying vWF and basement membrane collagen → endothelial cell stimulation to express procoagulant proteins (e.g., tissue factor) → local platelet aggregation & thrombus formation

Pathological: {balance between the opposing molecules is affected}

Dysfunctional endothelial cells can produce either more pro-coagulant factors (e.g., platelet adhesion molecules, tissue factor) or may synthesize less anticoagulant effectors (e.g., thrombomodulin, PGI_2, t-PA' Tissue plasminogen activator')

Endothelial **dysfunction** can be induced by a wide variety of insults:

- Hypertension
- turbulent blood flow
- bacterial endotoxins
- radiation injury
- metabolic abnormalities such as homocystinemia or hypercholesterolemia, and toxins absorbed from cigarette smoke

Platelets:

Function in maintaining the integrity of the vascular endothelium via endothelial repair

Production of PDGF (platelet drive growth factor)

Formation of the platelet plug

Promote the coagulation cascade through the platelet phospholipid complex (that provide an important surface for coagulation-protein activation)

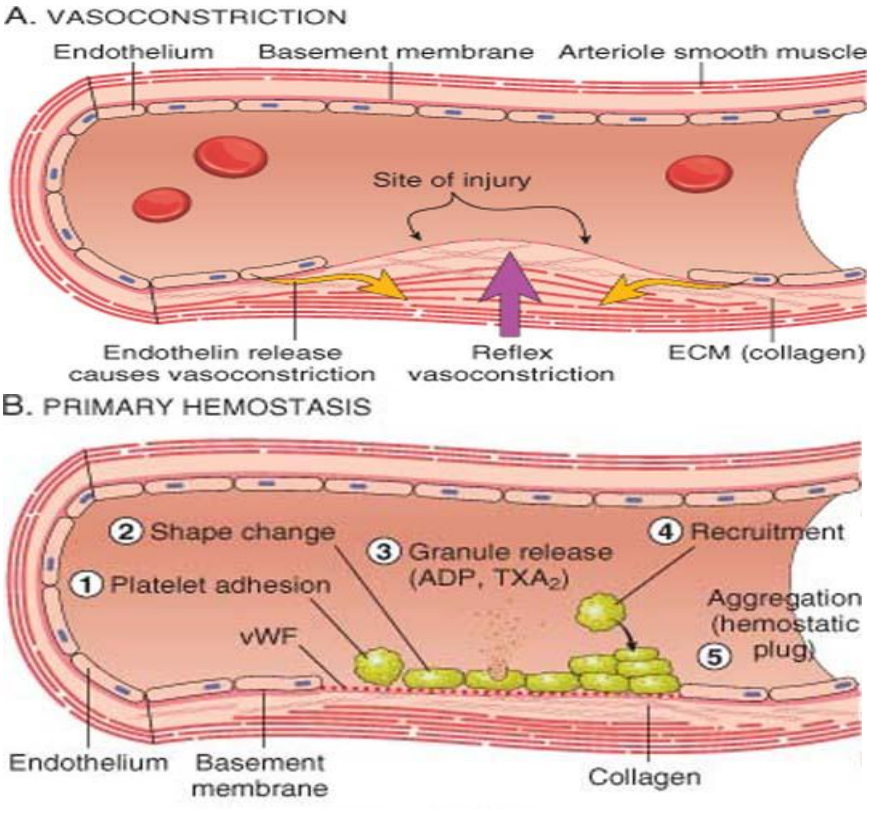
Coagulation Factors:

Coagulation occurs via the sequential enzymatic conversion of a cascade of circulating and locally synthesized proteins

Tissue factor elaborated at sites of injury is the most important initiator of the coagulation cascade

At the final stage of coagulation, **thrombin converts fibrinogen into insoluble fibrin**, which forms the definitive hemostatic plug

Steps of Thrombus Formation:



