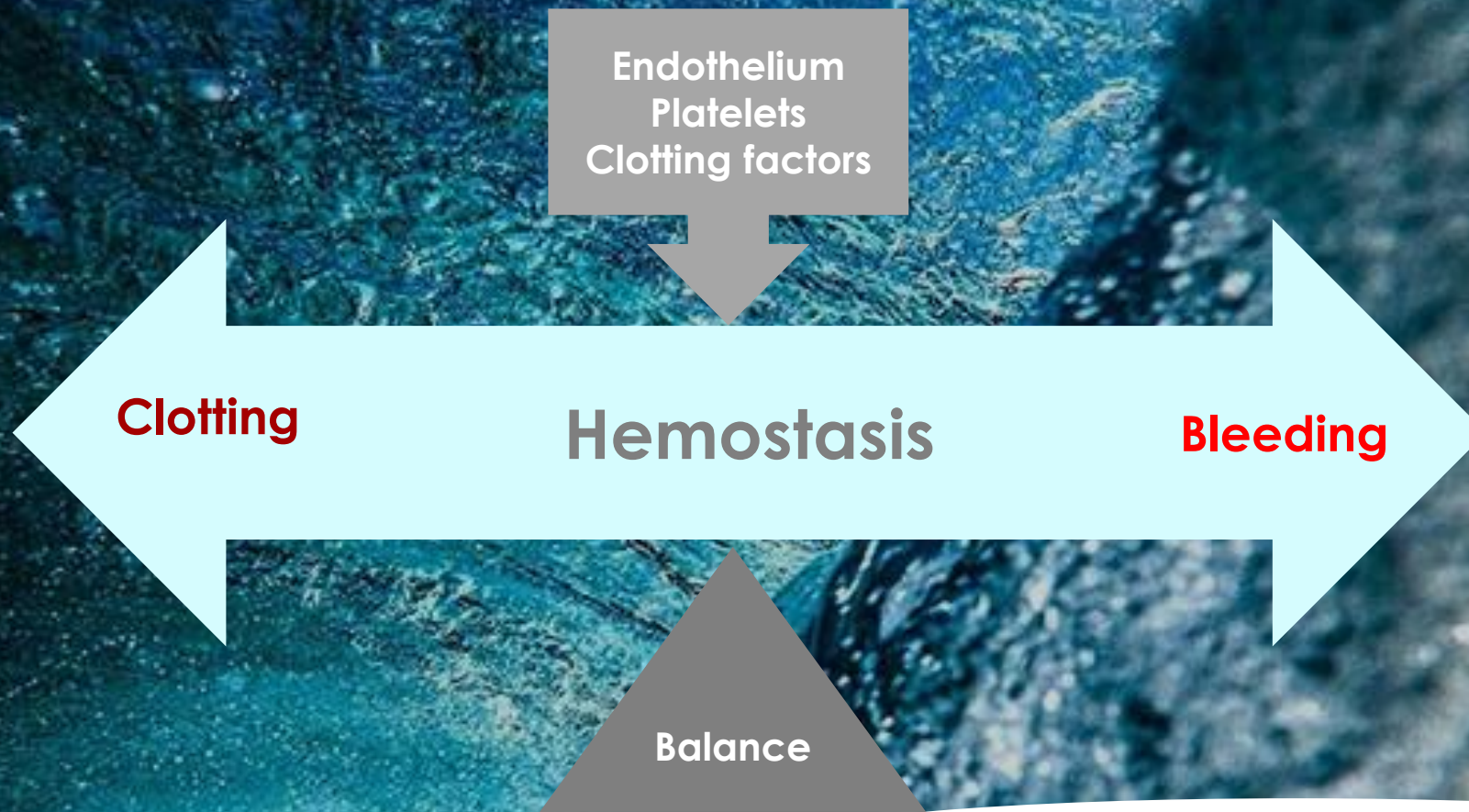




Hemodynamic Disorders III

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:

