Cardiovascular system

Lectures two and three

Risk factors and pathogenesis of atherosclerosis, Ischemic heart diseases: angina and myocardial infarction

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Objectives:

At the end of these two lectures, the student should:

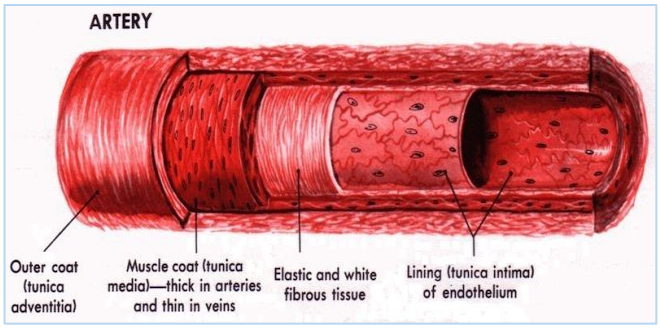
(1) Understand the pathogenesis and clinical consequences of atherosclerosis.
(2) Be able to discuss pathology and complications of ischemic heart diseases with special emphasis on myocardial infarction.
(3) Know how lifestyle modifications can reduce the risk of ischemic heart disease.

Key principles to be discussed:

1- Risk factors of atherosclerosis.
2- Pathogenesis of the fibrolipid atherosclerotic plaque.
3- Clinical complications of atherosclerosis.
4- Commonest sites for the clinically significant coronary atherosclerosis.
5- Macroscopic and microscopic changes in myocardial infarction.
6- Biochemical markers of myocardial infarction.
7- Complications of myocardial infarction: immediate and late.

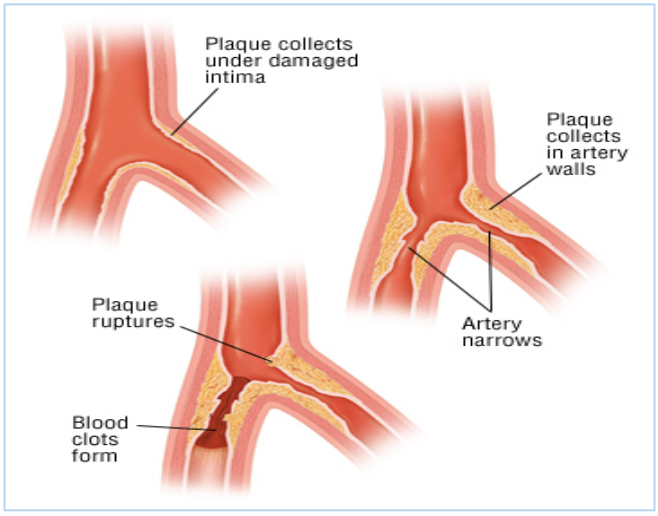
Atherosclerosis

Atherosclerosis (تصلب الشرايين) is characterized by intimal lesions called **atheroma, which** protrude into and obstruct vascular lumens and weaken the underlying media.



Intima: the inner layer of the vessels.
Media: the middle layer of the vessels.

Dr. Ahmad did not focus on this point, but it's one of the objectives so you should read it at least:
The most heavily involved vessels are the abdominal aorta then coronary arteries, the popliteal arteries, the internal carotid arteries, and the vessels of the circle of Willis.
Even in the same patient, atherosclerosis typically is more severe in the abdominal aorta than in the thoracic aorta.



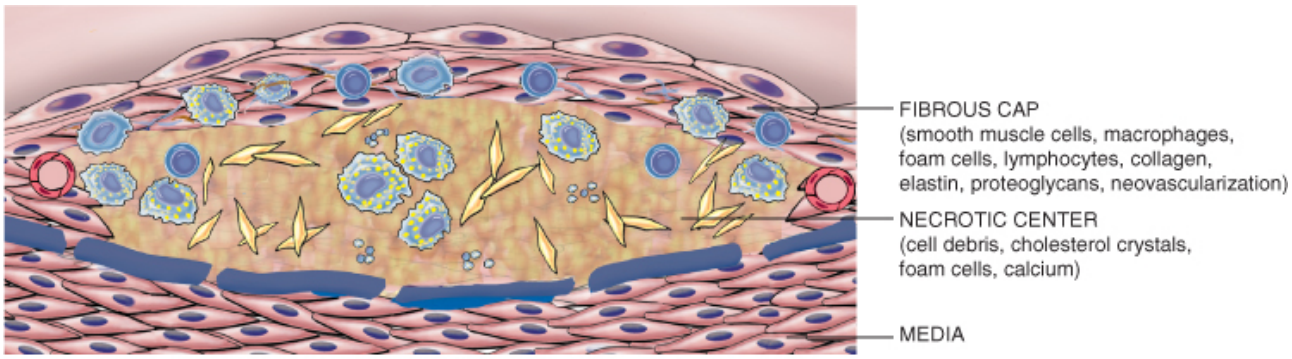
Vessels of the upper extremities usually are spared, as are the mesenteric and renal arteries, except at their ostia. Moreover, in any given vessel, lesions at various stages often coexist.

Atheroma: (Atherosclerotic Plaque)

The key characters of atheroma are: **intimal thickening and lipid accumulation.**
Atherosclerotic plaques contain 3 main components:

- **Cells**: smooth muscle cells, foam macrophages, lymphocytes.
- **Extracellular matrix**: collagen, elastic fibers.
- **Lipid**: intracellular and extracellular lipid.

Foam cells are large, lipid-laden (محملة بالدهون) macrophages derived from blood monocytes. But SMCs can also imbibe lipid to become foam cells.



