

CHAPTER 4

CORONARY THROMBUS

- Development
- Classification
- Fate
- Clinical Presentation
- Therapeutic Strategies

CORONARY THROMBUS

- Coronary thrombosis is usually a complication of intimal injury.
- It can obstruct coronary artery lumen partially or completely.
- In majority of cases coronary thrombi dissolve and disappear spontaneously due to natural body anticoagulant and fibrinolytic defenses. In other cases thrombi become incorporated in vessel wall or get fragmented and embolize distally.
- Coronary thrombi are responsible for the production of acute coronary syndromes.
- Management will depend upon the clinical situation and extent of coronary occlusion.

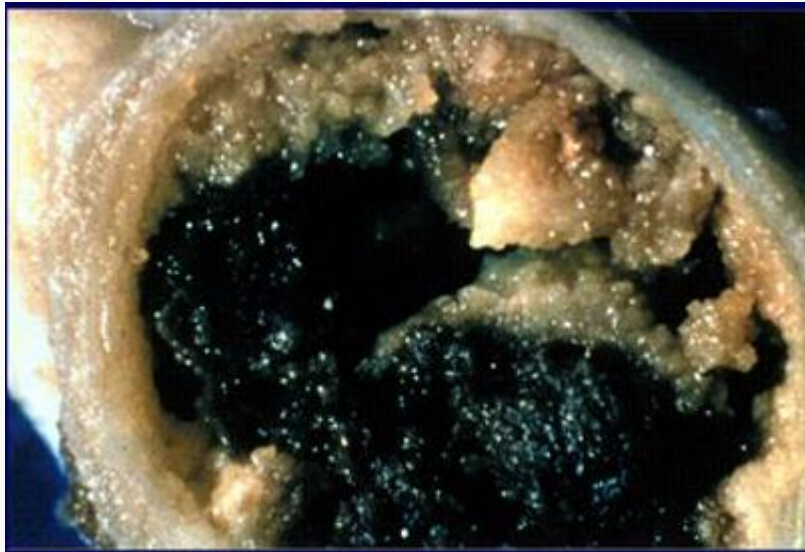


Figure (33): Ruptured atherosclerotic plaque with formation of intropiaque (mural) and luminal thrombi.

DEVELOPMENT OF CORONARY THROMBI

Endothelial Damage

- Endothelial denudation, erosion, rupture or tear will expose the underlying subintimal extracellular matrix to the coronary blood (Fig 11, 34).
- Subendothelial tissue contains collagen, elastin, smooth muscle cells, inflammatory and immune cells.
- Disruption of the atherosclerotic plaque will expose its lipid core (very strongly thrombogenic and rich in TF) to coronary blood.
- Tissue factor (TF) a very potent procoagulant glycoprotein, is normally shielded from blood by the healthy endothelium.

TF will come in contact with blood after endothelial damage or plaque disruption. Its main source are macrophages.

- Exposure of subendothelial structures will result in:
 1. Contact and adhesion of blood platelet to collagen and other adhesion molecules (von Willibrand factor, vitronectin) in the subendothelial space (Fig 34).
Platelet adhesion result in platelet activation followed by aggregation and formation of platelet thrombi.
 2. Interaction of TF with coagulation factor VIIa will activate extrinsic pathway of blood coagulation though activation of factors IX and X leading to thrombin and fibrin formation.