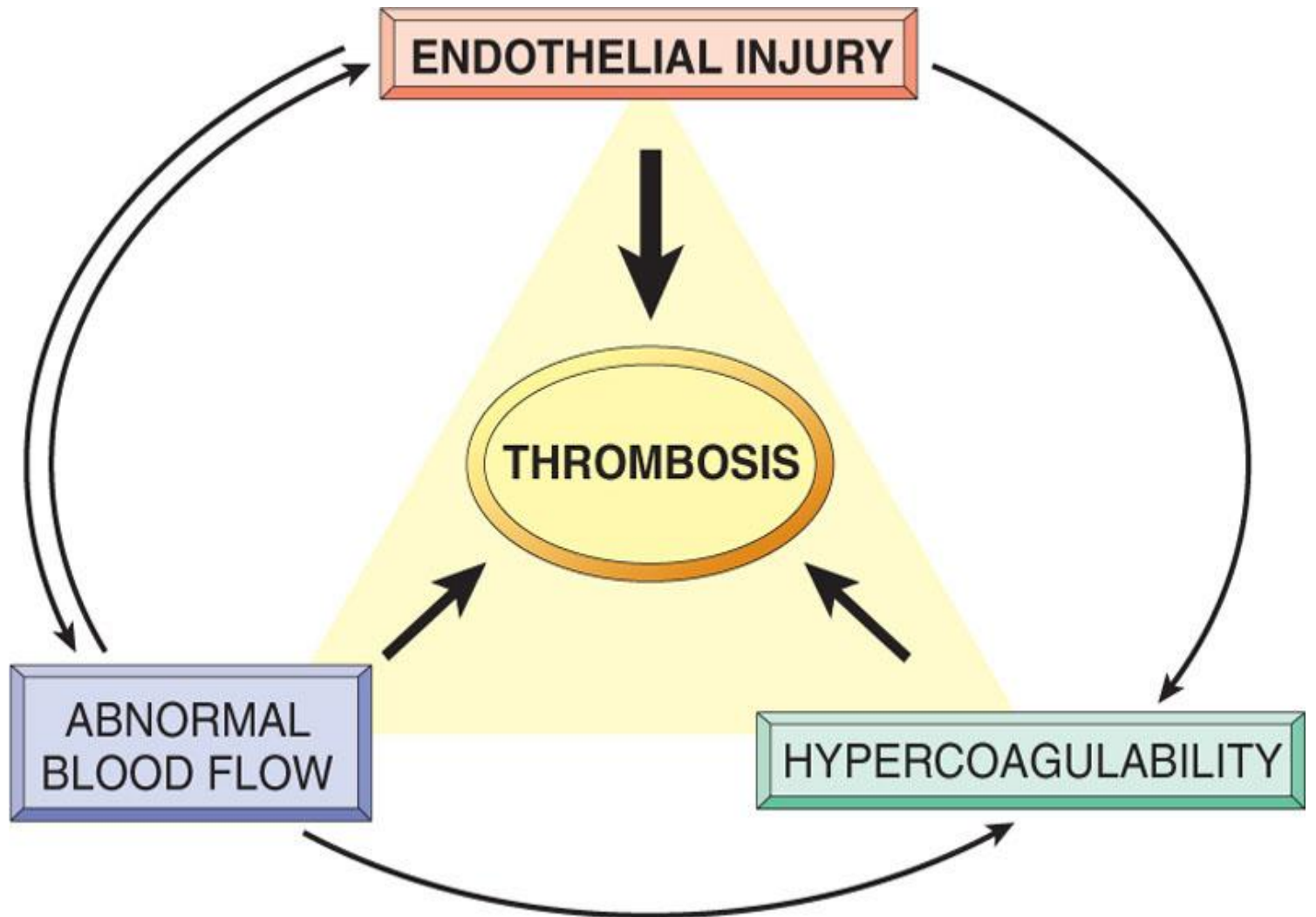
(1) Endothelial injury

(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)

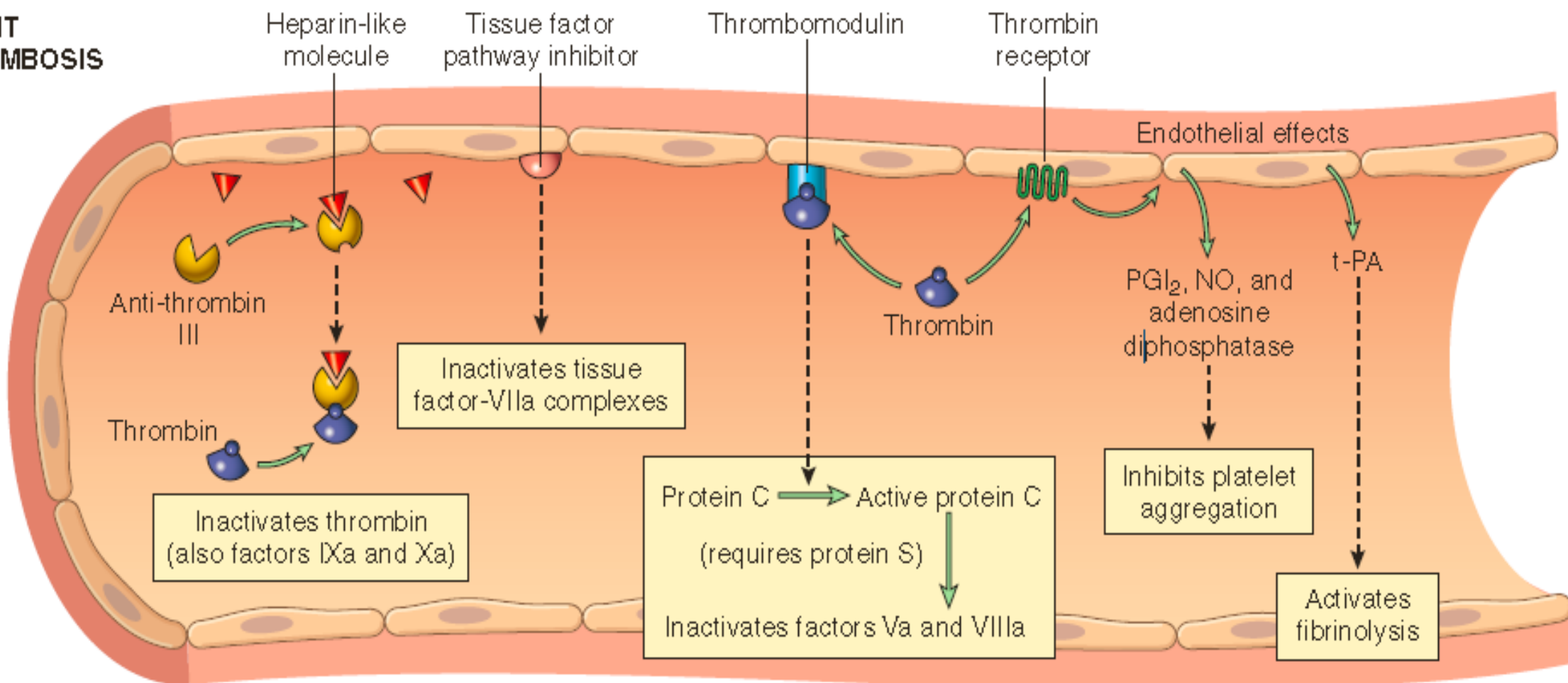
- An important role in triggering **arterial** thrombotic events.
- Produced by **physical injury, infectious agents, abnormal blood flow, inflammatory mediators, metabolic abnormalities** (hypercholesterolemia or homocystinemia), **and cigarette smoke toxins**.
- It shifts the pattern of gene expression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