Initial response is a transient **vasoconstriction** to prevent blood loss

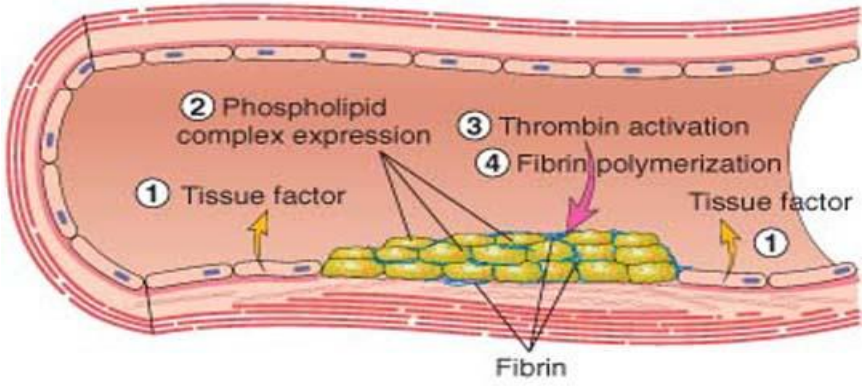
Platelets adherance to exposed extracellular matrix (ECM) by binding to von Willebrand factor (vWF)

Platelet activation, change in shape and granule release.

Released adenosine diphosphate (ADP) and thromboxane A_2 (TXA_2) lead to further **platelet aggregation** (via binding of fibrinogen to platelet GpIIb-IIIa receptors)

Formation of the primary hemostatic plug.

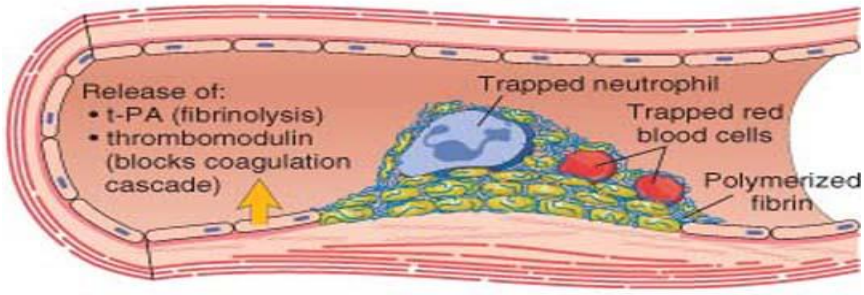
C. SECONDARY HEMOSTASIS



Local activation of the **coagulation cascade** (involving tissue factor and platelet phospholipids)

Fibrin polymerization, "cementing" the platelets into a definitive **secondary hemostatic plug**