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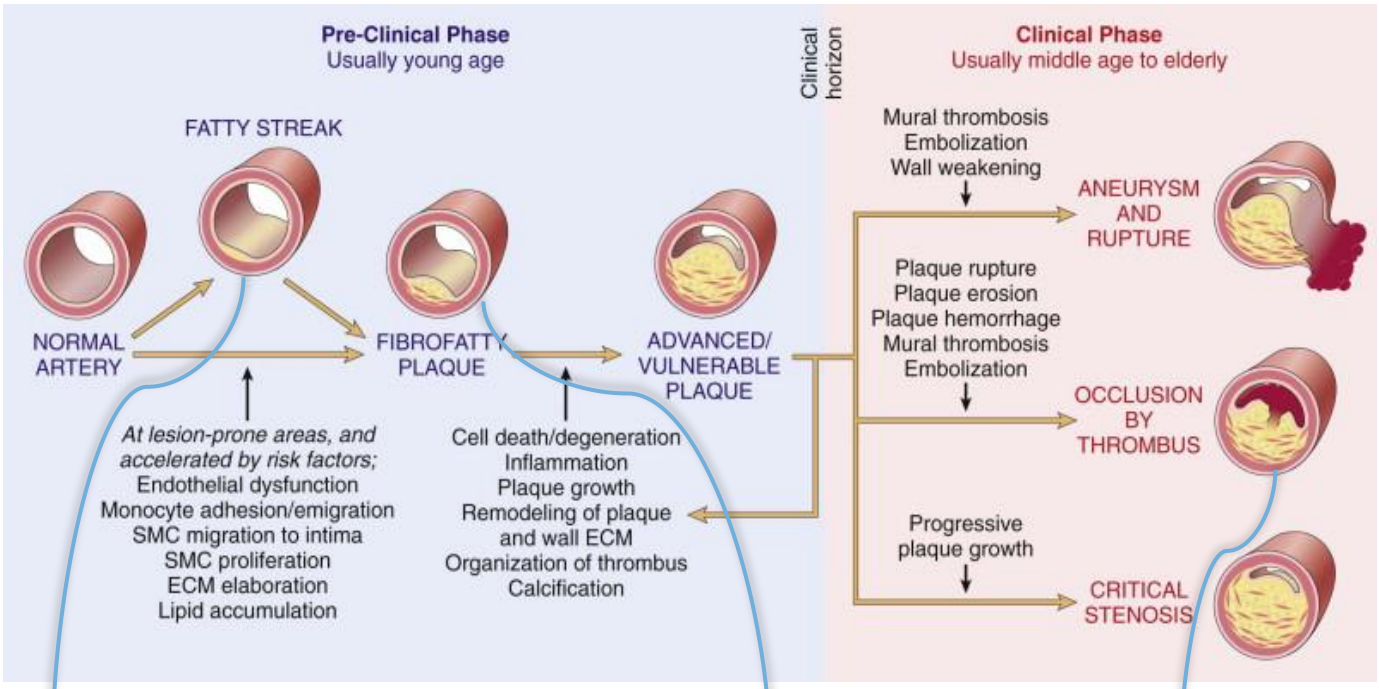
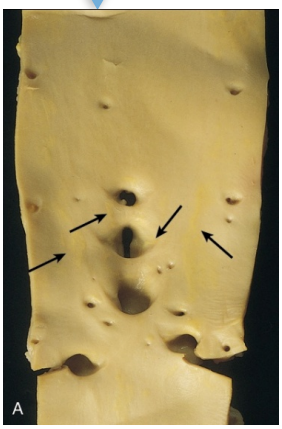
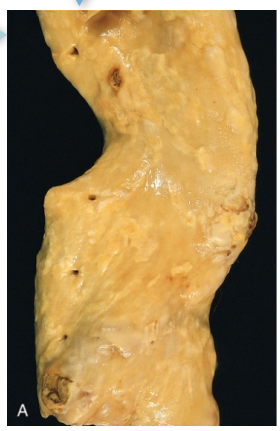
This picture below summarizes everything you need to know regarding the morphology:





Gross views of atherosclerosis in the aorta.
A. Mild atherosclerosis composed of fibrous plaques, one of which is denoted by the arrow.
B. Severe disease with diffuse and complicated lesions.