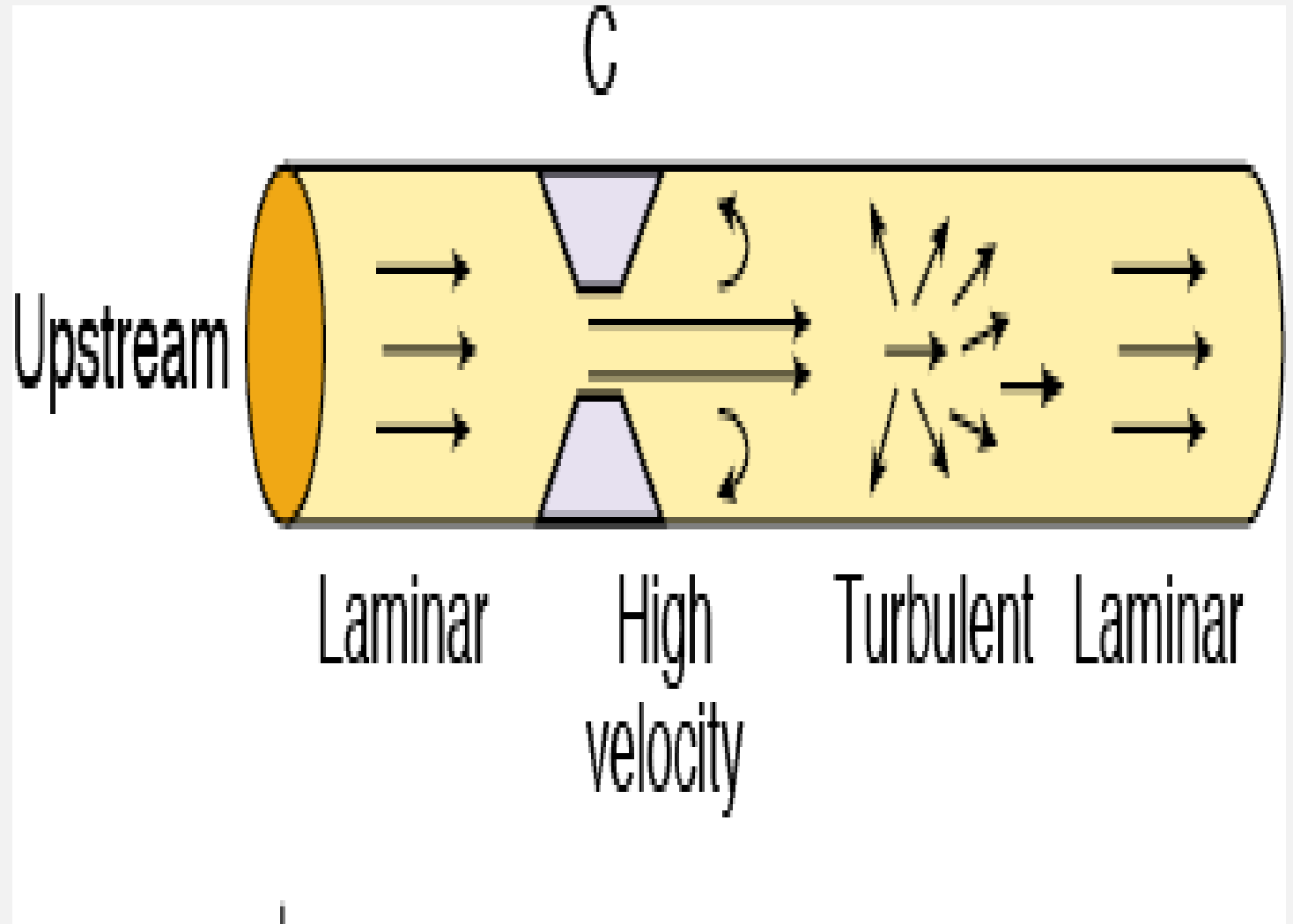
2. Anti-fibrinolytic effects: secrete **Plasminogen activator inhibitors (PAI)**, which downregulate the expression of t-PA.

