Pathology of cardiovascular system
6 lectures

1. Rheumatic Heart Disease………….Dr Rikabi
2. Ischemic Heart Disease
3. Atherosclerosis
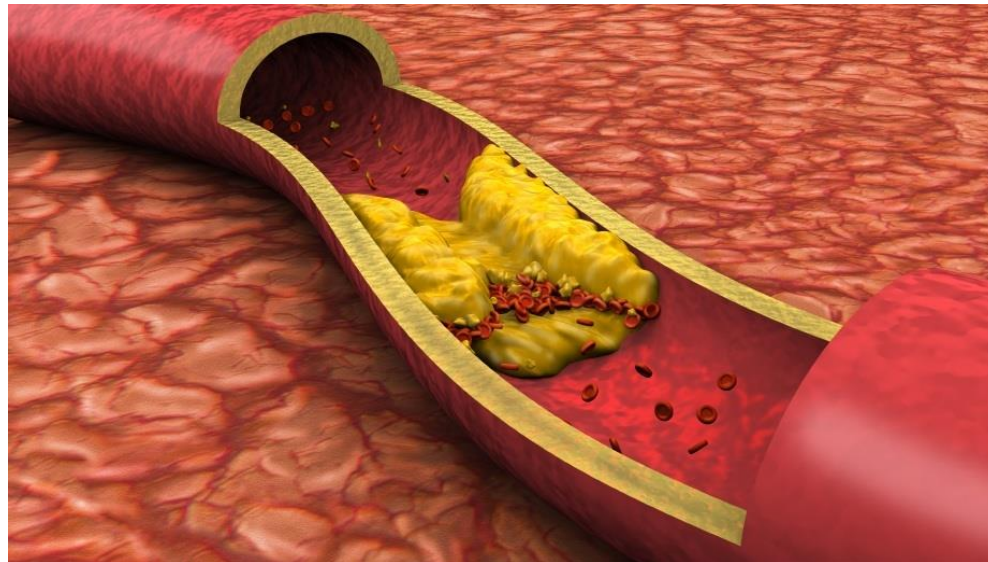4. Hypertension
5. Thromboembolism
6. Vasculitis

1

Revision

2

3,4

Revision

5

Atherosclerosis and ischemic heart disease
prof. Ahmed Alhumidi.
Pathology.
KSU. Riyadh.
2019

Objectives:

1. Understand the pathology, pathogenesis and clinical consequences of atherosclerosis.

2. Be able to discuss pathology and complications of ischaemic heart diseases with special emphasis on myocardial infarction.

3. Know how lifestyle modifications can reduce the risk of ischaemic heart disease.

Arteriosclerosis "hardening of the arteries") is a generic term for thickening and loss of elasticity of arterial walls.

Atherosclerosis

Mönckeberg medial calcific sclerosis
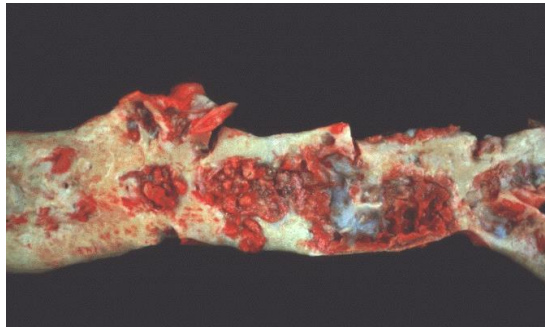
Old age