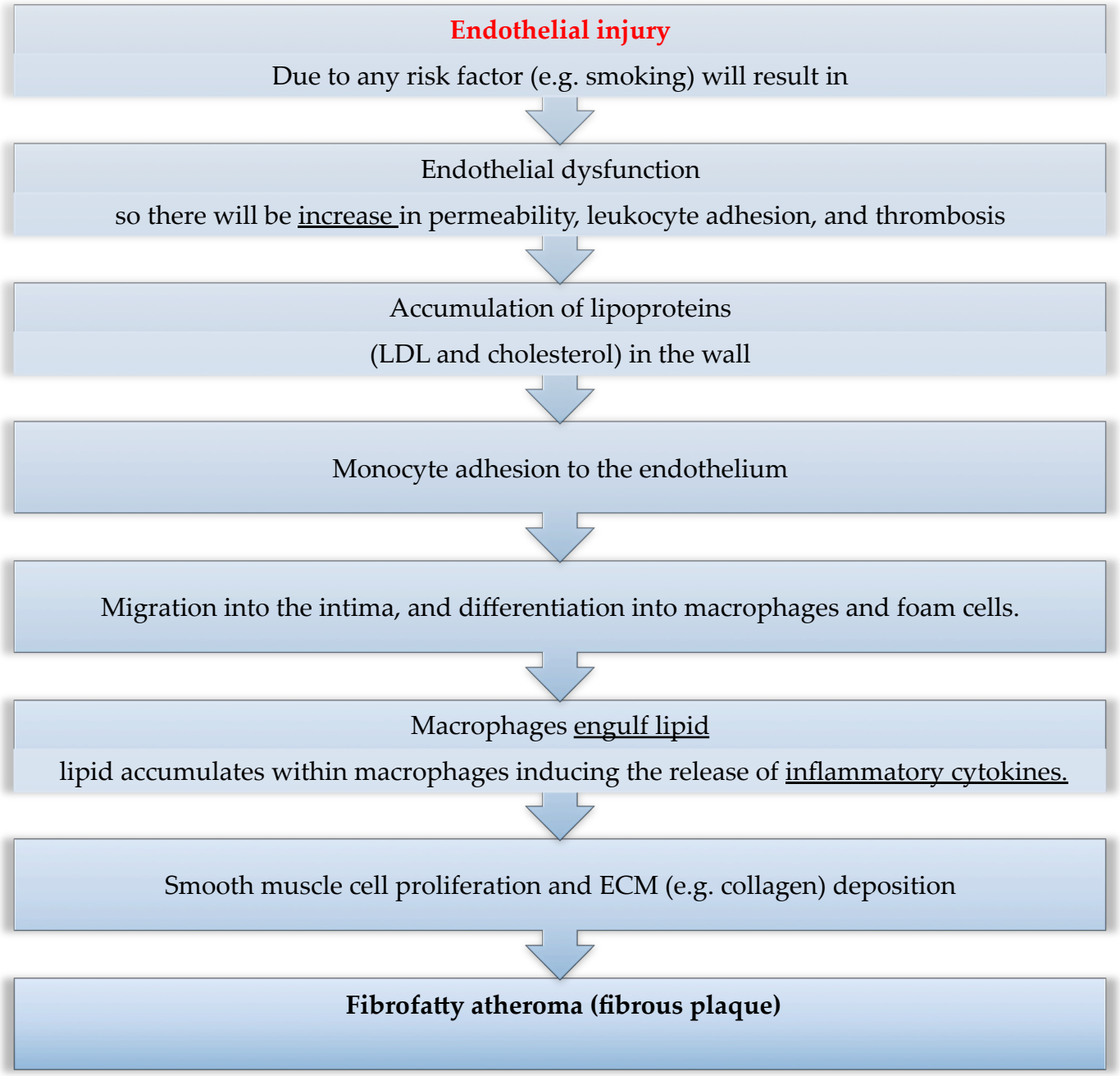
What you need to know from the graph above:

Fatty Streaks:

Fatty streaks are the earliest lesion of atherosclerosis they are a collection of lipid laden foam cells in the intima.
They do not cause any disturbance in blood flow. (**Asymptomatic**)
They are composed of lipid-filled foamy macrophages.
When fatty streaks obstruct 70-75% of the vessel (which is the Critical Stenosis stage) symptoms start to appear.

Pathogenesis of atherosclerosis:

The atheromatous plaques impinge on the lumen of the artery. They vary in size.
Atheromatous plaques usually involve only a partial circumference of the arterial wall ("eccentric" lesions) and are patchy and variable along the vessel length.



Still feel lost? Read it in detail below: (EXTRA FOR BETTER UNDERSTANDING)

1. Most commonly, plaques have a superficial fibrous cap composed of:
   - Smooth muscle cells.
   - Relatively dense collagen.
2. Where the cap meets the vessel wall (the "shoulder") is a more cellular area containing:
   - Macrophages.
   - T cells.
   - Smooth muscle cells.
3. Deep to the fibrous cap is a necrotic core, containing:
   - Lipid (primarily cholesterol and cholesterol esters)
   - Necrotic debris
   - Lipid-laden macrophages
   - Smooth muscle cells **(foam cells)**
   - Fibrin
   - Variably organized thrombus, and other plasma proteins.
4. The extracellular cholesterol frequently takes the forms of crystalline aggregates that are washed out during routine tissue processing, leaving behind empty "cholesterol clefts."
5. The periphery of the lesions shows **neovascularization** (proliferating small blood vessels).
6. The media deep to the plaque may be attenuated and exhibit fibrosis secondary to smooth muscle atrophy and loss.
7. Typical atheromas contain relatively abundant lipid, but some so-called fibrous plaques are composed almost exclusively of smooth muscle cells and fibrous tissue.
8. Plaques generally continue to change and progressively enlarge through cell death and degeneration, synthesis and degradation of ECM (remodeling), and thrombus organization.
9. Atheromas also often undergo calcification.

