Hemodynamic Disorders IV

Thrombosis

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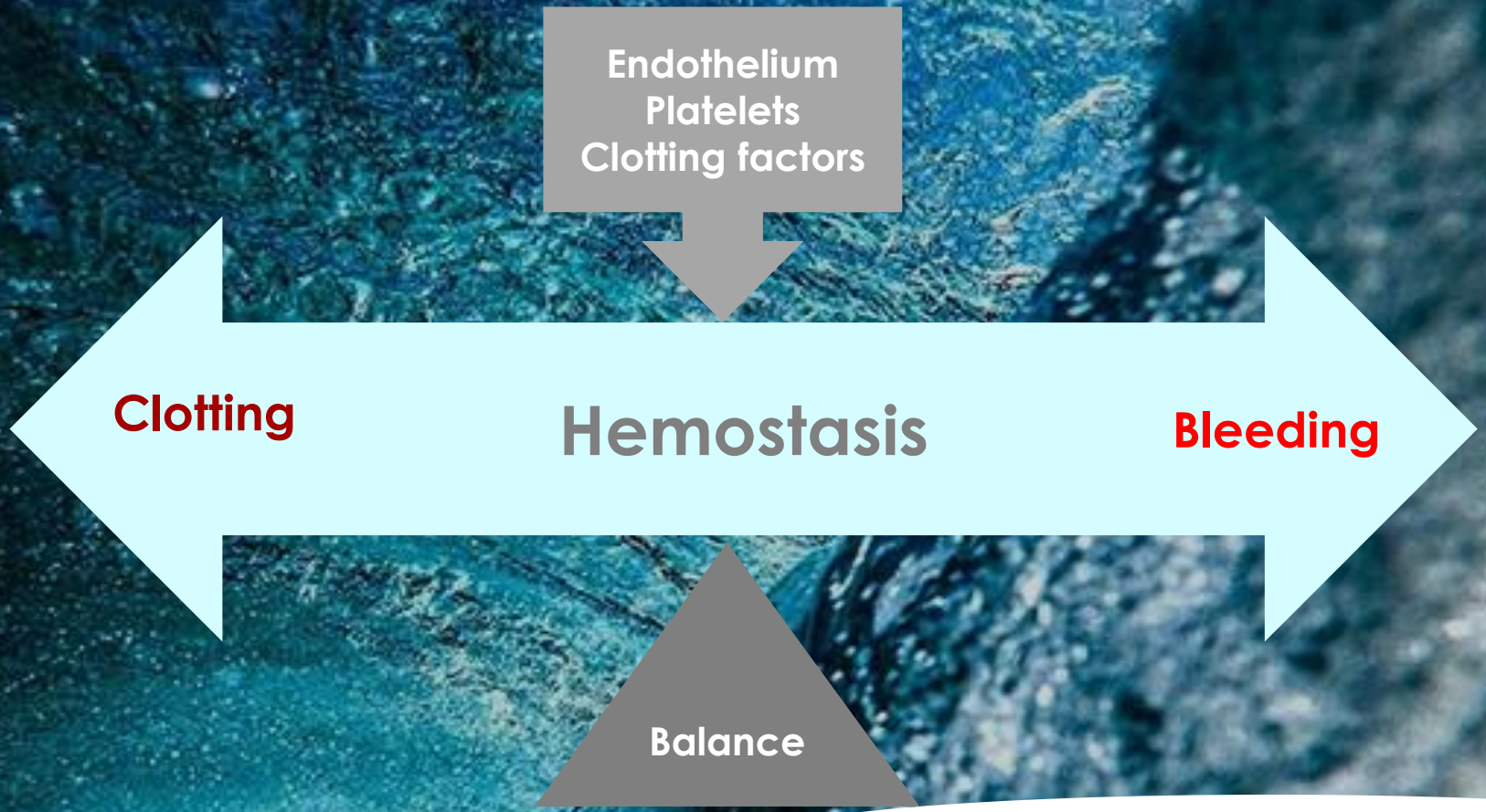


Platelets, clotting factors and endothelium act together to maintain the balance which is the process of **hemostasis**.
Abnormal clotting happens when the balance is shifted to the thrombosis side.

Thrombosis

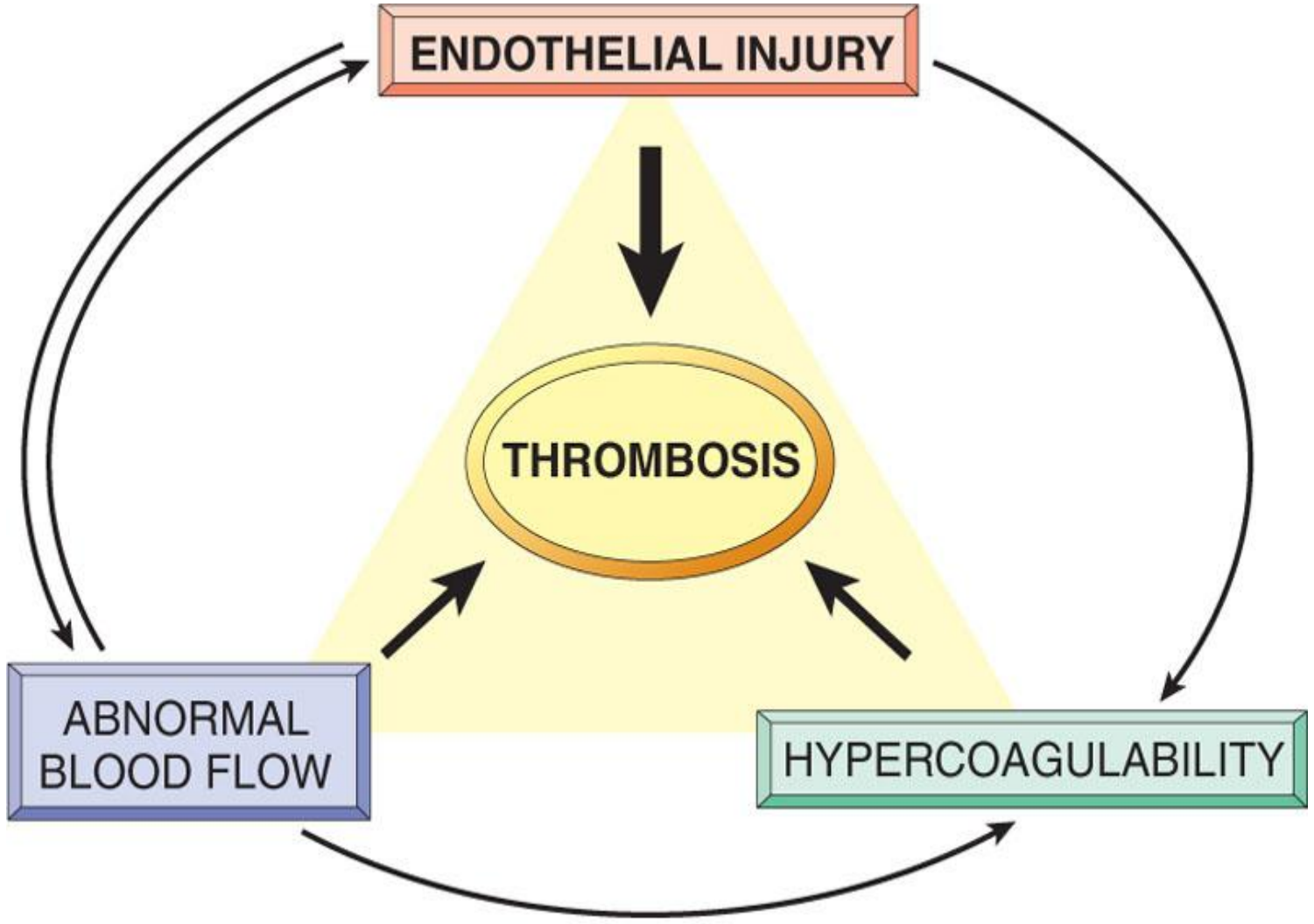
- The primary abnormalities that lead to intravascular thrombosis:

(1) Endothelial injury

(2) Stasis or turbulent blood flow
(3) Hypercoagulability of the blood

Called → "Virchow triad"

- Underlies the most serious and common forms of cardiovascular disease.