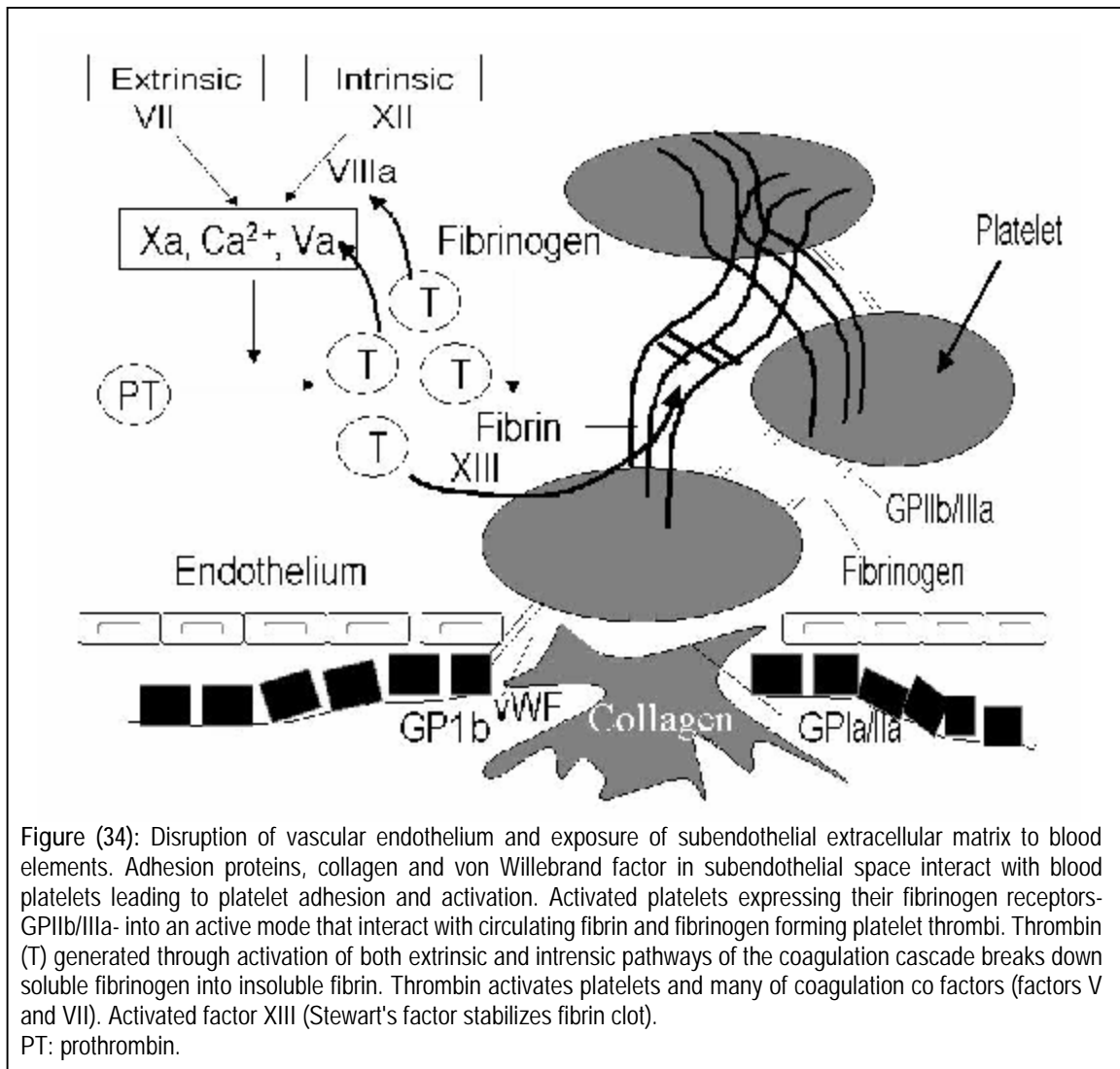
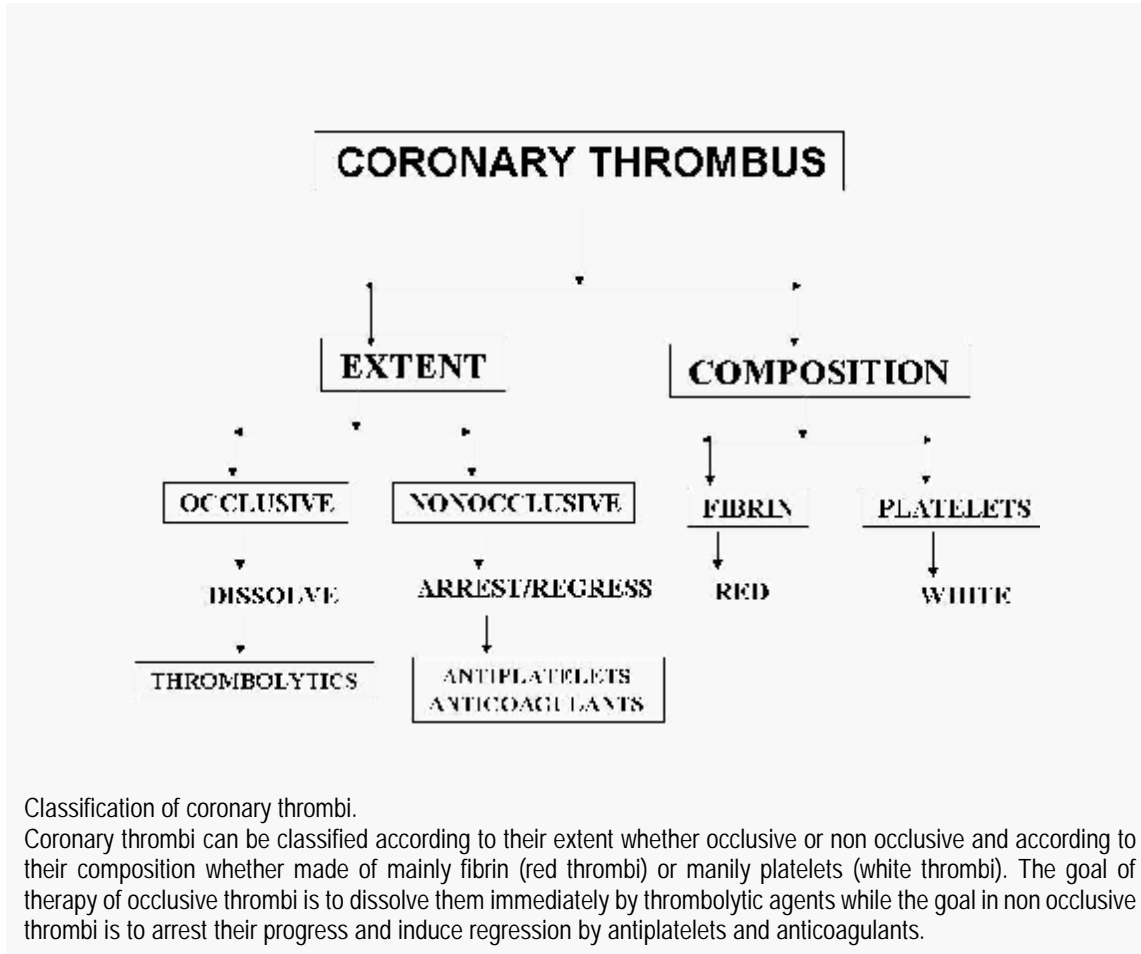