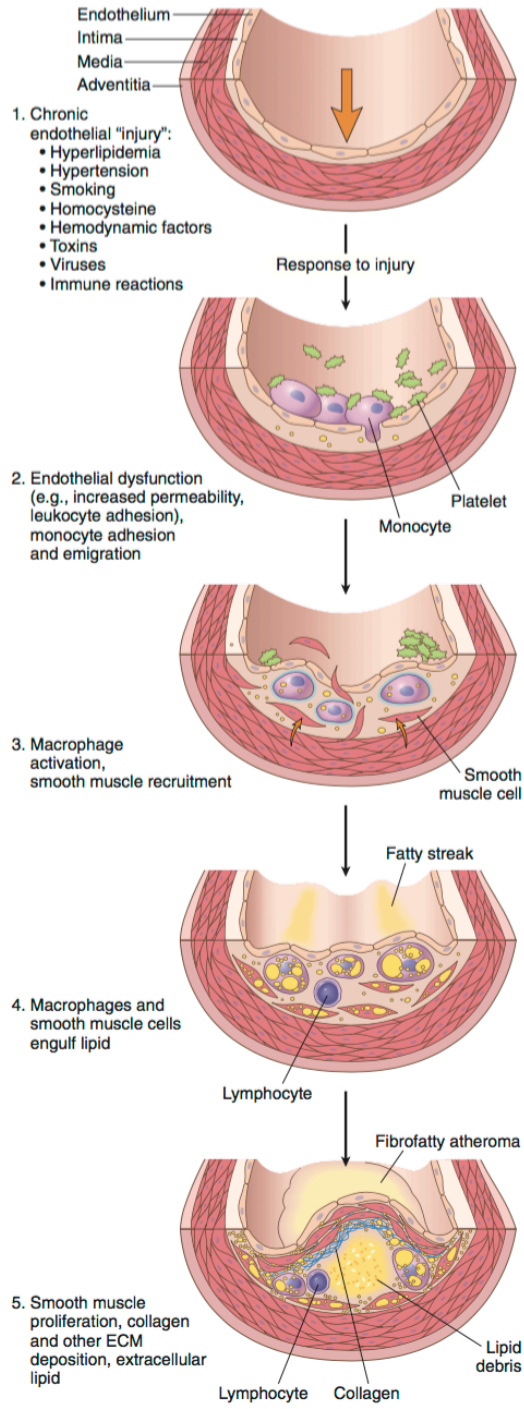


Figure 9–10 Response to injury in atherogenesis: **1,** Normal. **2,** Endothelial injury with monocyte and platelet adhesion. **3,** Monocyte and smooth muscle cell migration into the intima, with macrophage activation. **4,** Macrophage and smooth muscle cell uptake of modified lipids and further activation. **5,** Intimal smooth muscle cell proliferation with ECM elaboration, forming a well-developed plaque.

Risk Factors of Atherosclerosis:

MAJOR RISK FACTORS (مهم جدا)

NON-MODIFIABLE	POTENTIALLY MODIFIABLE
A. Increasing age **B. Gender** **C. Family history** **D. Genetic abnormalities**	**A. Diet (contributing to hyperlipidemia)** **B. Hypertension** **C. Diabetes** D. **Nicotine use (Tobacco smoking, chewing)**

MINOR / UNCERTAIN / NONQUANTITATED RISK FACTORS (اقرؤوها):

- Physical inactivity
- Stress ("type A" personality)
- Postmenopausal estrogen deficiency
- High carbohydrate intake
- Alcohol
- Lipoprotein Lp (a)
- Hardened (trans) unsaturated fat intake
- Chlamydia pneumoniae
- Obesity (mentioned in the slides its minor)

Importance of types of lipoproteins in hyperlipidemia:

- Low-density lipoproteins (LDLs):
  - When too much LDL (bad) cholesterol circulates in the blood, it promotes atherosclerosis and therefore contributes to heart disease.
- Very-low-density lipoproteins (VLDLs) is also considered to be a type of bad cholesterol and it promote atherosclerosis
- Chylomicrons promote atherosclerosis.
- **High-density lipoproteins (HDLs):** is known as "good" cholesterol, because high levels of HDL protects against heart attack. Low levels of HDL also increase the risk of heart disease. HDLs help to reverse the effects of high cholesterol.

Clinical Complications Of Atherosclerosis:

As we said atherosclerosis is a chronic disease that develops with time (years). The lesion with advanced AS is at a high risk of developing one or more of the following complications:

(Atherosclerosis complications make dealing with AS even harder and it may lead to death)

1. Calcification (accumulation of calcium salts in the wall blood vessel)
2. Hemorrhage into the plaque → which will make the plaque bigger in size → which might lead to blockage of the blood vessel (The hematoma may expand the plaque or induce plaque rupture).
3. Rupture, ulceration, or erosion of the luminal surface of atheromatous plaques which may induce thrombus formation (rupture of the fatty plaques leads to discharge of some components to the bloodstream that may lead to or induce thrombus formation)
4. Aneurysmal formation (which leads to weakening and dilatation of the blood vessels wall)
5. ***Superimposed thrombosis (the most serious complication (might embolize))***:
    a. Usually occurs on disrupted lesions (those with rupture, ulceration, erosion, or hemorrhage) the thrombus can lead to partial or complete occlusion of the lumen.
6. The embolism might lead to Coronary artery disease (myocardial infarction and angina), gangrene, cerebral infarct and Carotid atherosclerotic disease (stroke).
7. ***Note that:*** *Myocardial infarction, cerebral infarction, aortic aneurysms, and peripheral vascular disease (gangrene of extremities) are the major clinical consequences of atherosclerosis.*

Ischemic Heart Diseases:

Introduction:

It is one of the complications of atherosclerosis; it is the insufficient blood supply to the myocardium due to a disease in the coronary arteries resulting in a group of closely related syndromes:

- Angina pectoris.
- Acute myocardial infarction.
- Sudden cardiac death.
- Chronic ischemic heart disease with congestive heart failure.

Ischemic Heart diseases (IHD) are commonly caused by coronary artery atherosclerosis, less commonly caused by vasospasm and vasculitis.

Epidemiology:

- **Peak incidence:**
  - Males: at 60 years old
  - Females: at 70 years old.
  - Men are **affected more** than women.

- Contributing factors are same as that of atherosclerosis e.g.