Endothelial Injury

- Endothelial injury leading to platelet activation underlies thrombus formation in the heart & the arterial circulation, where the high rates of blood flow impede clot
- Cardiac and arterial clots are typically rich in platelets.
- platelet adherence and activation is a necessary for thrombus formation under high shear stress (arteries).
- **Which highlights the importance of aspirin** and other platelet inhibitors in **coronary artery disease and acute myocardial infarction.**

(1)Severe Endothelial injury triggers thrombosis by **exposed vWF tissue factor (severe injury), or ..**

(2) inflammation & other noxious stimuli endothelial **activation or dysfunction.**

Endothelial dysfunction (activation)

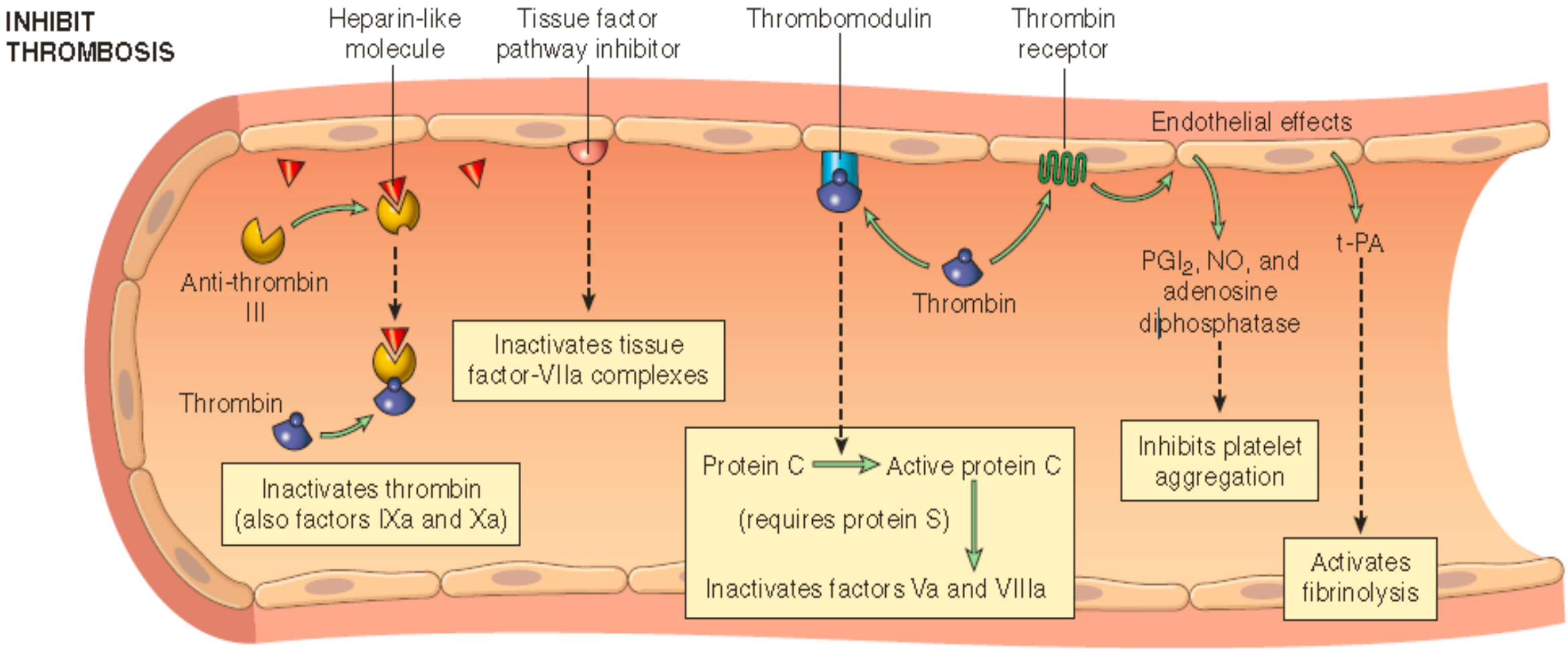
- An important role in triggering **arterial** thrombotic events.
- Produced by **physical injury, infectious agents, abnormal blood flow, inflammatory mediators, metabolic abnormalities (**hypercholesterolemia or homocystinemia), **and cigarette smoke toxins.**
- It shifts the pattern of gene expression in endothelium to: **"prothrombotic":**

1. Procoagulant changes:

+ Cytokines downregulate the expression of thrombomodulin →activation of thrombin → stimulate platelets and augment inflammation (PARs).

+ inflamed endothelium downregulates the expression anticoagulants (protein C & tissue factor protein inhibitor).

2. Anti-fibrinolytic effects: secrete **Plasminogen activator inhibitors (PAI),** which downregulate the expression of t-PA.