Figure (34): Disruption of vascular endothelium and exposure of subendothelial extracellular matrix to blood elements. Adhesion proteins, collagen and von Willebrand factor in subendothelial space interact with blood platelets leading to platelet adhesion and activation. Activated platelets expressing their fibrinogen receptors-GPIIb/IIIa- into an active mode that interact with circulating fibrin and fibrinogen forming platelet thrombi. Thrombin (T) generated through activation of both extrinsic and intrinsic pathways of the coagulation cascade breaks down soluble fibrinogen into insoluble fibrin. Thrombin activates platelets and many of coagulation co factors (factors V and VII). Activated factor XIII (Stewart's factor stabilizes fibrin clot). PT: prothrombin.



CLASSIFICATION OF CORONARY THROMBI

Coronary thrombi can be classified according to their:

- Composition.
- Site.
- Extent.

Composition

- Platelet rich thrombi
 - Appear white or grey-white on coronary angioscopic examination. *White Thrombus*
 - Resist fibrinolytic therapy.
 - Main reason for coronary occlusion in patients with non ST elevation ACS (NSTEMI-ACS).
 - Form the basal (vessel wall) part of mixed platelet and fibrin thrombi and are usually non-occlusive (Fig 35).

- Fibrin rich thrombi
 - Contain many RBCs which give their red appearance on angioscopic examination. *Red Thrombus*.
 - Can be dissolved by fibrinolytic agents.
 - Main reason for occlusion in SETMI.
 - Often protrude inside the coronary lumen and produce occlusion.

Site (Fig 35)

- Intraplaque
 - Limited to disrupted ASO plaque.
 - Composed of platelet mainly.
- Mural
 - Limited to the vessel wall.
 - Composed of platelets and some fibrin.
- Luminal
 - Mixture of fibrin, platelets and RBCs.
 - Form inside the coronary lumen produce partial or total occlusion.