Hypertension	Smoking	Genetic factors (direct or indirect)
Diabetes mellitus	High levels of LDL	Lack of exercise

Pathogenesis:

1. Role of *Critical stenosis* or obstruction:

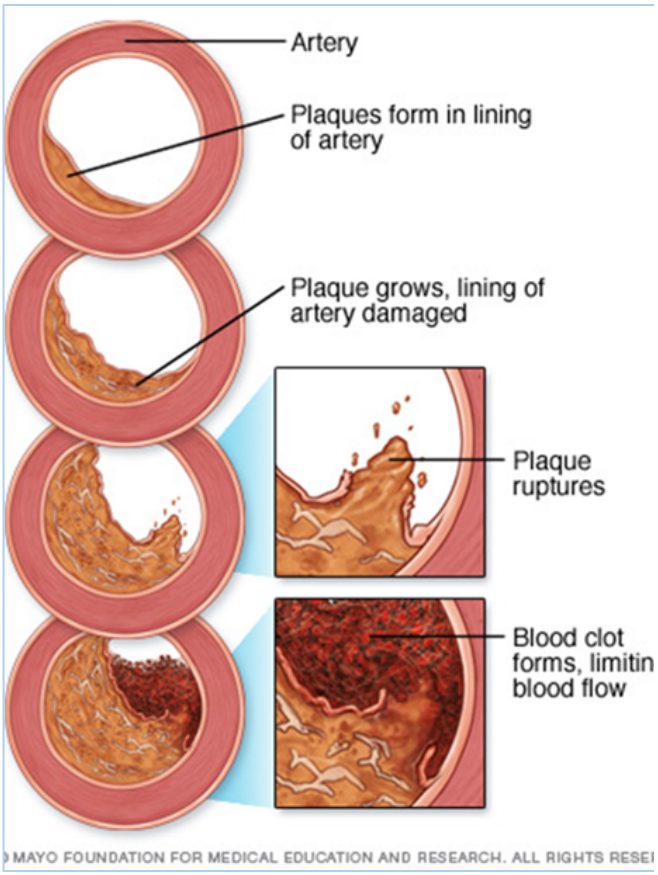
- A lesion obstructing **70% to 75%** or more of a vessel lumen-so-called critical stenosis-generally causes **symptomatic ischemia (angina)** only in the setting of **increased demand** ألم شديد عند بذل مجهود، كصعود الدرج مثلا
- A fixed **90% stenosis** can lead to inadequate coronary blood flow even **at rest** يظهرالألم حتى عند الراحة

2. Role of Acute Plaque Change:

In most patients, unstable angina, acute myocardial infarction and (most common) sudden cardiac death occur because of abrupt plaque change followed by thrombosis.

→ Disruption of a mildly stenosing plaque leading to rupture/ ulceration. This can lead to:

1. Hemorrhage into the atheroma, which will expand in volume.
2. Exposure of the thrombogenic basement membrane just below the endothelial lining followed by thrombosis



3. Role of Coronary Thrombus:

Partially stenotic plaque converts the thrombus to either a ***total occlusion*** leading to acute transmural MI or a ***partial occlusion*** which could lead to unstable angina, acute subendocardial infarction, or sudden cardiac death.

- Thrombus in coronary artery can also **embolize.**

4. Role of Vasoconstriction:

Reduces lumen size, therefore it may potentiate plaque disruption.

5. Role of Inflammation:

Play important roles at **all stages** of atherosclerosis.

What happens?

1. The initiating event typically is sudden disruption of partially occlusive plaque.

2. More than one mechanism of injury may be involved:

    a. Rupture, fissuring, or ulceration of plaques can expose highly thrombogenic constituents or underlying subendothelial basement membrane, leading to rapid thrombosis.

3. Fixed obstructions that occlude less than 70% of a coronary vessel lumen typically are asymptomatic, even with exertion.

4. Lesions that occlude more than 70% of a vessel lumen—resulting in critical stenosis— generally cause symptoms in the setting of increased demand; the patient is said to have stable angina.

5. A fixed stenosis that occludes 90% or more of a vascular lumen can lead to inadequate coronary blood flow with symptoms even at rest—one of the forms of unstable angina.

6. If an atherosclerotic lesion progressively occludes a coronary artery at a sufficiently slow rate over years, remodeling of other coronary vessels may provide compensatory blood flow for the area at risk; such collateral perfusion can subsequently protect against MI even if the vessel eventually becomes completely occluded. Unfortunately, with acute coronary blockage, there is no time for collateral flow to develop and infarction results.

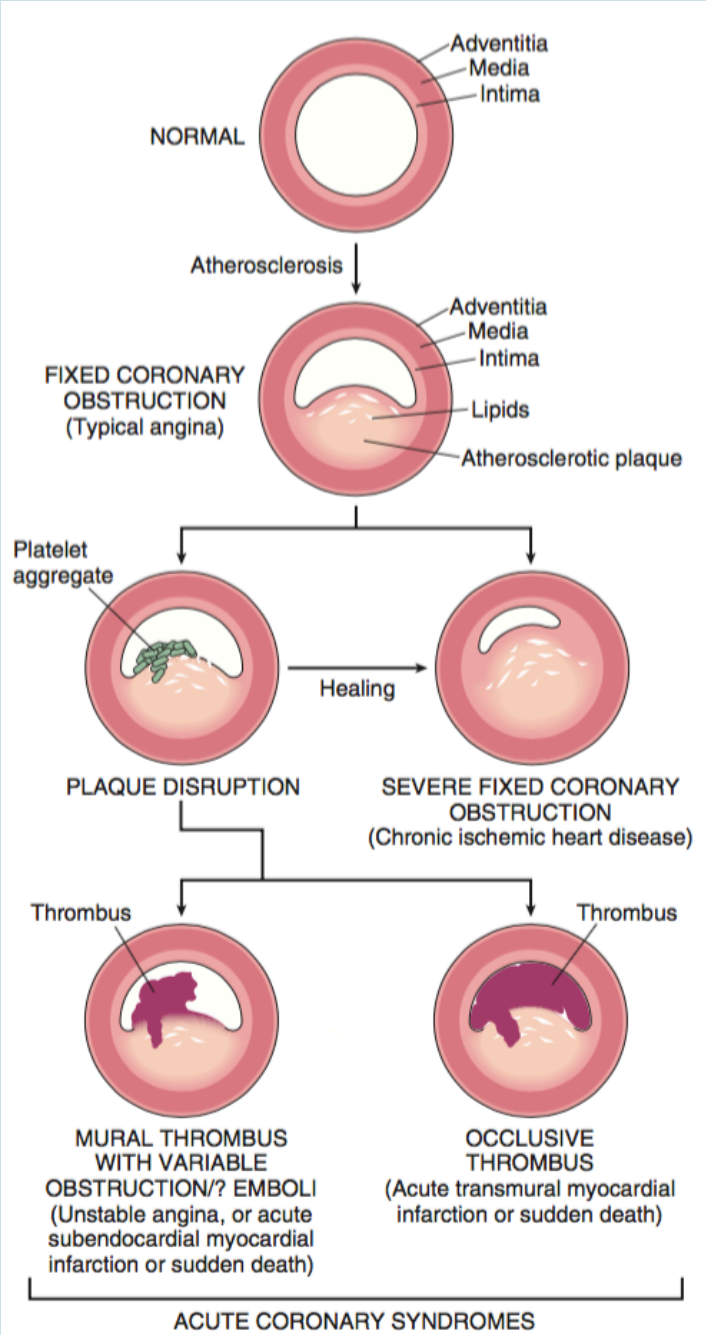
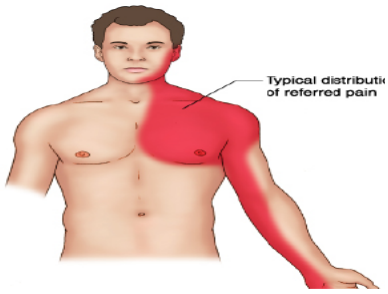