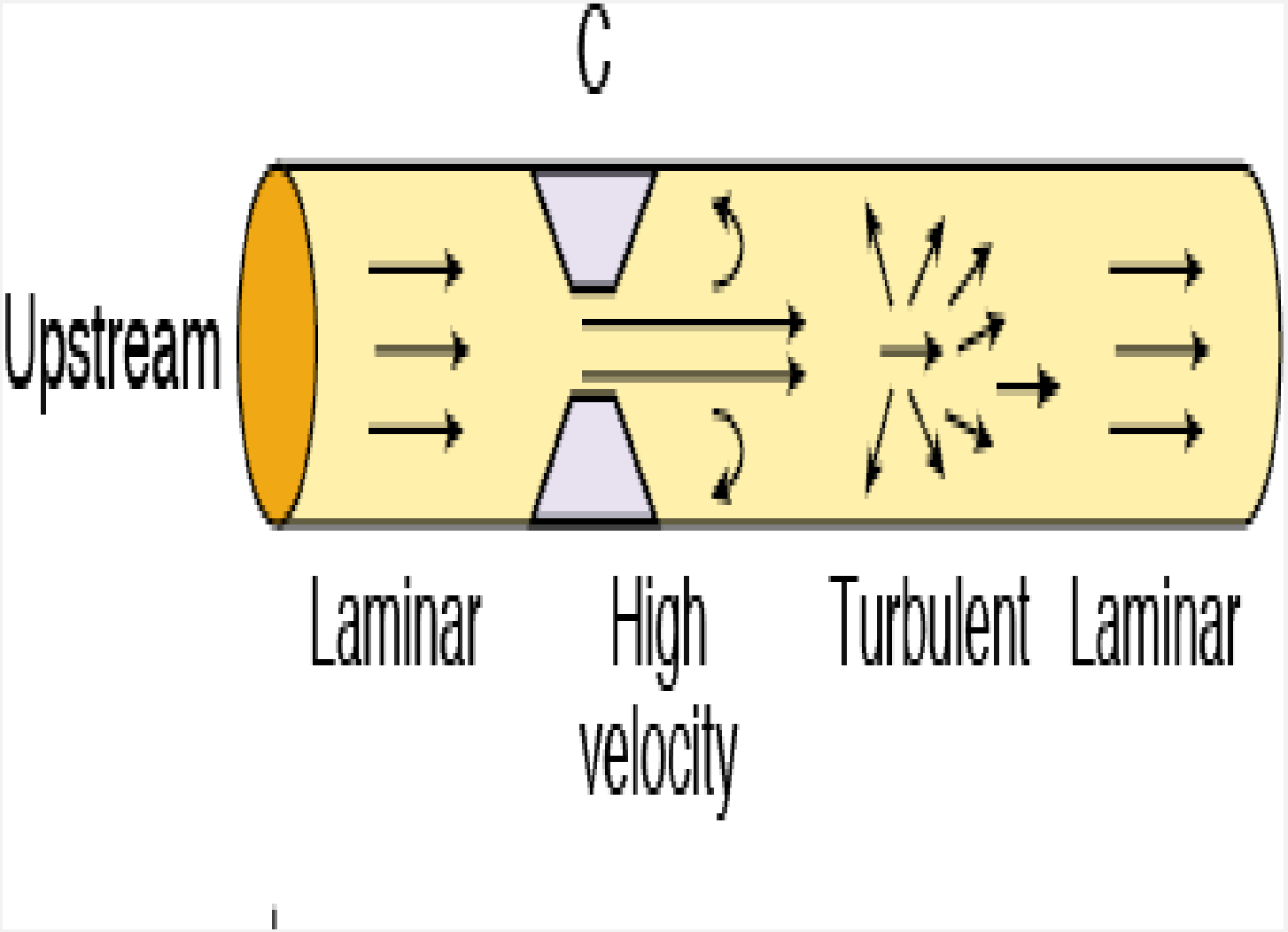

INHIBIT THROMBOSIS
Heparin-like molecule
Tissue factor pathway inhibitor
Thrombomodulin
Thrombin receptor
Endothelial effects
Anti-thrombin III
Thrombin
Inactivates tissue factor-VIIa complexes
Thrombin
Inactivates thrombin (also factors IXa and Xa)
Protein C
Active protein C
(requires protein S)
Inactivates factors Va and VIIIa
Thrombin
PGI2, NO, and adenosine diphosphatase
Inhibits platelet aggregation
t-PA
Activates fibrinolysis

Abnormal Blood Flow

- **Normal <u>laminar</u> blood** flow: platelets (& other blood cells) found mainly in the center of the vessel lumen, separated from the endothelium by a slower-moving layer of plasma.

- **Turbulence (chaotic blood flow)** contributes to **arterial and cardiac** thrombosis, causing endothelial injury or dysfunction, also forming countercurrents and local pockets of stasis.

- **Stasis** is a major factor in the development of **venous thrombi**.



How stasis and turbulence cause thrombosis ?

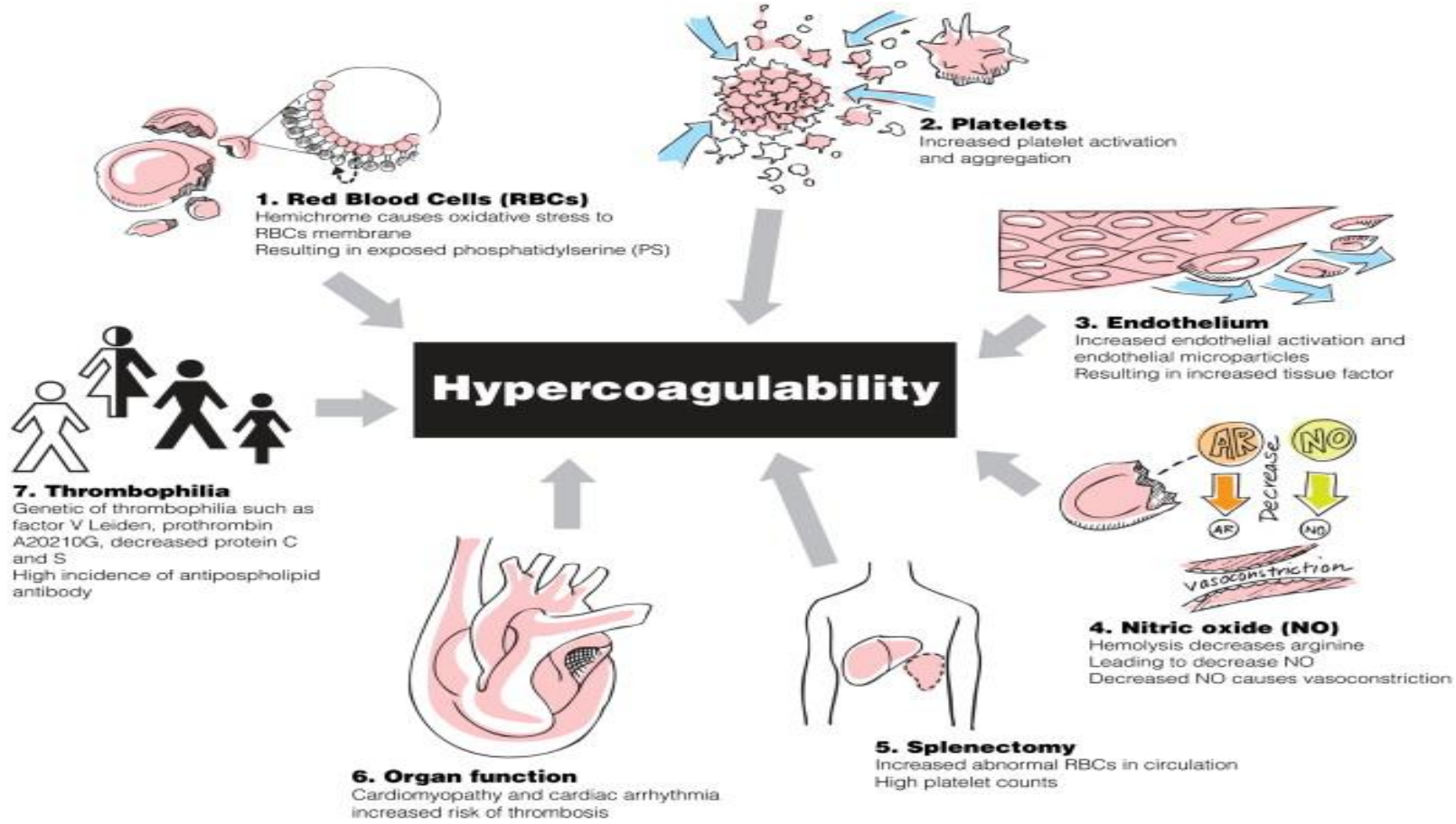
- Both promote endothelium activation & enhanced procoagulant activity.
- Stasis Allows platelets & leukocytes to come into contact with the endothelium when the flow is sluggish (slow & irregular)
- Stasis slows the washout of activated clotting factors & impedes the inflow of clotting factor inhibitors.
- Clinical Examples:

✓ Ulcerated atherosclerosis expose subendothelial ECM & cause turbulence.

✓ Abnormal aortic and arterial dilations (called aneurysms) create local stasis → fertile sites for thrombosis.

✓ Acute myocardial infarction → focally noncontractile myocardium → local blood stasis →cardiac mural thrombi.

✓ Deformed red cells in sickle cell anemia cause vascular occlusions → resultant stasis → thrombosis



Hypercoagulability

An abnormally high tendency of the blood to clot, and is typically caused by alterations in coagulation factors.