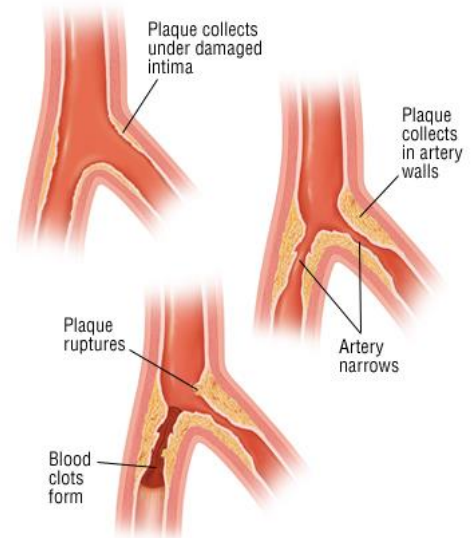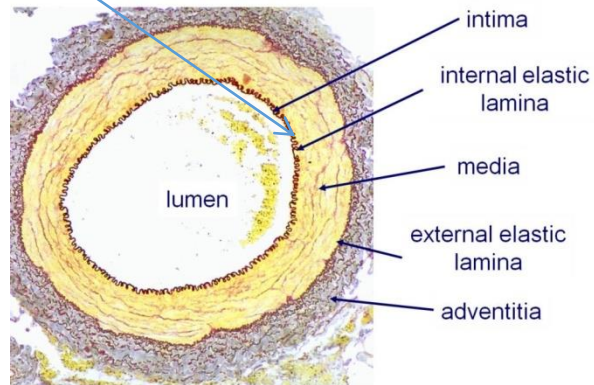*Arteriolosclerosis*

Hypertention

Atherosclerosis (AS)

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

Atheroma=   Intimal thickening + lipid accumulation

Normal histology of artery

Atheroma

Atherosclerotic plaques have three principal components:
1. **Cells**: SMCs, foam macrophages, lymphocytes
2. **Extracellular matrix**: collagen, elastic fibers
3. **Lipid**: Typical atheromas contain relatively abundant lipid both intracellular and extracellular lipid .

FIBROUS CAP
(smooth muscle cells, macrophages, foam cells, lymphocytes, collagen, elastin, proteoglycans, neovascularization)

NECROTIC CENTER
(cell debris, cholesterol crystals, foam cells, calcium)

MEDIA

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Pre-Clinical Phase
Usually young age

Clinical horizon

Clinical Phase
Usually middle age to elderly

FATTY STREAK

Mural thrombosis
Embolization
Wall weakening

ANEURYSM AND RUPTURE

NORMAL ARTERY

FIBROFATTY PLAQUE

ADVANCED/ VULNERABLE PLAQUE

Plaque rupture
Plaque erosion
Plaque hemorrhage
Mural thrombosis
Embolization

OCCLUSION BY THROMBUS

At lesion-prone areas, and accelerated by risk factors:
Endothelial dysfunction
Monocyte adhesion/emigration
SMC migration to intima
SMC proliferation
ECM elaboration
Lipid accumulation

Cell death/degeneration
Inflammation
Plaque growth
Remodeling of plaque and wall ECM
Organization of thrombus
Calcification