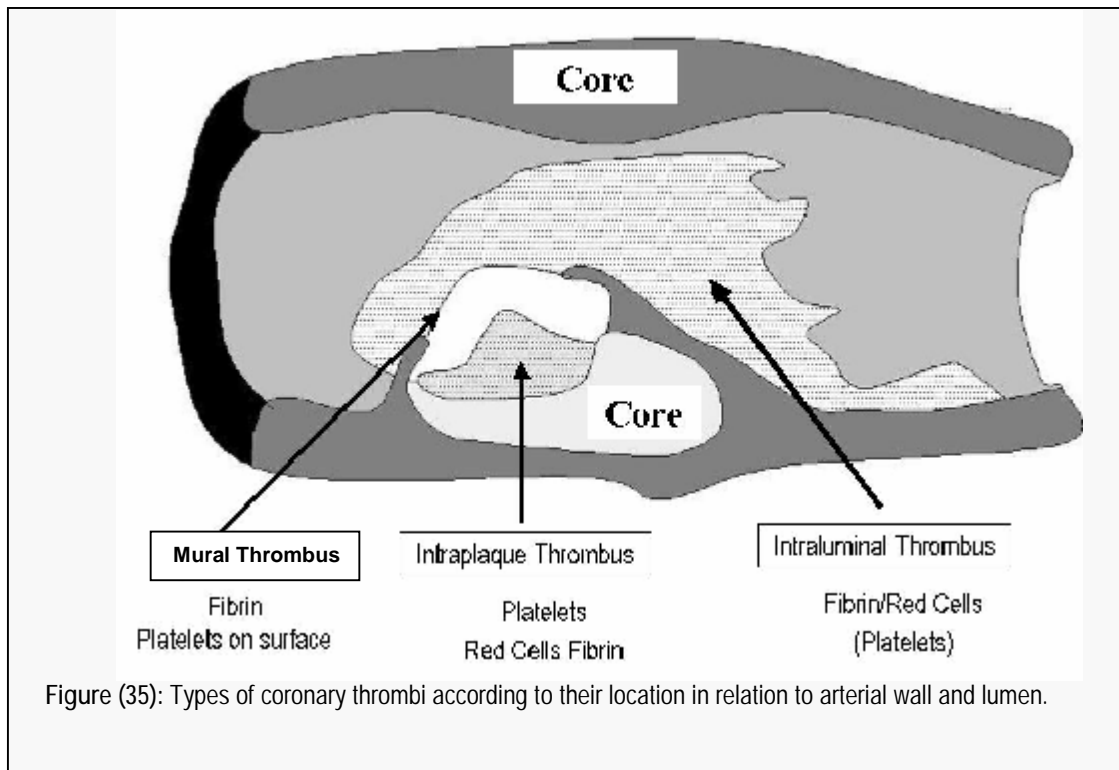


Figure (35): Types of coronary thrombi according to their location in relation to arterial wall and lumen.

Extent

- Non obstructive.
- Partially obstructive-non occlusive.
- Totally obstructive – occlusive.

FATE OF CORONARY THROMBI

The process of coronary thrombosis is dynamic with clot formation and dissolution occurring almost simultaneously.

Resolution

Intact natural intrinsic anticoagulant and fibrinolytic defenses with a weak thrombotic stimulus result in partial or complete resolution of the thrombus.

Detection of Intracoronary Thrombus in Patients with Unstable Angina Using Angiographic Examination

Time from chest pain to examination	Rate of intracoronary thrombus
Less than 2 hours	68%
2-4 hours	66%
4-6 hours	33%
More than 6 hours	23%

In unstable angina there is rapid resolution of thrombi as detected by angioscopic examination.

Source: Bertrand, 1999.

Progression and growth

If local and systemic prothrombotic factors overcome the natural anticoagulant and fibrinolytic defenses, coronary thrombi will persist, progress and grow to occlude partially or completely the lumen.

Incorporation in vessel wall

Mural or non-occlusive thrombus is organized, invaded by fibroblasts and collagen tissue and is covered by endothelium.

Fragmentation and embolization

Natural or pharmacologic lysis can fragment thrombi into small particles that embolize distally in the coronary microcirculation.

WHAT MAKES THROMBI DISAPPEAR?

NATURAL DEFENSES AGAINST THROMBOSIS

- Natural antiplatelets.
- Natural anticoagulants.
- Natural fibrinolytics.

Three different defense mechanisms help maintain blood in a fluid state and prevent development and progression of intravascular thrombi.

Natural Antiplatelets

- *Prostacyclin*:
 - Inhibits platelet aggregation.
- *Nitric oxide (NO)*:
 - inhibits platelet adhesion and aggregation.
 - Released locally in response to thrombin, bradykinin, TXA₂, histamine, shear stress and aggregating platelets.