Primary (Genetic)
Common (>1% of the Population)
Factor V mutation (G1691A mutation; factor V Leiden)
Prothrombin mutation (G20210A variant)
Increased levels of factor VIII, IX, or XI or fibrinogen
Rare
Anti-thrombin III deficiency
Protein C deficiency
Protein S deficiency
Very Rare
Fibrinolysis defects
Homozygous homocystinuria (deficiency of cystathione β-synthetase)
Secondary (Acquired)
High Risk for Thrombosis
Prolonged bed rest or immobilization
Myocardial infarction
Atrial fibrillation
Tissue injury (surgery, fracture, burn)
Cancer
Prosthetic cardiac valves
Disseminated intravascular coagulation
Heparin-induced thrombocytopenia
Anti-phospholipid antibody syndrome
Lower Risk for Thrombosis
Cardiomyopathy
Nephrotic syndrome
Hyperestrogenic states (pregnancy and postpartum)
Oral contraceptive use
Sickle cell anemia
Smoking

- Hypercoagulability:

+ infrequently contributes to arterial or intracardiac thrombosis.

+ important risk factor for venous thrombosis.

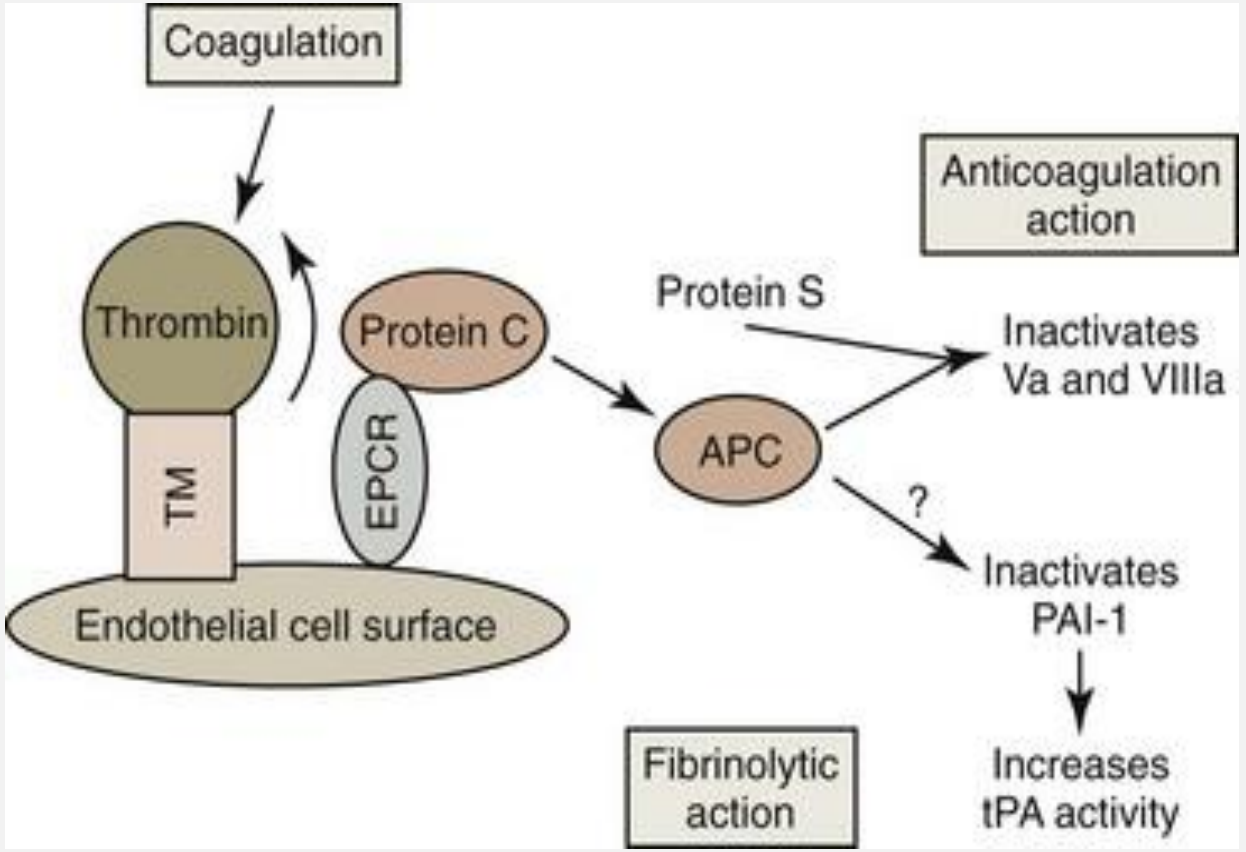
The alterations of the coagulation pathways that predispose to thrombosis are divided:

+ primary (genetic) disorders

+ secondary (acquired) disorders

Primary (inherited) hypercoagulability - factor V

- 2% to 15% of whites carry factor V mutation (called the Leiden mutation)
- In 60% of people with recurrent deep venous thrombosis.
- A mutation that renders factor V resistant to proteolysis of by protein C → an important anti-thrombotic counter-regulatory mechanism is lost.
- Heterozygotes → fivefold increased risk for venous thrombosis, while homozygotes having a 50-fold increased risk.



Primary (inherited) hypercoagulability, cont..

- Mutation of **prothrombin** gene is a fairly common (1%–2% of general population), results in increased prothrombin transcription.

- Elevated levels of **homocysteine** contribute to **arterial and venous** thrombosis, also the development of atherosclerosis. (thioester linkages between homocysteine metabolites and a variety of proteins, including **fibrinogen**)

- Less commonly, inherited deficiencies of **anti-coagulants (antithrombin III, protein C, or protein S)** ; affected patients typically present with venous thrombosis and recurrent thromboembolism in adolescence or in early adult life.

Secondary (acquired) hypercoagulability

(1) Prolonged bed rest or immobilization (reduce the milking action of leg muscles and → slow venous return)

(2) Cancer (procoagulant products (e.g., mucin from adenocarcinoma)

(3) Tissue damage (surgery, fracture, burns).

(4) Disseminated intravascular coagulation (DIC).

(5) Prosthetic cardiac valves .

(6) Heparin-induced thrombocytopenia (5% of patients treated with unfractionated heparin as anticoagulant, induces autoantibody against platelets membrane protein → activation, aggregation, and consumption (hence thrombocytopenia)

(7) Anti-phospholipid antibody syndrome (auto antibody against a plasma protein antigen, that is associated with prothrombin).