Progressive plaque growth

CRITICAL STENOSIS

COMPLICATIONS

1. Rupture, ulceration
2. Hemorrhage
3. thrombosis,
4. Aneurysmal dilation.

Fatty streaks = macrophage-derived foam cells

fibrous plaques

complicated lesions
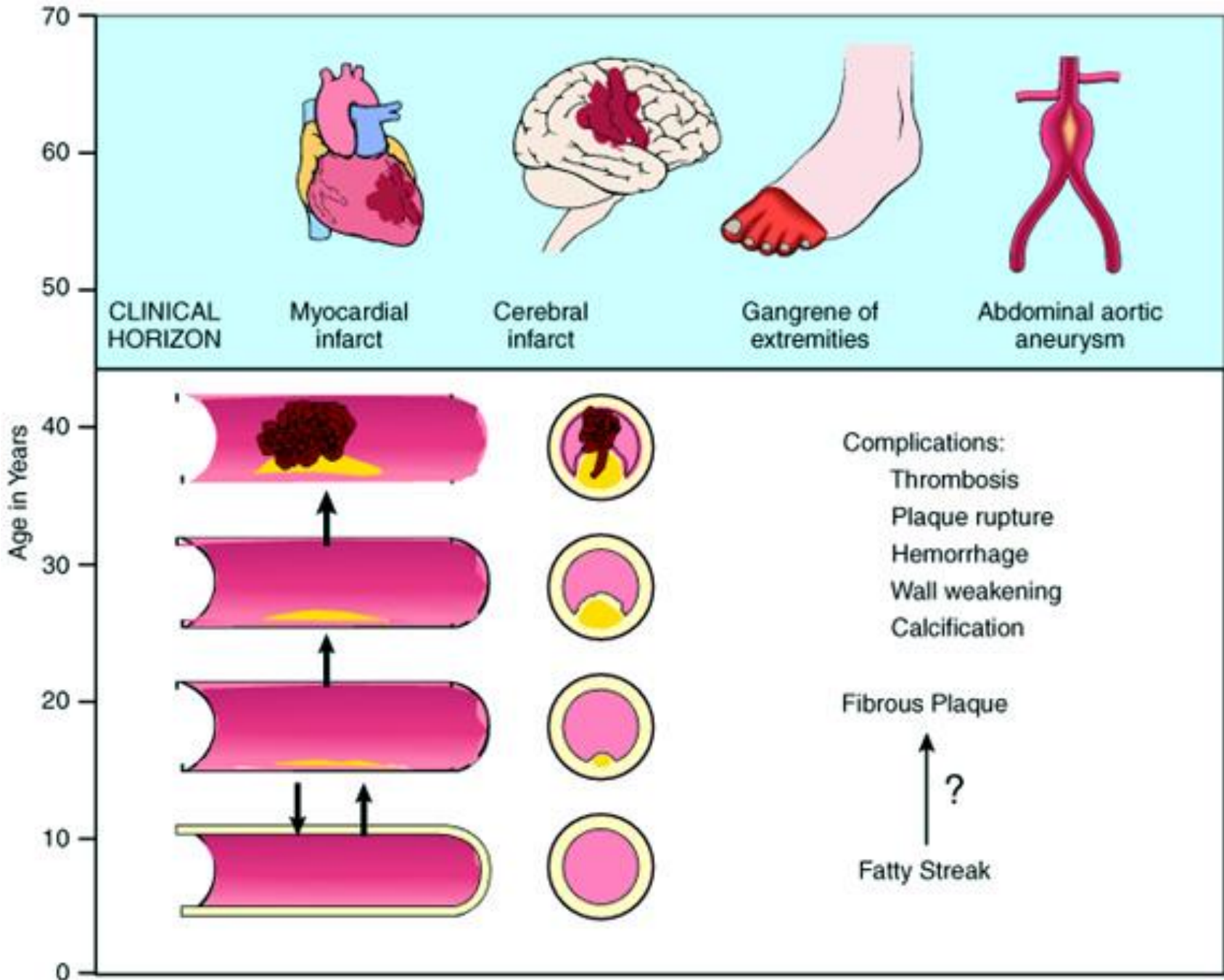
Natural history of atherosclerosis

Slide 12.5

Risk Factors for Atherosclerosis

MINOR/UNCERTAIN/NONQUANTITATED RISK FACTORS
Obesity
Physical inactivity
Stress ("type A" personality)
Postmenopausal estrogen deficiency
High carbohydrate intake
Alcohol
Lipoprotein Lp(a)
Hardened (trans)unsaturated fat intake
Chlamydia pneumoniae

MAJOR RISK FACTORS	
NON-MODIFIABLE	POTENTIALLY MODIFIABLE
Increasing age	Hyperlipidemia
Male gender	Hypertension
Family history	Cigarette smoking
Genetic abnormalities	Diabetes

(i) anti-C. pneumoniae antibodies
(ii) detection of the organism within atherosclerotic lesions,

Importance of types of lipoproteins in hypelipidemia

- Low-density lipoproteins (LDLs)
- Very-low-density lipoproteins (VLDLs)
- Chylomicrons

High-density lipoproteins (HDLs)

"good" cholesterol, because high levels seem to protect against heart attack.