INHIBIT THROMBOSIS



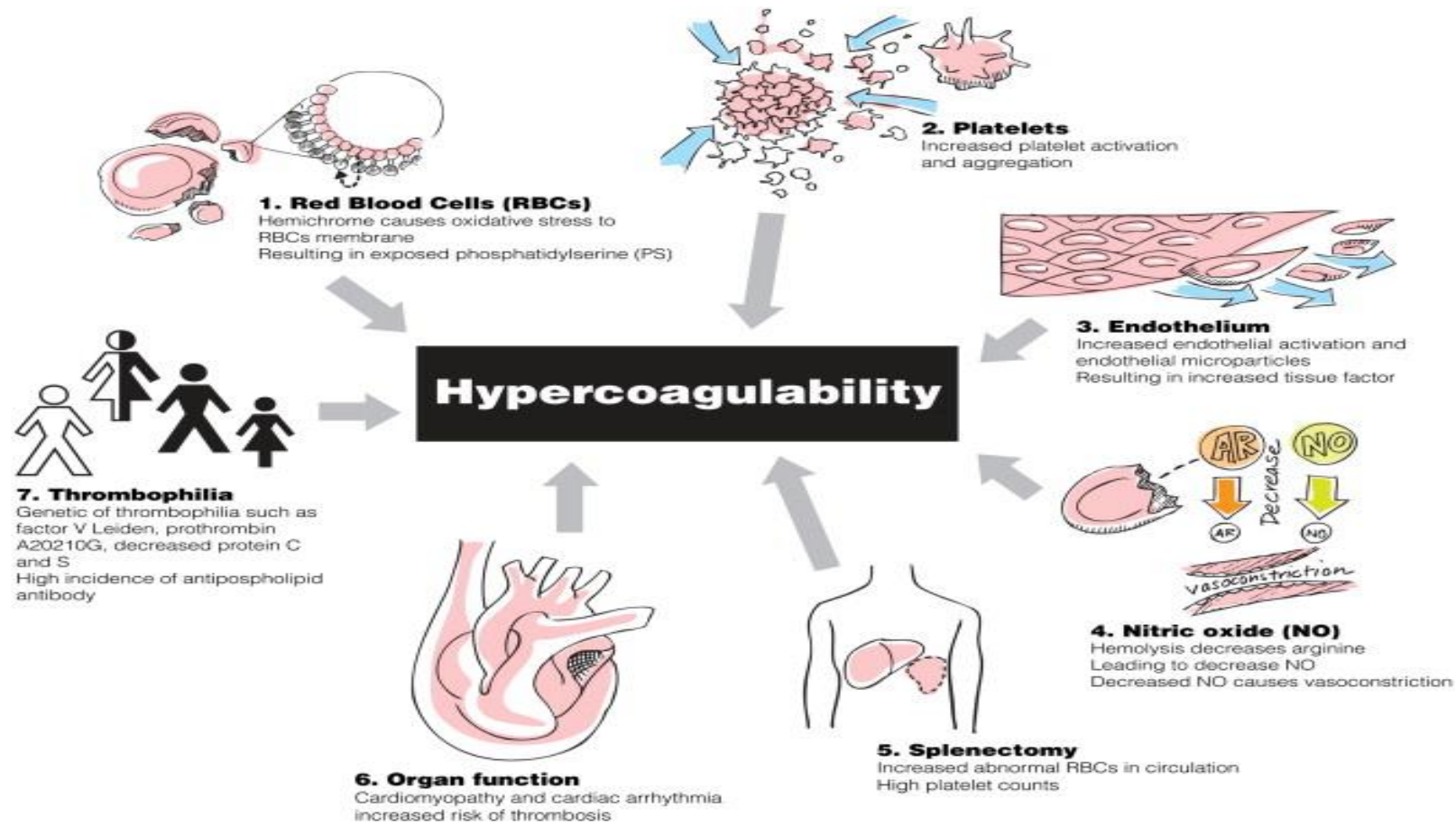
Abnormal Blood Flow

- **Normal laminar 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.

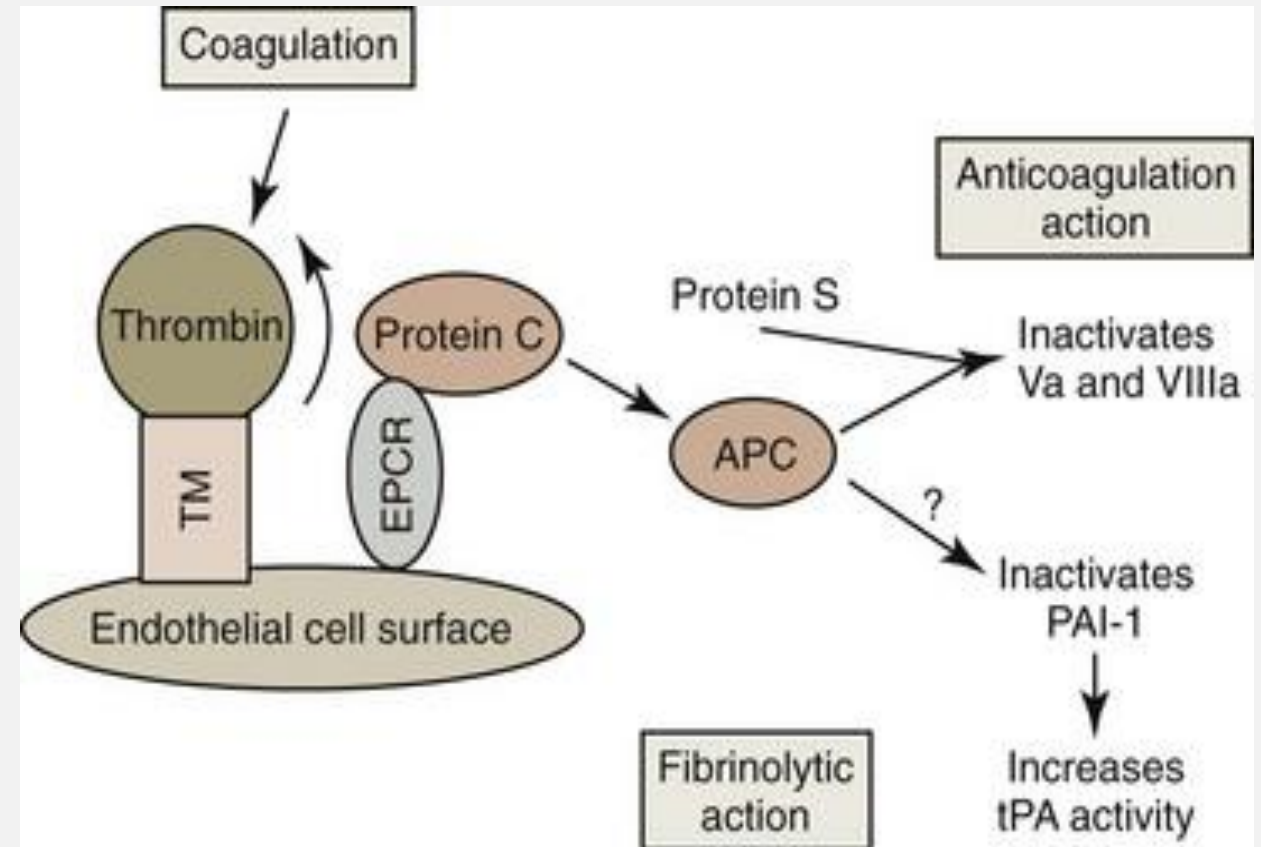
- + **important risk factor for venous thrombosis.**

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.