D. THROMBUS AND ANTITHROMBOTIC EVENTS

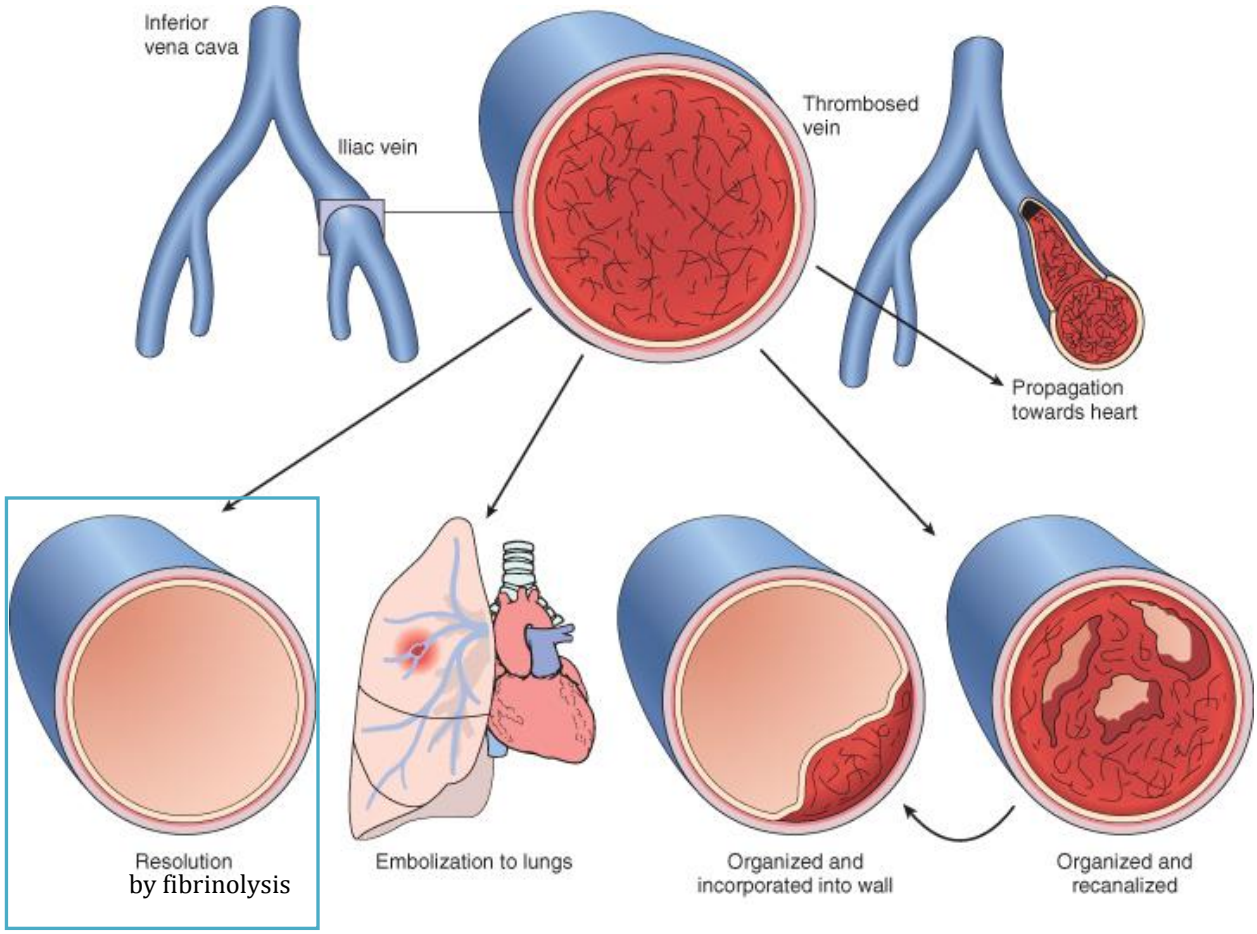


Limiting the hemostatic process to the site of injury by:

Counter-regulatory mechanisms; such as release of:

- t-PA (tissue plasminogen activator) a fibrinolytic product
- thrombomodulin, which interferes with the coagulation cascade

Fate of the Thrombus:



Thrombi are focally attached to the underlying vascular surface. When the attachment is lost they become emboli.

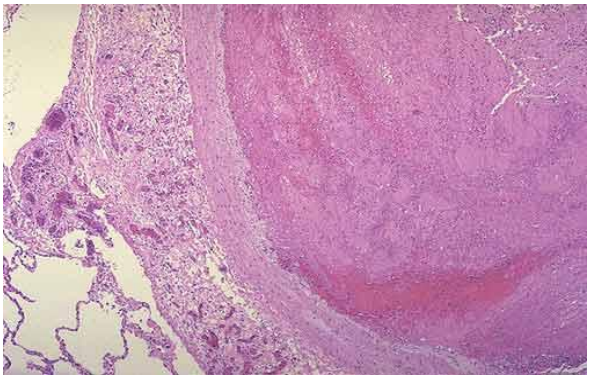
Thrombi often have grossly and microscopically apparent laminations called lines of Zahn

These represent pale platelet and fibrin deposits alternating with darker red cell–rich layers.
Such laminations signify that a thrombus has formed in flowing blood → indicate ante mortem thrombosis

Thrombi on heart valves are called vegetations

Postmortem clots are different in that they:

- Have an upper yellow and gelatinous portion. Described as "chicken fat"
- Have a dark red dependent portion where red cells have settled by gravity
- Are usually not attached to the underlying wall