Morphology

- Thrombi develop anywhere :

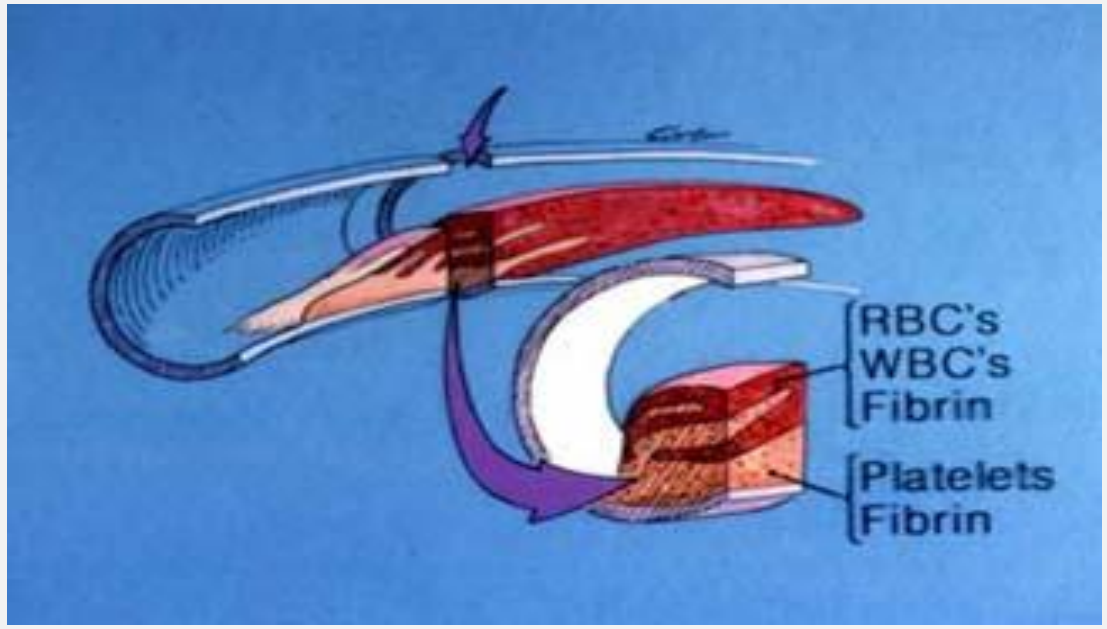
  +Arterial or cardiac thrombi: sites of endothelial injury or turbulence.

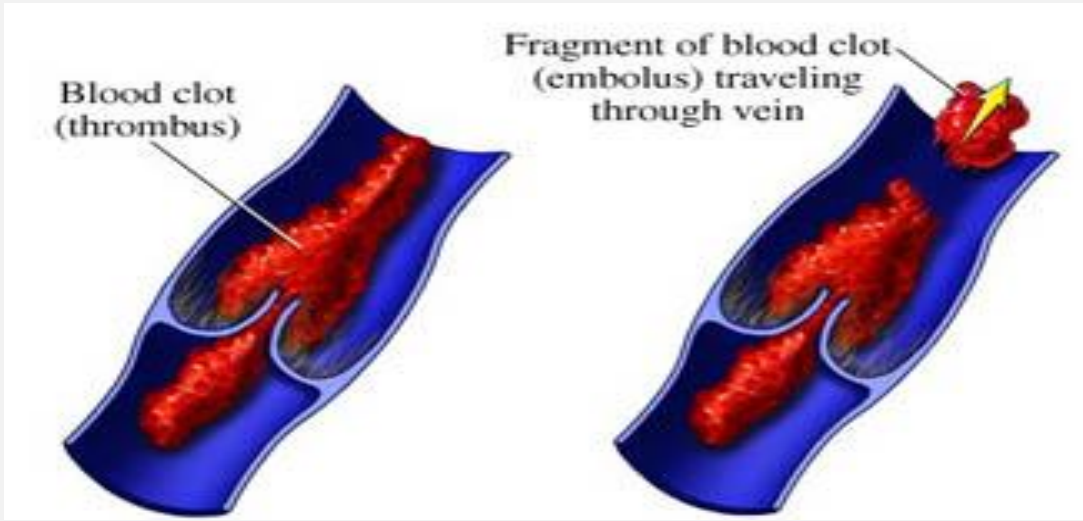
  +venous thrombi: sites of stasis.

- Thrombi are focally attached to the vascular surface and **tend to propagate (progressively spread) toward the heart**;

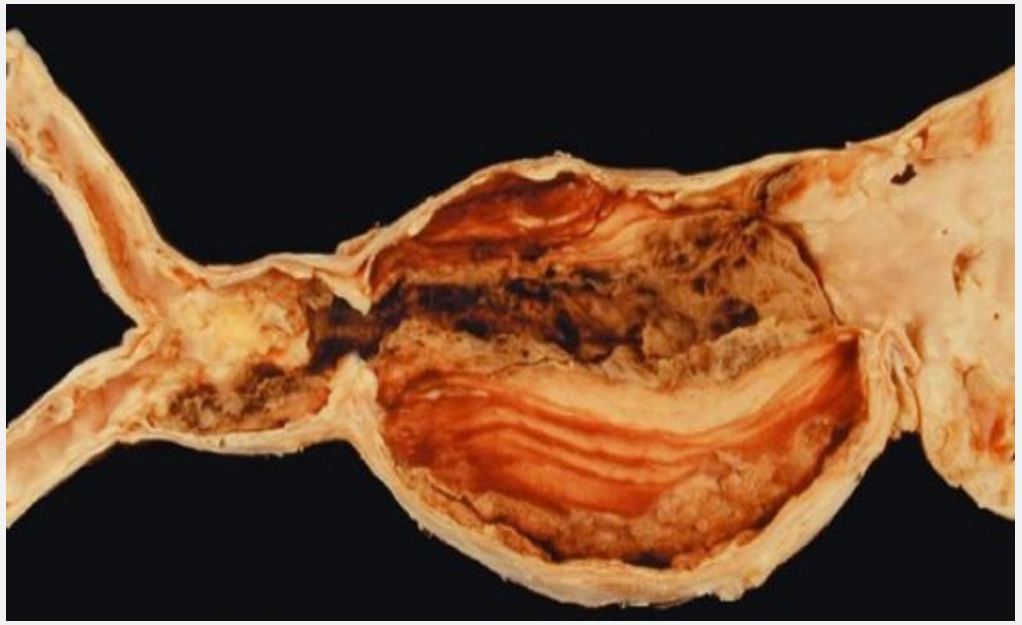
  +arterial thrombi grow in **a retrograde direction** from the point of attachment.
  +venous thrombi extend in **the direction of blood flow.**

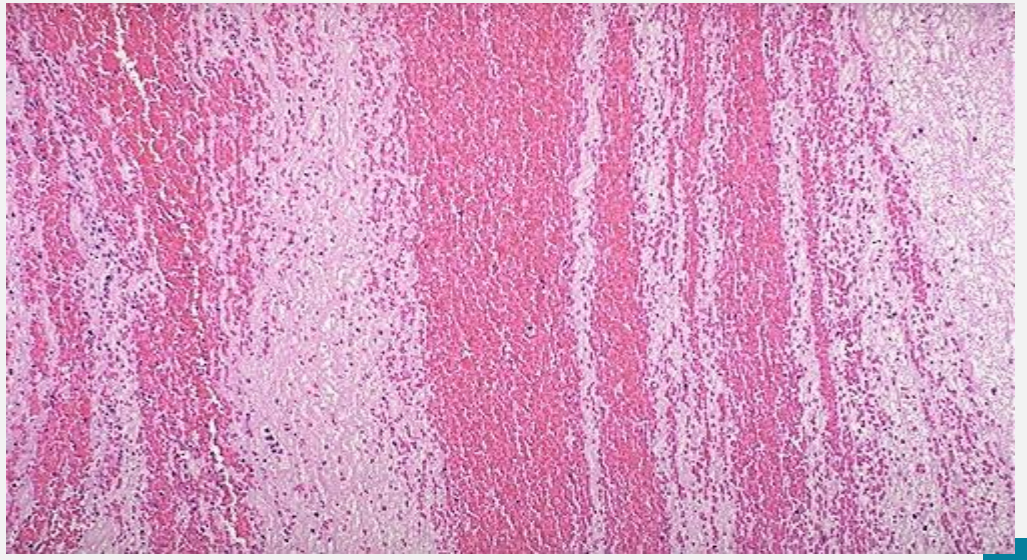
- The propagating portion of a thrombus is poorly attached → → prone to fragmentation and migration through the blood as an **embolus.**