Endothelium
Intima
Media
Adventitia

Risk Factors

1. Chronic endothelial "injury":
 • Hyperlipidemia
 • Hypertension
 • Smoking
 • Homocysteine
 • Hemodynamic factors
 • Toxins
 • Viruses
 • Immune reactions

PATHOGENESIS

Response to injury

2. Endothelial dysfunction (e.g., increased permeability, leukocyte adhesion) Monocyte adhesion and emigration.

3. Smooth muscle emigration from media to intima. Macrophage activation.
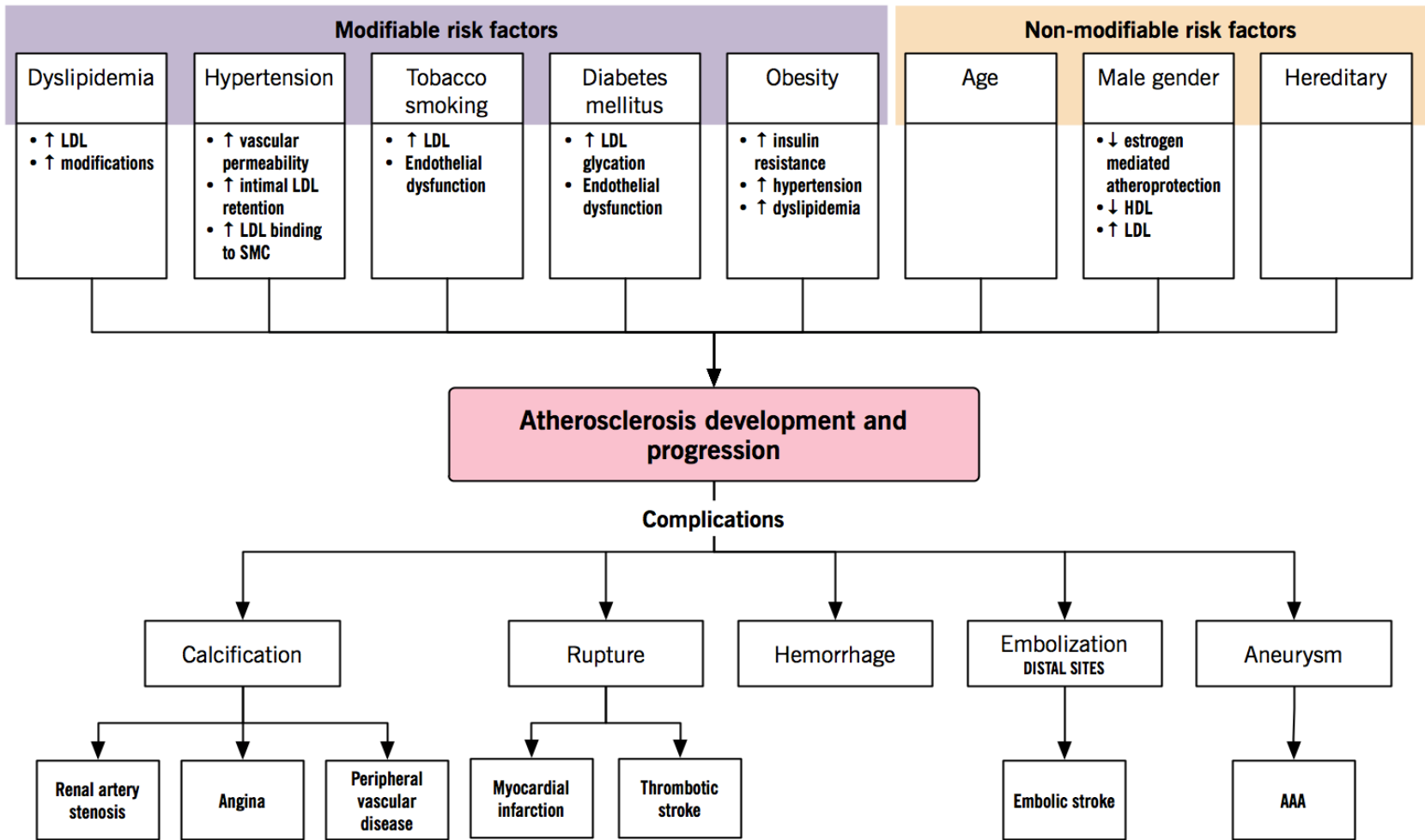
Fatty streak
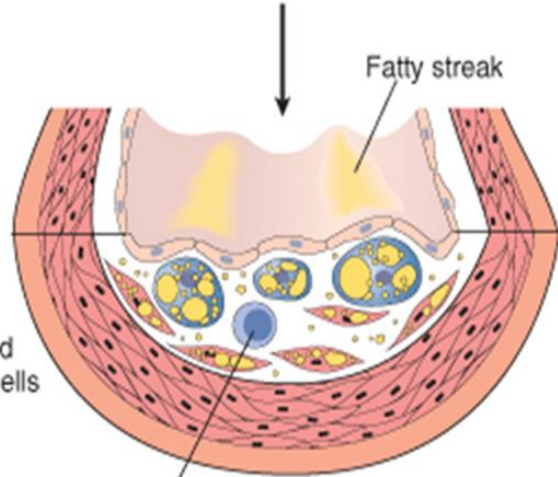
4. Macrophages and smooth muscle cells engulf lipid