Natural Anticoagulants

- *Heparin-like molecules*:
 - Synthesized by endothelial cells.
 - Interact with antithrombin and heparin cofactors (located on endothelial surface) neutralizing procoagulant proteins.
- *Antithrombin*
 - Plasma glycoprotein capable of neutralizing the coagulation proteins thrombin and factors IXa, Xa, XIa and XIIa.
- *Protein C*:
 - Circulates in plasma and when activated (APC) through binding with thrombomodulin (thrombin receptor on endothelial cells), it interacts and inhibits coagulation factors Va and VIIIa.
- *Protein S*:
 - Facilitates APC action and inhibits factors Va and VIIIa.
- *Tissue factor pathway inhibitor (TFPI)*:
 - § Located on endothelial surface.
 - § Inhibits the extrinsic coagulation pathway.
 - § It is released by unfractionated heparins.

Natural Fibrinolytics

- Plasminogen activators:
 - § Produced by endothelial cells and convert plasminogen to plasmin.
 - § Plasmin is an enzyme that proteolytically degrades fibrin and fibrinogen.
 - § Tissue plasminogen activator (TPA) generate plasmin locally, therefore fibrinolysis is limited to the immediate environment.

FACTORS FAVORING THROMBOSIS PROGRESSION

- Systemic factors – systemic prothrombotic – (procoagulant) state
 - Increased plasma coagulation factors: fibrinogen and factor VII.
 - Increased plasma TF.
 - Increased plasma antifibrinolytic factors platelet activating factor: PAF-1 and antiplasmin.
 - Decreased anticoagulant factors: antithrombin, thrombomodulin and protein C.
 - Other hypercoagulable states
 - § Hemocentration.
 - § Hypercholesterolemia (↑LDL-C).
 - § Infection.
 - § Sympathetic activation.
 - § RAS activation.
- Local factors
 - Extensive endothelial injury.
 - Extensive ASO plaque disruption.
 - Severe inflammatory reaction.
 - Increased TF and tissue lipids.
 - Significant stenosis.
 - Increased platelet activity.

CLINICAL PRESENTATION OF CORONARY THROMBOSIS

- *Silent*
 - Majority of coronary thrombi are asymptomatic.
- *Worsening angina*
 - Chronic recurrent ASO plaque rupture of mild to moderate severity is followed by thrombosis with each episode.
 - Multilayered thrombus is growing inside and over the plaque (Fig 18).
 - Obstructive lesions develops gradually as a combination of healed plaque and layers of aged thrombus, consisting primarily of platelets in a tightly packed fibrin network.

- *Acute coronary syndromes*
 - These include unstable angina, non-ST elevation MI (NSTEMI) and ST-elevation MI (STEMI).
 - The clinical conversion from asymptomatic CAD or stable angina to ACS is usually the result of coronary ASO plaque fissuring, disruption and intraluminal thrombosis.
 - Coronary thrombi formation can occlude coronary lumen partially or totally. ASO thrombus formation favours further coronary occlusion through:
 - § Coronary spasm- result of vasoconstrictors (serotonin, endothelin TXA₂) released form activated platelets and damaged endothelium.
 - § Thrombin generated from thrombus causing vasoconstriction and further fibrin and thrombin formation.
- *Clinical manifestations*
 - Result from intermittent thrombus formation with intermittent coronary spasm.
 - Depend upon duration of occlusion:
 - § Occlusion lasts for few minutes. It results in unstable angina or angina at rest.
 - § If it is more prolonged to less than one hours it produces NSTEMI.
 - § Complete and persistent occlusion for more than one hour results in STEMI.
 - The results of coronary occlusion by thrombus will depend upon:
 1. *Occlusion*: degree, duration, acuteness, distribution.
 2. *Collateral circulation*: available or recruited at time of occlusion.
 3. *Myocardial oxygen requirements* at time of occlusion. Blood pressure, heart rate, myocardial contractility.

THERAPEUTIC STRATEGIES AGAINST ACUTE CORONARY THROMBI

- Goals
 - Lysis: Dissolve.
 - Arrest: Prevent growth and progression.
 - Prevention: Prevent development of new ones.
- Approaches:
 - Depend upon the clinical situation and degree of coronary occlusion.
 - In total occlusion (STEMI).
The immediate concern is lysis through fibrinolytics.
 - In partial occlusion (NSTE-ACS).
The goal is to arrest and prevent progression or recurrence of thrombosis through aggressive antiplatelet and antithrombotic agents.