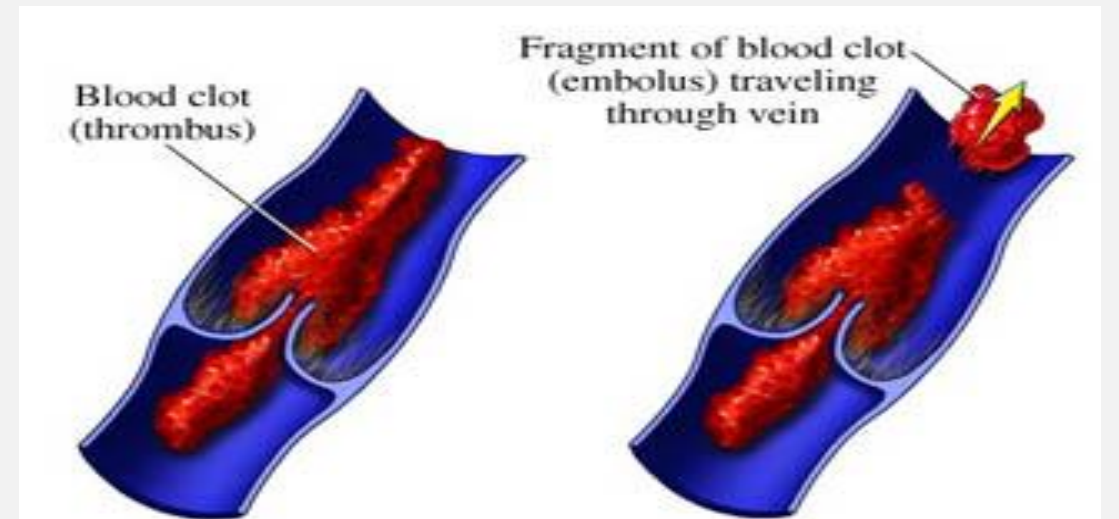
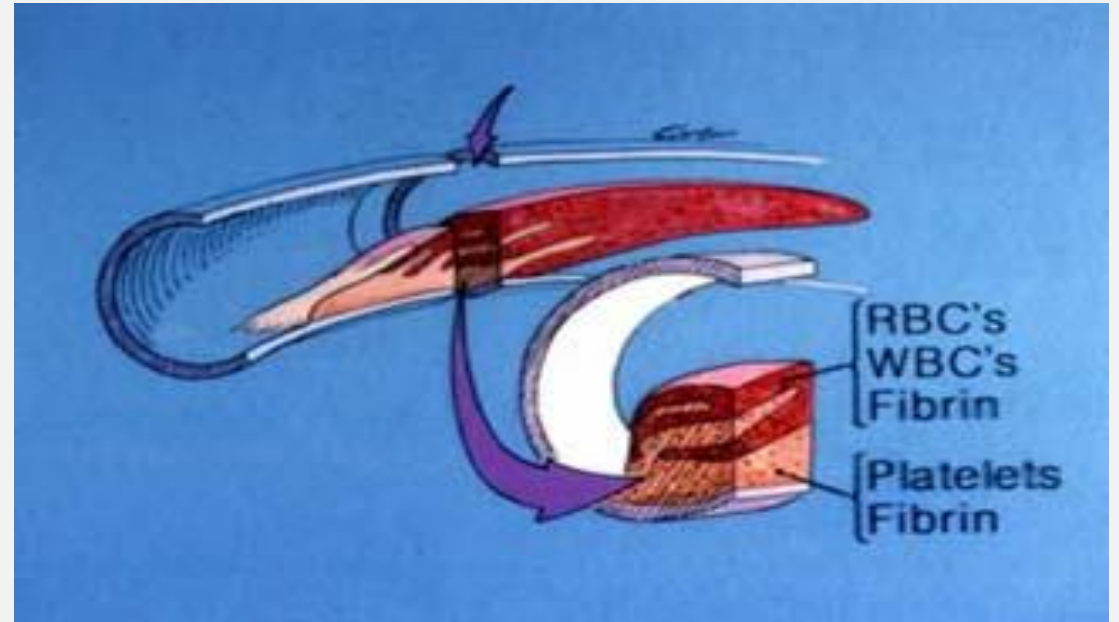
Secondary (acquired) hypercoagulability

- (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).

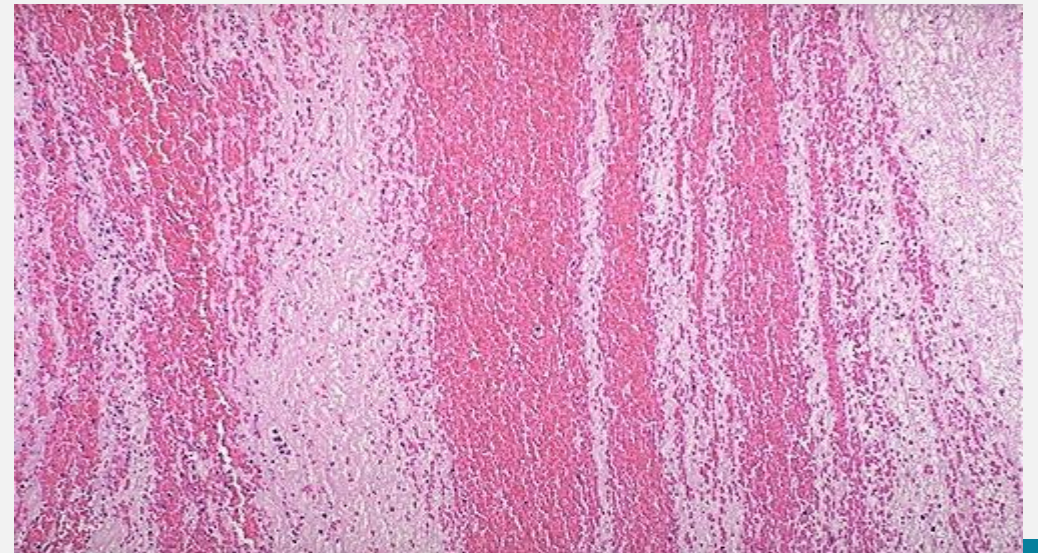
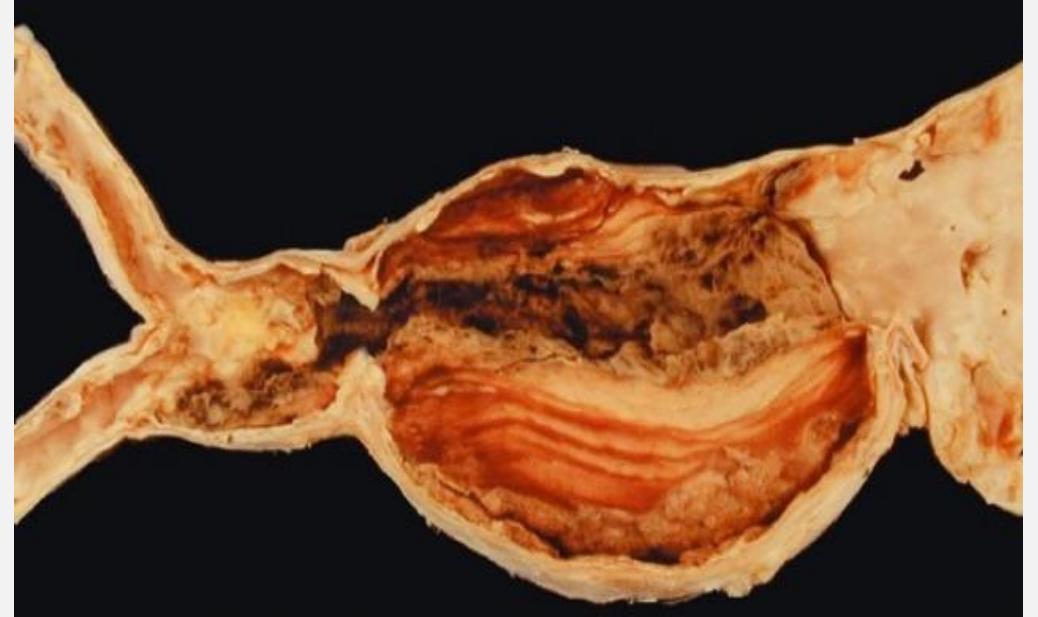
An aerial photograph of a river delta system, showing a large distributary channel branching off from the main river. The water is a deep blue-green color, and the surrounding land is a lighter, textured brown. The word "Morphology" is overlaid in white text on the left side of the image.