Lymphocyte

Fibrofatty atheroma

5. Smooth muscle proliferation, collagen and other ECM deposition, extracellular lipid

Lymphocyte   Collagen

Lipid debris

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SUMMARY

ATHEROSCLEROSIS | Risk factors and complications of atherosclerosis

Modifiable risk factors					Non-modifiable risk factors		
Dyslipidemia	Hypertension	Tobacco smoking	Diabetes mellitus	Obesity	Age	Male gender	Hereditary
• ↑ LDL • ↑ modifications	• ↑ vascular permeability • ↑ intimal LDL retention • ↑ LDL binding to SMC	• ↑ LDL • Endothelial dysfunction	• ↑ LDL glycation • Endothelial dysfunction	• ↑ insulin resistance • ↑ hypertension • ↑ dyslipidemia		• ↓ estrogen mediated atheroprotection • ↓ HDL • ↑ LDL	

Atherosclerosis development and progression

Complications

- Calcification
  - Renal artery stenosis
  - Angina
  - Peripheral vascular disease
- Rupture
  - Myocardial infarction
  - Thrombotic stroke
- Hemorrhage
- Embolization DISTAL SITES
  - Embolic stroke
- Aneurysm
  - AAA

treatment : Angioplasty
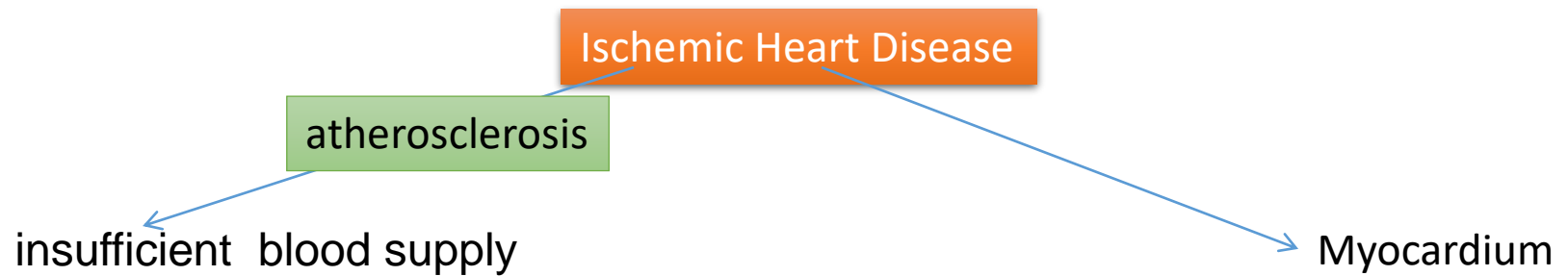
http://www.pathophys.org/