Arterial Thrombi	Venous Thrombi
• **frequently occlusive (more dangerous)** • also called cardiac thrombi • **usually begin at sites of turbulence or endothelial injury** • the most common sites in decreasing order of frequency are: Coronary Cerebral Femoral • Although these are usually superimposed on a ruptured atherosclerotic plaque, other vascular injuries (vasculitis, trauma) may be the underlying cause.	• almost invariably occlusive • also called **phlebothrombosis** • characteristically occur at sites of stasis **(when blood flow is sluggish)** • they tend to contain more enmeshed red cells (and relatively few platelets) and are therefore **known as red/ stasis thrombi** • **more pron to embolus formation** • The veins of the **lower extremities** are most commonly involved (90% of cases)

Disseminated Intravascular Coagulation (DIC):

Also called consumption coagulopathy

Considered a pathological emergency!

Sudden or insidious onset of numerous widespread fibrin thrombi in the microcirculation (capillaries) found throughout the whole body.

Can cause **diffuse circulatory insufficiency**, particularly in the brain, lungs, heart, and kidneys

It can evolve into a bleeding catastrophe:

- The abnormal formation of these thrombi results in consumption of most if not all available platelet and coagulation protein (hence the synonym consumption coagulopathy)
- When these factors are needed at sites of injury they are insufficient and result in bleeding
- At the same time, fibrinolytic mechanisms are activated

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

Deep venous thrombosis (DVT):

Occurs in the larger leg veins, at or above the knee (e.g., popliteal, femoral, and iliac veins)

More often embolize to the lungs and give rise to pulmonary infarction

Although they can cause local pain and edema, the venous obstruction from DVTs can be rapidly offset (resolved) by collateral channels*.

Consequently, DVTs are asymptomatic in 50% cases

*collateral channels: secondary channels that form after obstruction in order to maintain the flow of blood

Predisposing factors:

(similar to those of the hypercoagulable status)

–Bed rest and immobilization

–Congestive heart failure (a cause of impaired venous return)

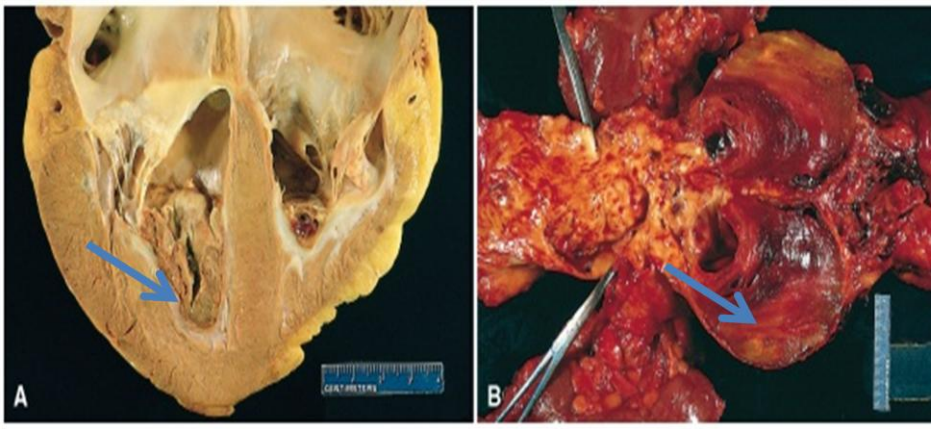
–Trauma, surgery, and burns (immobilization and are also associated with vascular insults)

–Pregnancy:

- late pregnancy and the postpartum period are also associated with systemic hypercoagulability

–Tumors

–Advanced age



A, Mural thrombi, Thrombus in the left and right ventricular apices, overlying white fibrous scar.

B, Laminated thrombus in a dilated abdominal aortic aneurysm.
Numerous friable mural thrombi are also superimposed on advanced atherosclerotic lesions of the more proximal aorta.

Embolism:

Is a detached intravascular solid (fat, foreign body-bullet, atherosclerotic debris-cholesterol, bone marrow or tumor fragments), liquid (amniotic fluid), or gaseous (air of nitrogen droplets) mass that is carried by the blood to a **site distant** from its point of origin.