- Thrombi have laminations called **lines of Zahn;** (grossly and microscopically)**.**
- Represent pale platelet and fibrin layers alternating with darker red cell–rich layers.
- only found in thrombi that form in **flowing blood;** usually distinguish antemortem thrombosis from the bland nonlaminated clots that form in the postmortem state.
- Thrombi in the "low-flow" venous system superficially resemble postmortem clots, **careful evaluation generally shows ill-defined laminations.**





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

- **cardiac mural thrombi:**

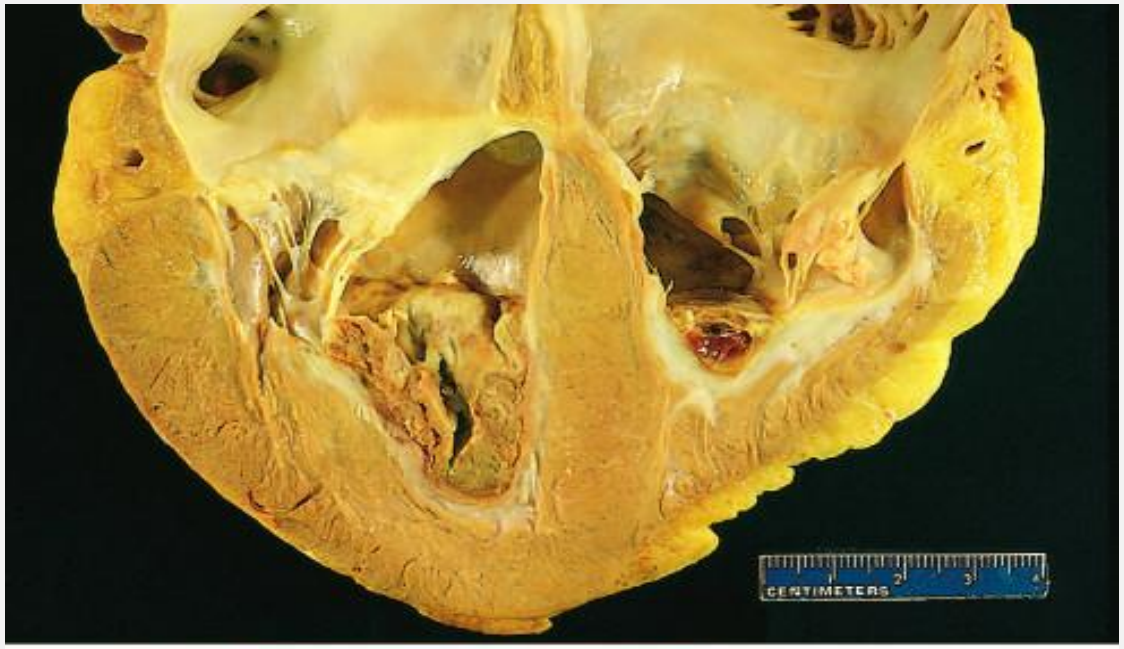
  + Abnormal myocardial contraction(arrhythmias, dilated cardiomyopathy, or myocardial infarction)

  + Endomyocardial injury (myocarditis, catheter trauma)

- **aortic thrombi**

  + ulcerated atherosclerotic plaques.

  + aneurysmal dilation.



- **Arterial thrombi:**

+ frequently occlusive.

+ rich in platelets, develop by endothelial injury which lead to platelet activation.

+ usually superimposed on a ruptured atherosclerotic plaque.

+ Also vascular injuries (vasculitis, trauma)

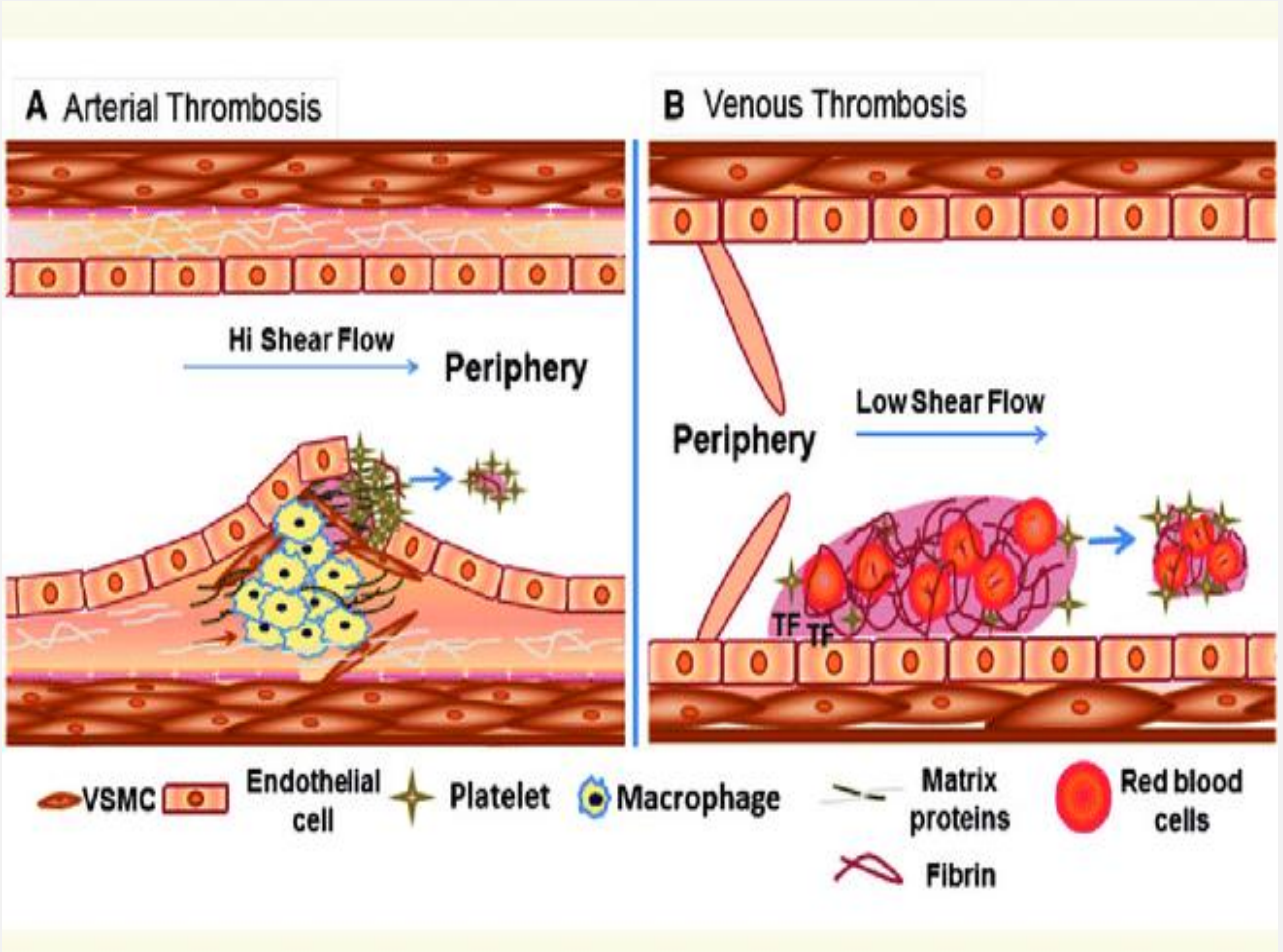
- **Venous thrombi (phlebothrombosis)**

+ almost invariably occlusive.