Ischemic Heart Disease

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2019

Reference: Robbins & Cotran Pathology and Rubin's Pathology

Ischemic Heart Disease

atherosclerosis

insufficient blood supply → Myocardium

✓Angina pectoris (chest pain).
✓Acute myocardial infarction.
✓Sudden cardiac death.
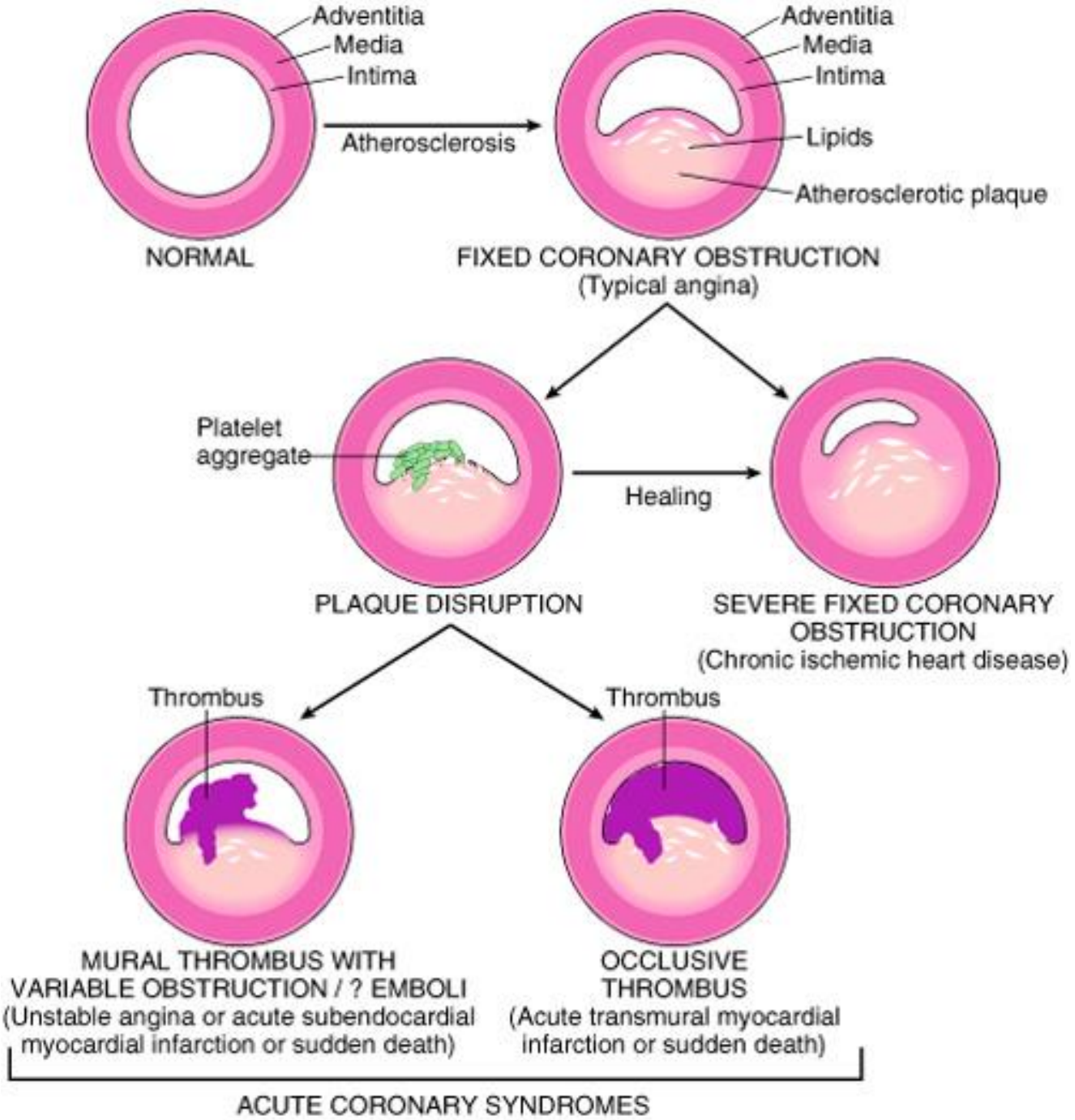✓Chronic ischemic heart disease