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.

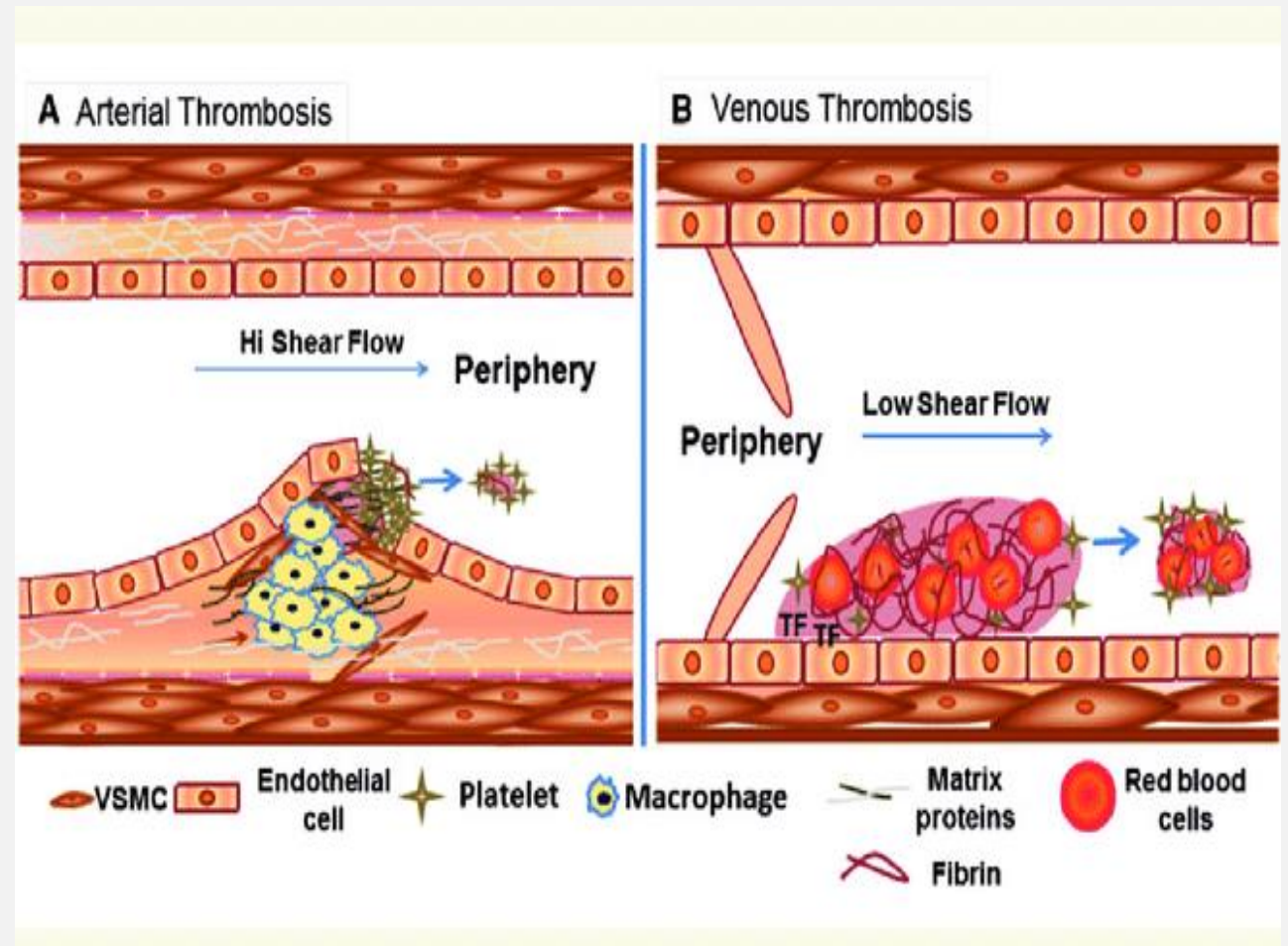


- **Arterial thrombi:**

- + 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)**

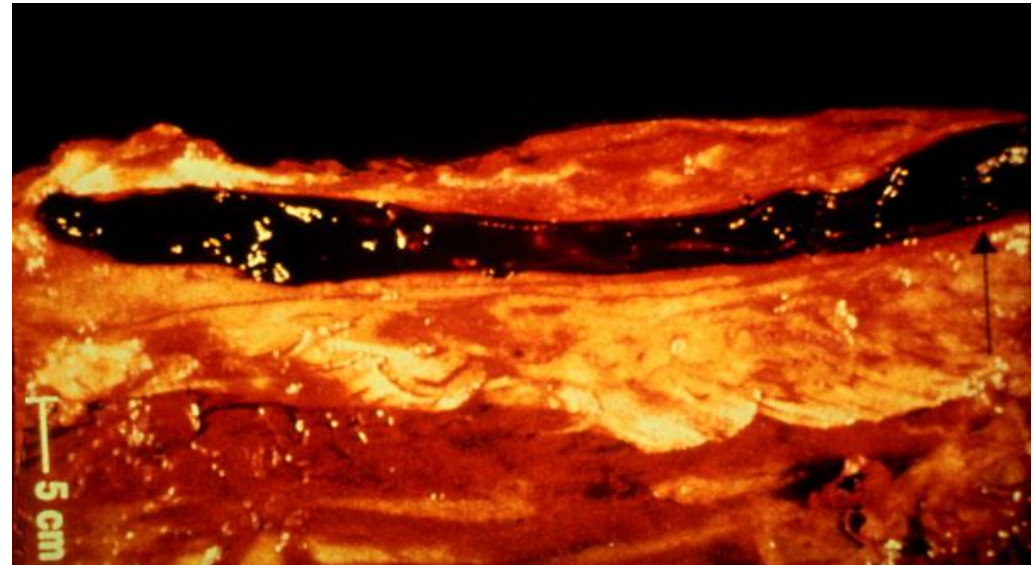
- + almost invariably occlusive.
- + frequently propagate to heart (have long cast in lumen) → give rise to emboli.