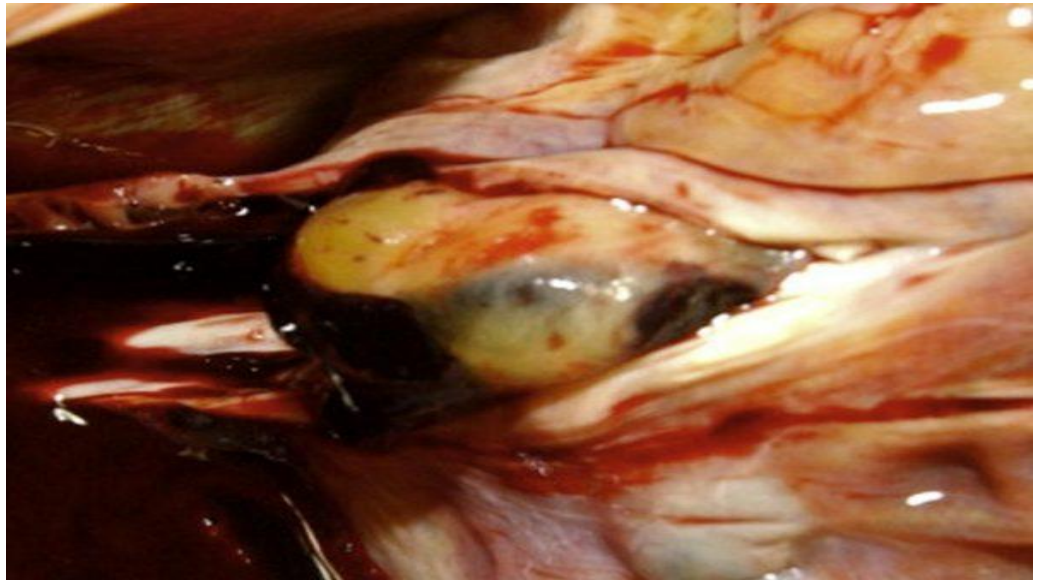
+ frequently propagate to heart (have long cast in lumen) → give rise to emboli.

+ rich in red cells, develop in sluggish venous circulation (**red, or stasis, thrombi)**

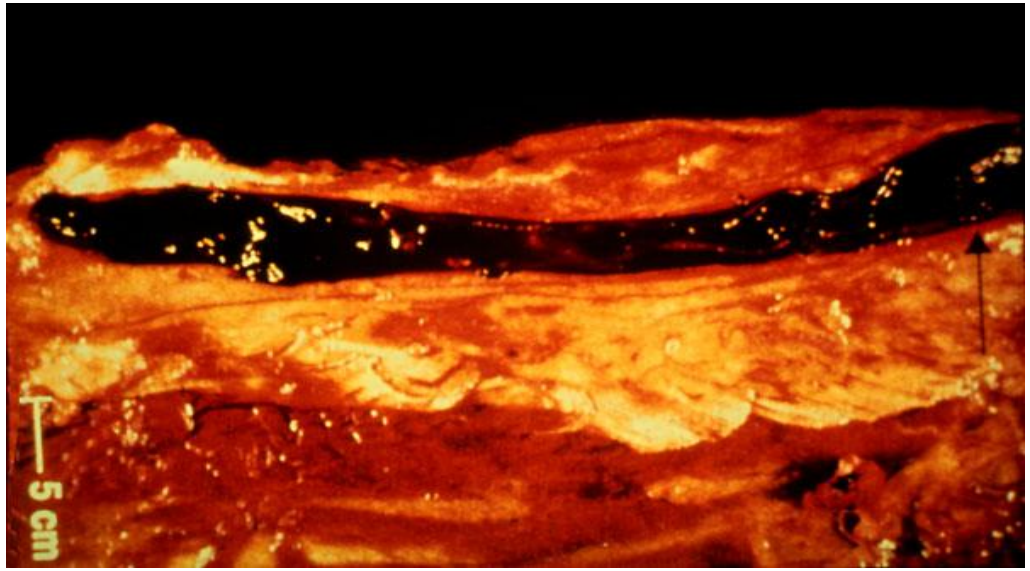
+ 90% veins of the lower extremities.

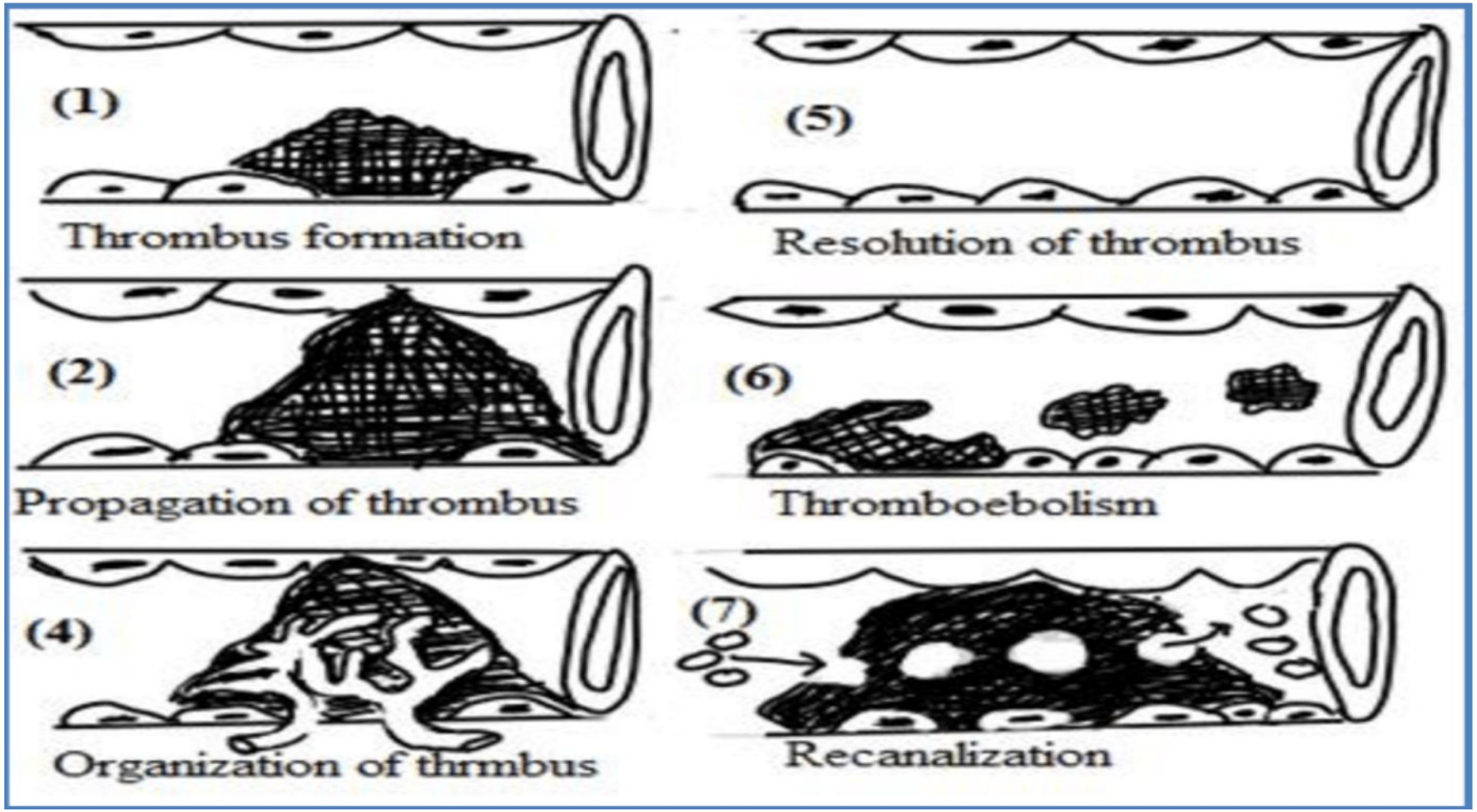


postmortem clots can sometimes be mistaken for venous thrombi: it is gelatinous & because of red cell settling they have a dark red dependent portion & a yellow "chicken fat" upper portion; they also are usually not attached to the underlying vessel wall.



red thrombi (venous): firm, focally attached to vessel, & they contain gray strands of deposited fibrin (lines of Zahn).