Pathogenesis

- 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

- A fixed 90% stenosis can lead to inadequate coronary blood flow even at rest

In most patients, unstable angina, infarction, occur because of <u>abrupt plaque change</u> followed by thrombosis

Rupture, fissuring, or ulceration

NORMAL

FIXED CORONARY OBSTRUCTION
(Typical angina)

- Adventitia
- Media
- Intima
- Lipids
- Atherosclerotic plaque

Atherosclerosis

Platelet aggregate

PLAQUE DISRUPTION

Healing

SEVERE FIXED CORONARY OBSTRUCTION
(Chronic ischemic heart disease)

Thrombus

Thrombus

MURAL THROMBUS WITH VARIABLE OBSTRUCTION / ? EMBOLI
(Unstable angina or acute subendocardial myocardial infarction or sudden death)

OCCLUSIVE THROMBUS
(Acute transmural myocardial infarction or sudden death)

ACUTE CORONARY SYNDROMES

Angina pectoris

▸ Angina pectoris is a type of IHD characterized by paroxysmal and usually recurrent attacks of *substernal* chest discomfort (variously described as constricting, crushing, squeezing, choking, or knifelike). May radiate down the left arm or to the left jaw *(referred pain)* .

Intermittent chest pain caused by transient, reversible ischemia

1. Typical (stable) angina
   - pain on exertion
   - fixed narrowing of coronary artery
2. Unstable (pre-infarction) angina
   - increasing pain with less exertion
   - plaque disruption and thrombosis
3. Prinzmetal (variant) angina   ذبحة صدرية مخالفة للمعتاد،
   - pain at rest
   - coronary artery spasm of unknown etiology
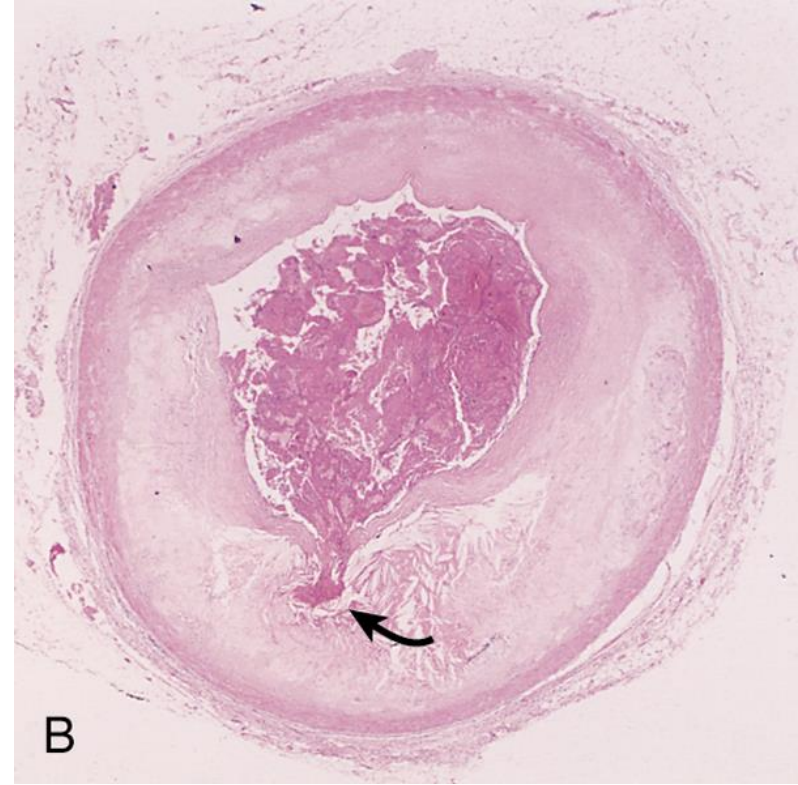
Myocardial Infarction

- Definition: MI, also known as "heart attack," is the death of cardiac muscle resulting from ischemia.