- + rich in red cells, develop in sluggish venous circulation (**red, or stasis, thrombi**)
- + 90% veins of the lower extremities.

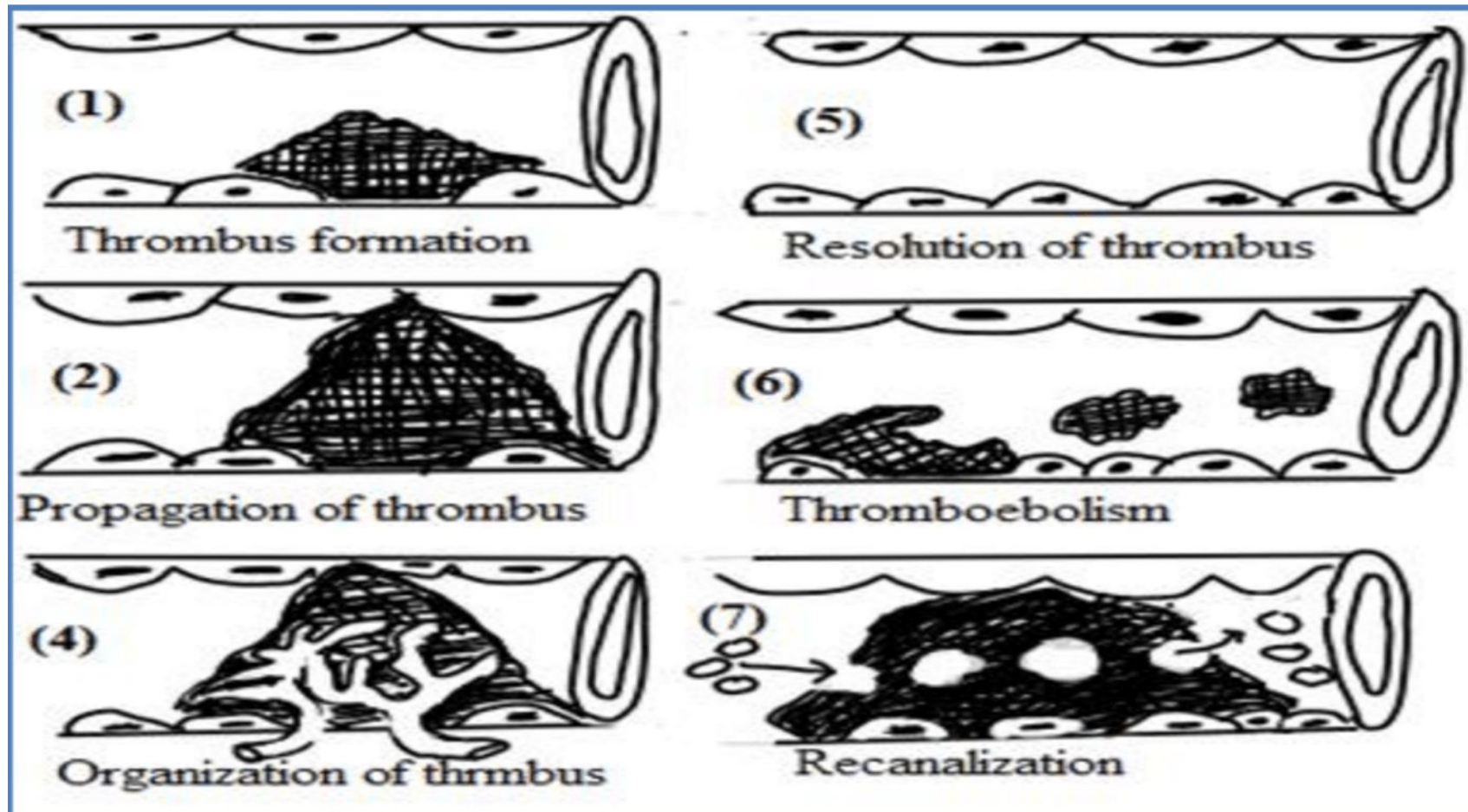


postmortem clots can sometimes be mistaken for venous thrombi: it is gelatinous & because of red cell settling they have a dark red dependent portion & a yellow “chicken fat” upper portion; they also are usually not attached to the underlying vessel wall.