99% of cases are thromboemboli (a dislodged thrombus or a part of one)

Fat Embolism:

Microscopic fat globules

May be found in the circulation after **fractures of long bones** (which contain **fatty marrow**), burns or after soft-tissue trauma

Fat embolism syndrome is characterized by:

- pulmonary insufficiency
- neurologic symptoms
- anemia
- thrombocytopenia

Although fat and marrow embolism occurs in some 90% of individuals with severe skeletal injuries, fewer than 10% of such patients show any clinical findings.

Amniotic embolism:

A **grave** case but fortunately uncommon

Is a **complication of labour** and the immediate postpartum period

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**

Onset: sudden severe dyspnea, cyanosis, and hypotensive shock, followed by seizures and coma

If the patient survives the initial crisis, the patient may develop:

–pulmonary edema and diffuse alveolar damage

–**disseminated intravascular coagulation (DIC),** due to release of thrombogenic substances from amniotic fluid

Air embolism:

Enters the circulation during obstetric procedures or as a consequence of chest wall injury

Generally, more than 100 mL of air are required to produce a clinical effect

Decompression sickness:

occurs when individuals are exposed to **sudden changes in atmospheric pressure** (e.g. Scuba and deep-sea divers are at risk

When air is breathed at high pressure during dive→ increased amounts of gas (particularly nitrogen) become dissolved in the blood and tissues → if the diver then ascends (depressurizes) too rapidly → the **nitrogen expands** in the tissues and bubbles out of solution in the blood → forms gas embolus

can induce focal ischemia in a number of tissues:

–brain and heart
–skeletal muscles , causing pain (the bends)
–lungs, causing respiratory distress, (the chokes)

Pulmonary Thromboembolism: [Venous]

In more than 95% of cases, venous emboli originate from deep leg vein thrombi above the level of the knee → travel via progressively larger channels and pass to the right side of the heart → entering the pulmonary vasculature

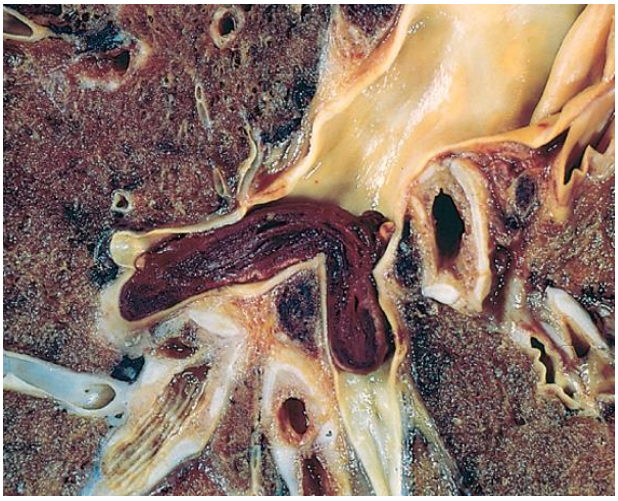
Depending on the size of the embolus, it may:

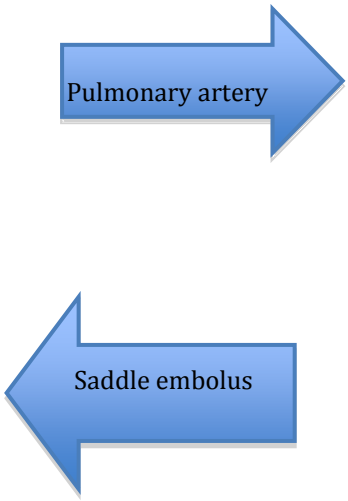
–occlude the main pulmonary artery

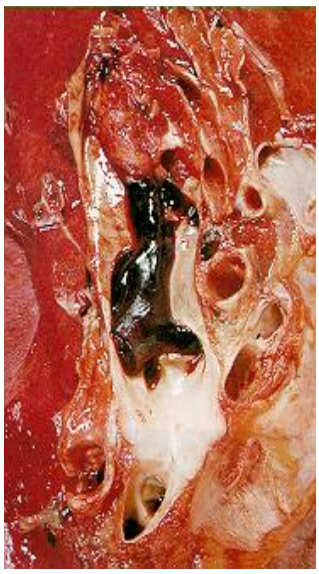
–impact across the bifurcation (*saddle embolus*)