Figure 10–7 Diagram of sequential progression of coronary artery lesions leading to various acute coronary syndromes.

Angina pectoris:

Angina pectoris is a **type of IHD** characterized by **paroxysmal** and usually recurrent attacks of substernal or precordial chest discomfort, described as constricting, crushing, squeezing, choking, or knifelike pain.

The pain may radiate down the left arm or to the left jaw *(called as referred pain)* . Intermittent chest pain caused by transient, reversible ischemia



The pain probably is a consequence of the ischemia-induced release of **adenosine, bradykinin**, and other molecules that stimulate the **autonomic afferents**.

Angina pectoris is due to **inadequate perfusion** and is caused by transient (15 seconds to 15 minutes) myocardial ischemia that falls short of inducing the cellular necrosis that defines infarction (duration and severity is not sufficient for infarction).

There are three types of angina pectoris:

1. **Stable angina or typical angina pectoris:**
   - Most common form of angina.
   - It is caused by atherosclerotic disease with usually 70% to 75% narrowing of **lumen.**
     This reduction (70 to 75% stenosis) of coronary vessels makes the heart vulnerable, so whenever there is increased demand (e.g. physical activity, emotional excitement, or any other cause of increased cardiac workload), there is **angina pain**.
   - The chest pain is **episodic and associated with exertion or some other form of stress.**
   - Is usually relieved by rest (thereby decreasing demand) or with a **strong vasodilator like nitroglycerin**.
2. **Unstable or crescendo angina:**
   - It is an **unstable and progressive** condition (90% narrowing (fixed) of **lumen**).
   - Pain occurs with **progressively increasing frequency**, and is precipitated with progressively less exertion, even at rest, and tends to be of more prolonged duration.
   - It is induced by disruption or rupture of an **atheroma plaque** with **superimposed partial thrombosis**.
   - **Unstable angina** is often the precursor of subsequent acute MI. Thus also called as **preinfarction angina**.
3. **Prinzmetal or variant angina:**
   - An uncommon pattern of episodic angina that occurs **at rest due to coronary artery spasm.**
   - Prinzmetal angina generally responds promptly to vasodilators, such as **nitroglycerin** and **calcium channel blockers**.
   - It is **not** related to **atherosclerotic disease.**
   - **The etiology is not clear**.

Myocardial infarction:

Also known as "heart attack", *is necrosis of heart muscle resulting from ischemia.*
Half - Third of the people suffering from MI usually die before they get to the hospital .
Risk factors are the same in atherosclerosis .

Pathogenesis of MI:

Most common cause is thrombosis on a preexisting disrupted atherosclerotic plaque. In the typical case of MI, the following sequence of events can be proposed:

- **Acute plaque change:**

  A sudden change in the structure of an atheromatous plaque, like disruption, ulceration, or rupture and intraplaque hemorrhage.
- Exposure of the thrombogenic subendothelial basement membrane and necrotic plaque contents resulting in thrombus formation.
- Myocardial necrosis begins within 20-30 minutes (mostly starting at the subendocardial region) (because it is less perfused and has high intramural pressure).
- Infarct reaches its full size within 3-6 hrs. (During this period, lysis of the thrombus by streptokinase or tissue plasminogen activator, *may limit the size of the infarct.*)
- Irreversible cell injury: When ischemia lasts for 20-40 min
- With more prolonged ischemia, a wave-front of cell death moves through other regions of the myocardium, with the infarct usually achieving its full extent within 3 to 6 hours; in the absence of intervention, the infarct can involve the entire wall thickness **(transmural infarct).**

Types of MI:

1. **Transmural:** Full thickness (>50% of the wall).
2. **Subendocardial:**

   Inner 1/3 of myocardium. As already mentioned, the subendocardial region is most vulnerable to hypoperfusion and hypoxia.