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.

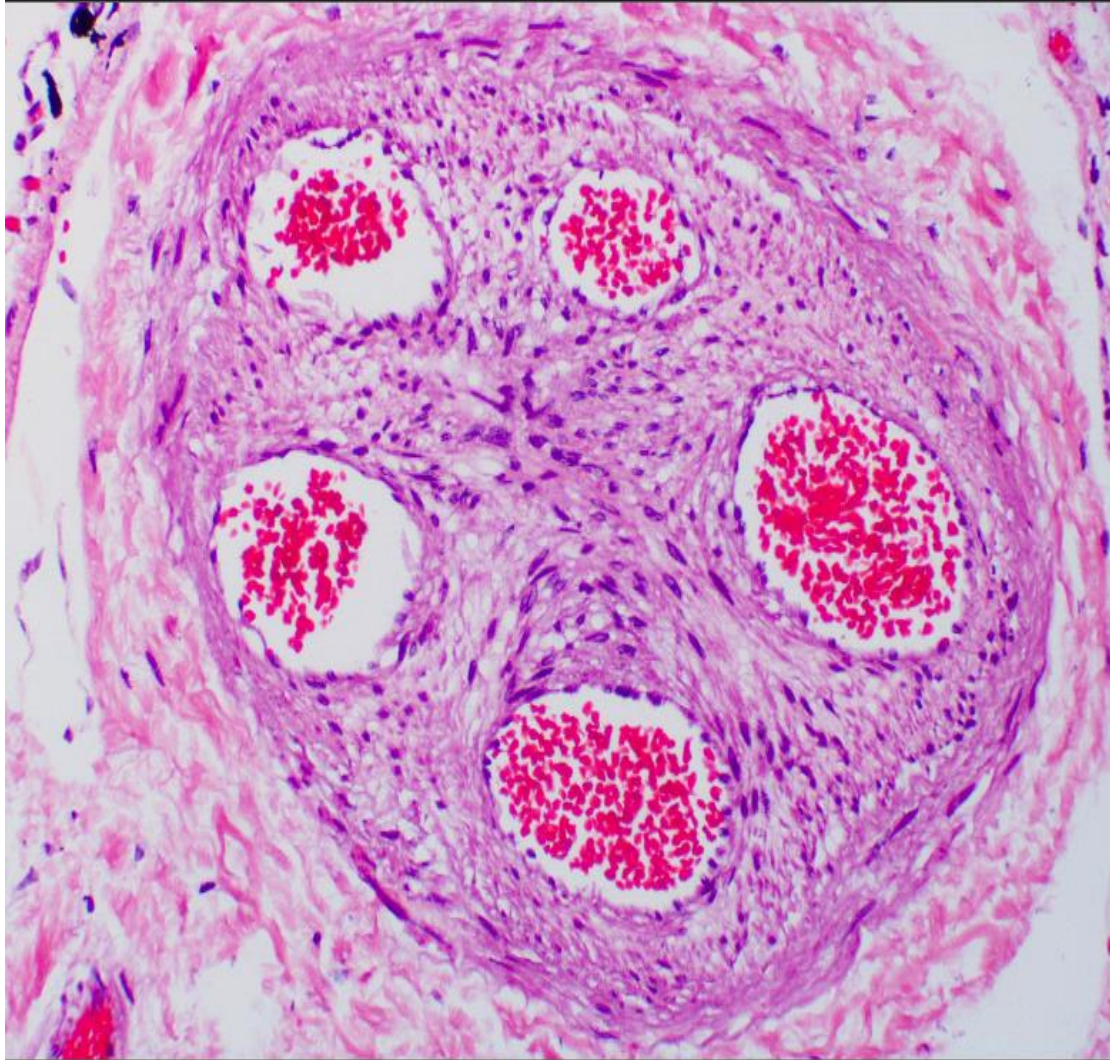
2 • **Embolization:** Part or all of the thrombus is dislodged & transported elsewhere in the vasculature.

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

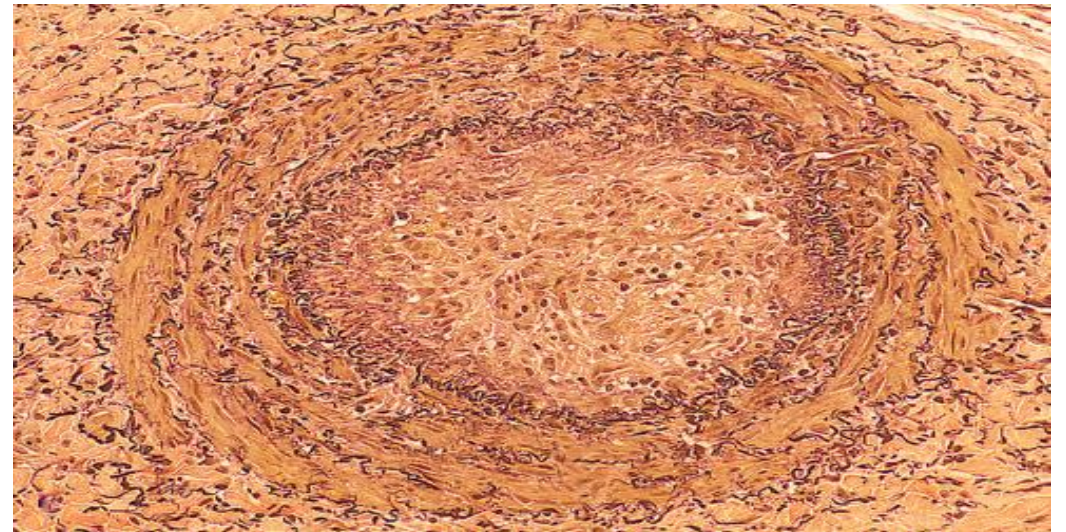
+ older thrombi; extensive fibrin deposition & polymerization make it more resistant to plasmin-induced proteolysis.

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