–pass out into the smaller, branching arterioles

In general, the patient who has had one pulmonary embolus is at high risk of having more







Consequences:

60% to 80% are clinically silent because they are small (they eventually become organized and become incorporated into vascular wall)

IF 60% or more of the pulmonary circulation is obstructed with emboli, one of these may occur:

–sudden death

–right ventricular failure (*cor pulmonale*)

–cardiovascular collapse

Embolic obstruction of medium-sized arteries can cause pulmonary hemorrhage but usually **not** pulmonary infarction because the lung has a dual blood supply and the intact bronchial arterial circulation continues to supply blood to the area

Embolic obstruction of small end-arteriolar pulmonary branches usually does result in associated infarction

Multiple emboli occurring over a period of time may cause pulmonary hypertension resulting in right ventricular failure

Paradoxical embolism:

Rarely! And only when the interatrial or interventricular septa are defected, the embolus may pass through and enter the systemic circulation.

Systemic Thromboembolism: [arterial]

Most (80%) arise **from intra-cardiac mural thrombi**:

- two-thirds of which are associated with **left ventricular wall infarcts**
- quarter with dilated left atria (e.g., secondary to mitral valve disease)

The remainder originate from:

- aortic aneurysms
- thrombi on ulcerated atherosclerotic plaques
- fragmentation of valvular vegetations

The **major sites** for **arteriolar embolization:**

- the lower extremities (75%)
- the brain (10%),
- the intestines, kidneys, and spleen (affected to a lesser extent)

Thrombi on Heart Valves:

large **thrombotic masses** on heart valves are called **vegetations**

Usually result from bacterial or fungal blood-bourne infections (**infective endocarditis**)

Nonbacterial thrombotic endocarditis:
Sterile vegetation can also develop on non-infected valves in patients with hypercoagulable states

Less commonly, noninfective, **verrucous (Libman-Sacks) endocarditis** attributable to elevated levels of circulating immune complexes may occur in patients with systemic lupus erythematosus (SLE)

Summary

Thrombosis :

Thrombus development depends on the relative contribution of the components of Virchow's triad:
1- Endothelial injury (e.g., by toxins, hypertension, inflammation, or metabolic products)
2- Abnormal blood flow - stasis or turbulence (e.g., due to aneurysms, atherosclerotic plaque)
3- Hypercoagulability, which can be either primary (e.g., factor V Leiden, increased prothrombin synthesis, antithrombin III deficiency) or secondary (e.g., bedrest, tissue damage, malignancy). Thrombi may propagate, resolve, become organized, or embolize.Thrombosis causes tissue injury by local vascular occlusion or by distal embolization.

Embolism :

- An embolus is any detached solid, liquid, or gaseous mass carried by the blood to a site distant from its origin; the vast majority are part of a dislodged thrombus.
- Pulmonary emboli derive primarily from lower extremity deep vein thrombosis; their effect (sudden death, right heart failure, pulmonary hemorrhage, or infarction) depends on the size of the embolus.
- Systemic emboli derive primarily from cardiac mural or valvular thrombi, aortic aneurysms, or atherosclerotic plaque; whether an embolus causes tissue infarction depends on the site of embolization and collateral circulation.

Questions

1-A 25-year-old woman has had multiple episodes of deep venous thrombosis during the past 10 years and one episode of pulmonary thromboembolism during the past year. Prothrombin time, partial thromboplastin time, platelet count, and platelet function studies are all normal. Which of the following risk factors has most likely contributed to the patient's condition?

A) Factor V mutation
B) Antithrombin III deficiency
C) Mutation in protein C
D) Hyperhomocysteinemia
E) Smoking cigarettes

2- Which of the following is the main cause of thrombosis?

A) Abnormal blood flow
B) hypercoagulability
C)Endothelial injury

3-what is the main characteristic of ante mortem clot ?
A) Chicken fat apparent
B) not attached to the underlying wall
C)lines of zahn
D)b & c

Answers: A, C, C