Morphology:

Read this:

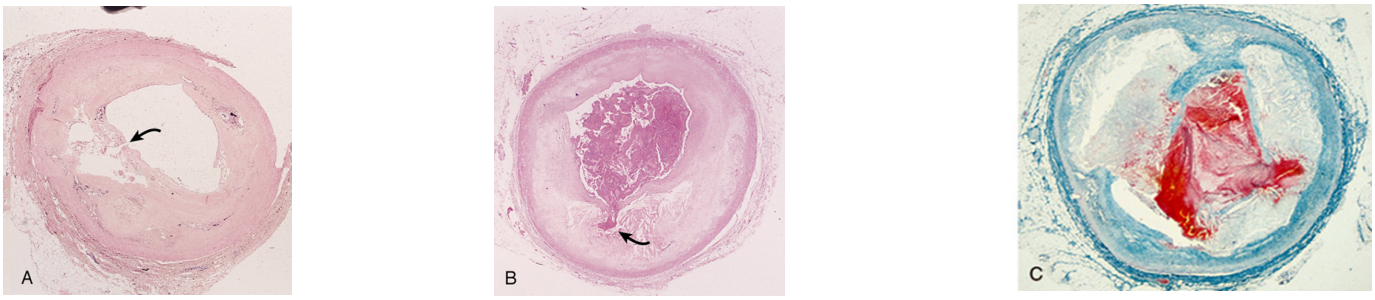
ıble 10–3 Evolution of Morphologic Changes in Myocardial Infarction

me Frame	Gross Features	Light Microscopic Findings	Electron Microscopic Findings
eversible Injury			
-1½ hours	None	None	Relaxation of myofibrils; glycogen loss; mitochondrial swelling
reversible Injury			
–4 hours	None	Usually none; variable waviness of fibers at border	Sarcolemmal disruption; mitochondrial amorphous densiti
12 hours	Occasionally dark mottling	Beginning coagulation necrosis; edema; hemorrhage	
–24 hours	Dark mottling	Ongoing coagulation necrosis; pyknosis of nuclei; hypereosinophilic appearance of myocytes; marginal contraction band necrosis; beginning neutrophilic infiltrate	
3 days	Mottling with yellow-tan infarct center	Coagulation necrosis with loss of nuclei and striations; interstitial infiltrate of neutrophils	
7 days	Hyperemic border; central yellow-tan softening	Beginning disintegration of dead myofibers, with dying neutrophils; early phagocytosis of dead cells by macrophages at infarct border	
10 days	Maximally yellow-tan and soft, with depressed red-tan margins	Well-developed phagocytosis of dead cells; early formation of fibrovascular granulation tissue at margins	
–14 days	Red-gray depressed infarct borders	Well-established granulation tissue with new blood vessels and collagen deposition	
8 weeks	Gray-white scar, progressive from border toward core of infarct	Increased collagen deposition, with decreased cellularity	
months	Scarring complete	Dense collagenous scar	

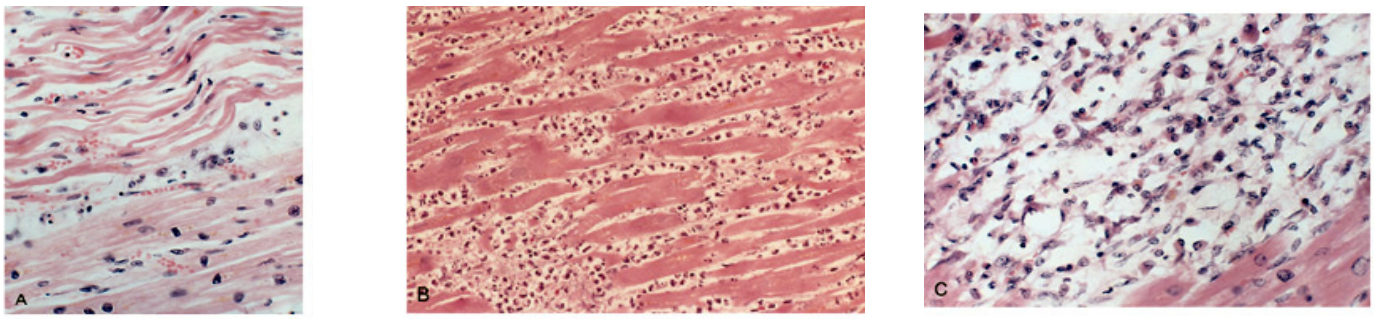
Morphologic Changes in Myocardial Infarction (Study this):

Time	Gross changes	Microscopic changes
0-4h	None	
4-12h	Mottling تبقع	Coagulation necrosis
12-24	Mottling	More coagulation necrosis; Neutrophils come in
1-7d	Yellow infarct center	Neutrophils die, macrophages come to eat dead cells
1-2w	Yellow center, red borders	Granulation tissue
2-8w	Scar	Collagen

You can skip this page if you understood Morphology well

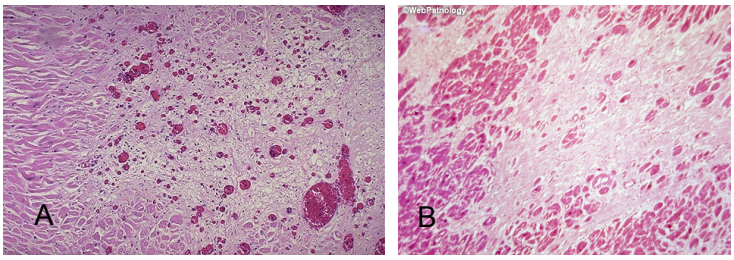


A. Plaque rupture without superimposed thrombus in a patient who died suddenly.
B. Acute coronary thrombosis superimposed on an atherosclerotic plaque with focal disruption of the fibrous cap, triggering fatal myocardial infarction.
C. Massive plaque rupture with superimposed thrombus, also triggering a fatal myocardial infarction (special stain highlighting fibrin in red). In both