Fate of the Thrombus

Fate of the Thrombus

1• **Propagation:** enlarges through the accumulation of platelets & fibrin, increasing the odds of vascular occlusion or embolization.

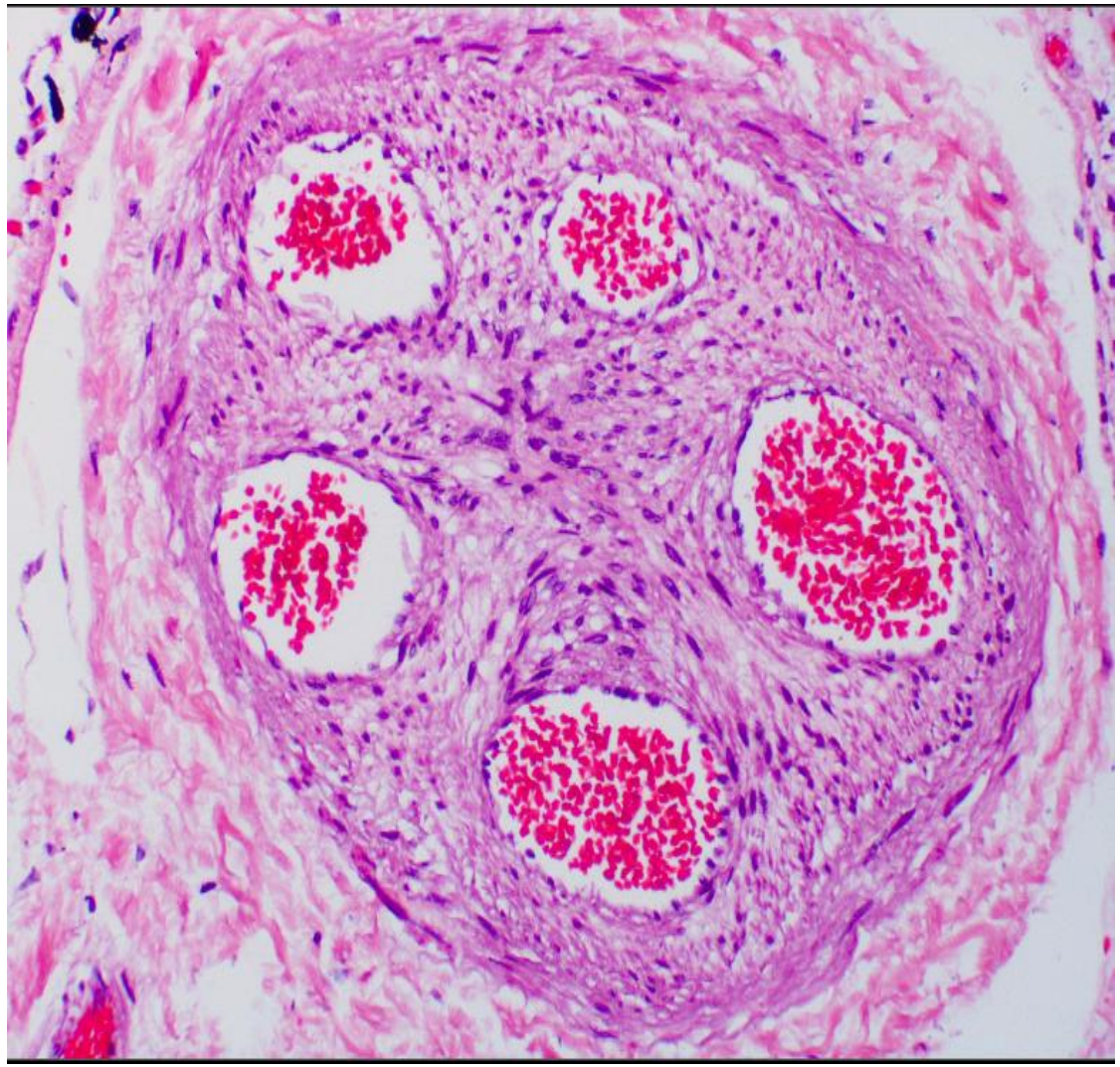
2• **Embolization:** Part or all of the thrombus is dislodged & transported elsewhere in the vasculature.

3• **Dissolution**. + In newly formed; fibrinolytic factors lead to its rapid shrinkage and complete dissolution.

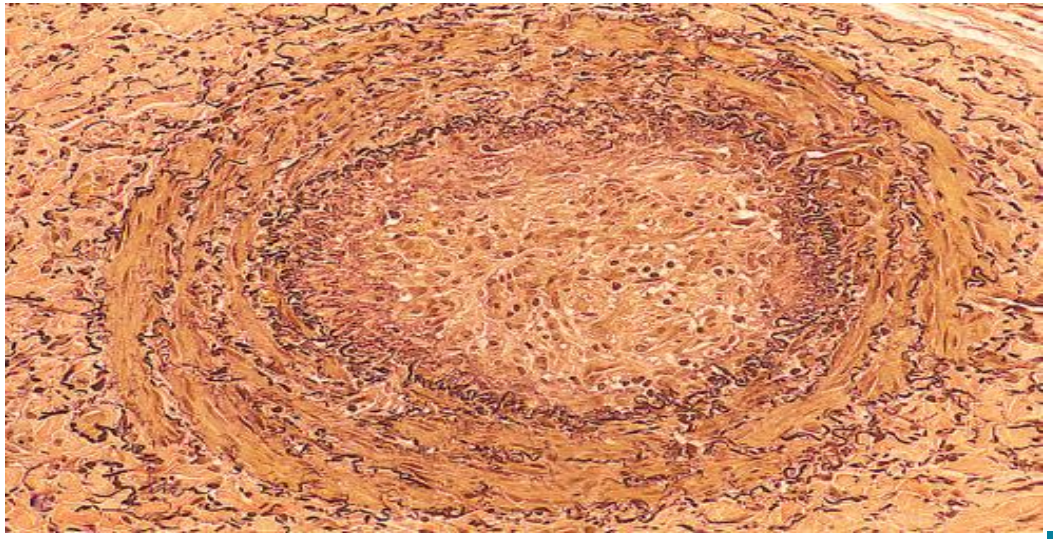
+ older thrombi; extensive fibrin deposition &polymerization make it more resistant to plasmin-induced proteolysis.

This acquisition of resistance to lysis has clinical significance, as therapeutic administration of fibrinolytic agents (like t-PA in the setting of acute coronary thrombosis) is not effective unless administered within a few hours of thrombus formation.

4• Organization and recanalization



- Older thrombi become organized: ingrowth of endothelial cells, smooth muscle cells, & fibroblasts.
- In time, capillary channels are formed reestablishing the continuity of the original lumen.
- sometimes convert a thrombus into a vascularized mass of connective tissue (remodeled vessel).



THANK YOU