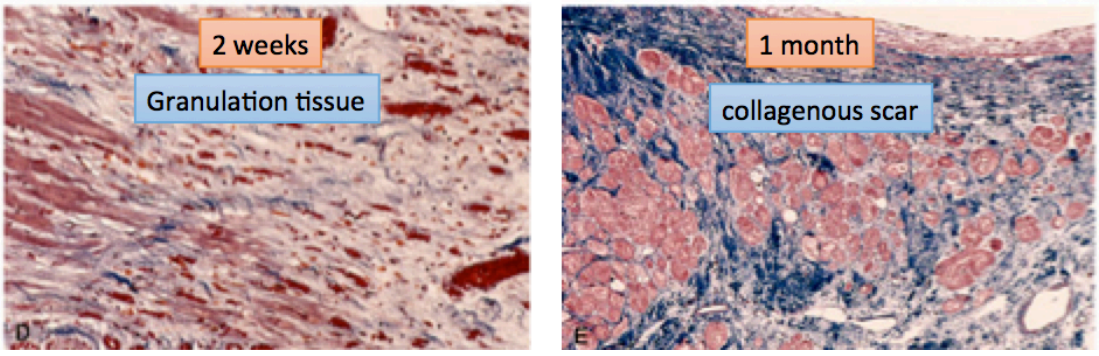


Microscopic features of myocardial infarction.

A. One-day-old infarct showing coagulative necrosis with few neutrophils, wavy fibers with elongation, and narrowing, compared with adjacent normal fibers (lower right).
B. Dense neutrophilic infiltrate in an area of acute myocardial infarction of 3 to 4 days' duration.
C. C. Nearly complete removal of necrotic myocytes by phagocytosis (approximately 7 to 10 days).



A. Granulation tissue approx. 3 weeks post MI
B. Healed MI with replacement of the necrotic fibers by dense collagenous scar. Residual cardiac muscle cells are present



Clinical Features:

- **Pain:**
  - Severe crushing sub-sternal chest pain, which may radiate to the neck, jaw, epigastrium, shoulder or left arm.
  - Pain lasts for hours to days and is not relieved by nitroglycerin.
  - Absent in 20% of patients (diabetics, hypertensive, elderly).
- **Pulse is rapid and weak.**
- **Diaphoresis (sweating)**
- **Dyspnea.**
- **Cardiogenic shock[1] in massive MI (>40%of lt. ventricle).**
- **ECG shows typical findings of ischemia.**

Biochemical markers of myocardial infarction:

- Best marker - Tnt, Tnl (more specific) - Not normally detectable in circulation. - After acute MI both troponins become detectable with in 2-4 hrs. - Peaks at 48 hrs. - Remains elevated 7-10 days.	**Troponin[2]**
- Second best marker - Begins to rise after 2-4 hrs. of MI - Peaks at 24-48 hrs. - Returns to normal within 72 hrs.	**CK-MB[3]**
- Rise 24 hrs. - Peaks at 72 hrs. - Persist 72 hrs.	**Lactate dehydrogenase [4](LD) LD1**

[1] Low blood perfusion to tissues.
[2] Troponins are regulatory proteins (troponin C, troponin I, and troponin T) that are integral to muscle contraction.
[3] An enzyme expressed by various tissues and cell types 3 iso-types CK-MM, CK-BB and CK-MB. [M: muscle B brain]
[4] A **lactate dehydrogenase** (**LDH** or **LD**) is an enzyme found in nearly all living cells [LDH-1— heart RBC, brain].

Complications:

- No complications in 10-20%.
- 80-90% experience one or more of the following complications:
  1. **Cardiac arrhythmia** (75-90%):

     Myocardial ischemia also contributes to arrhythmias, probably by causing **electrical instability (irritability)** of ischemic regions of the heart. Although massive myocardial damage can cause a fatal mechanical failure, sudden cardiac death in the setting of myocardial ischemia most often is due to ventricular fibrillation caused by myocardial irritability.

  2. **Left ventricular failure** with mild to severe **pulmonary edema** (60%).
  3. **Cardiogenic shock** (10%).
  4. **Myocardial rupture:**

     Rupture of free wall, septum, rupture of papillary muscle (leading to papillary muscle and associated valve incompetence/dysfunction)
  5. **Thromboembolism** (15-49%).

     The combination of a local myocardial abnormality in contractility (causing stasis) with endocardial damage (causing a thrombogenic surface) can foster mural thrombosis and, potentially, thromboembolism
  6. **Pericarditis**
  7. **Ventricular aneurysm** in which the ventricle is dilated and the wall is thinned out.
  8. **External rupture** of the infarct with associated bleeding into the pericardial space (hemopericardium).
  9. **Progressive late heart failure** in the form of chronic IHD.
  10. **Contractile dysfunction**
  11. **Right ventricular infarction**
  12. **Reperfusion injury:**
      - → Mediated in part by oxygen free radicals generated by the increased number of infiltrating leukocytes facilitated by reperfusion.
      - → Reperfusion-induced microvascular injury causes not only haemorrhage but also endothelial swelling that occludes capillaries and may prevent local blood flow (called *no-reflow*).
      - → A reperfused infarct usually has haemorrhage because the vasculature injured during the period of ischemia is leaky after flow is restored

Chronic ischemic heart disease:

1. Progressive heart failure due to ischemic injury, either from:

- Prior infarction (most common).
- Chronic low- grade ischemia.

2. Sudden cardiac death:

- Unexpected death from cardiac causes either without symptoms or within 1 to 24 hours of symptom onset.
- Results from a fatal arrhythmia, most commonly in patients with severe coronary artery disease.

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قال صلى الله عليه وسلم: من سلك طريقًا يلتمس فيه علمًا سهّل الله له به طريقًا إلى الجنة

دعواتنَا لكم بالتوفيق.