- Risk factors are the same as those of atherosclerosis.

Disruption of an atherosclerotic plaque results in the formation of thrombus
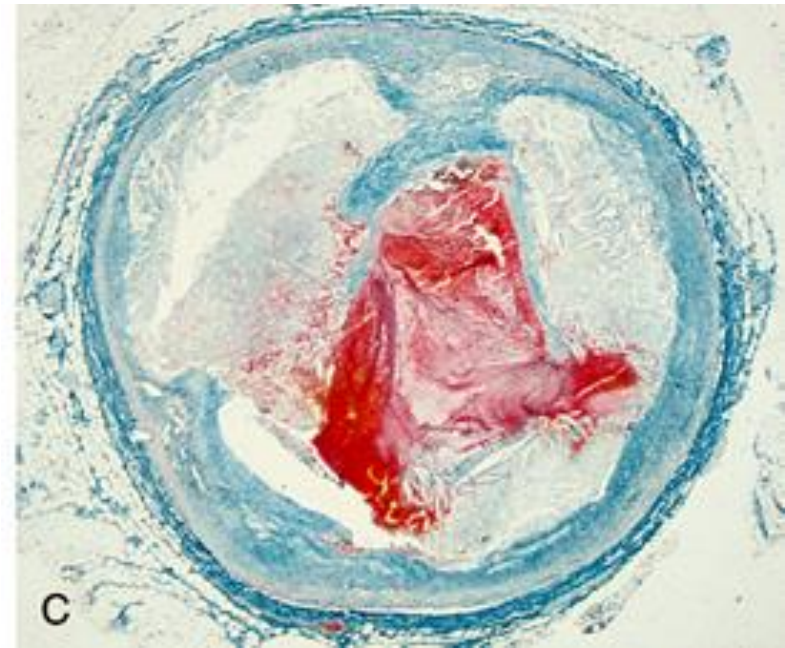

Blocked right coronary artery
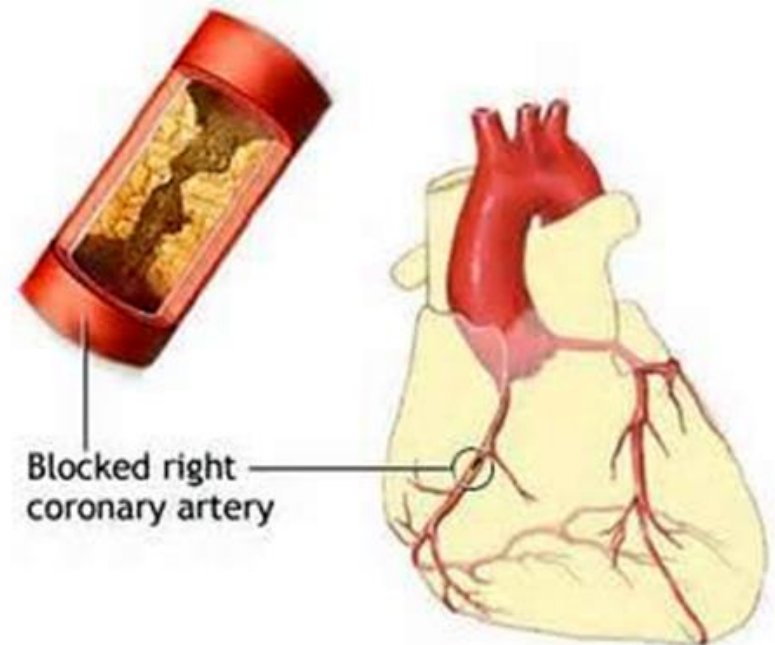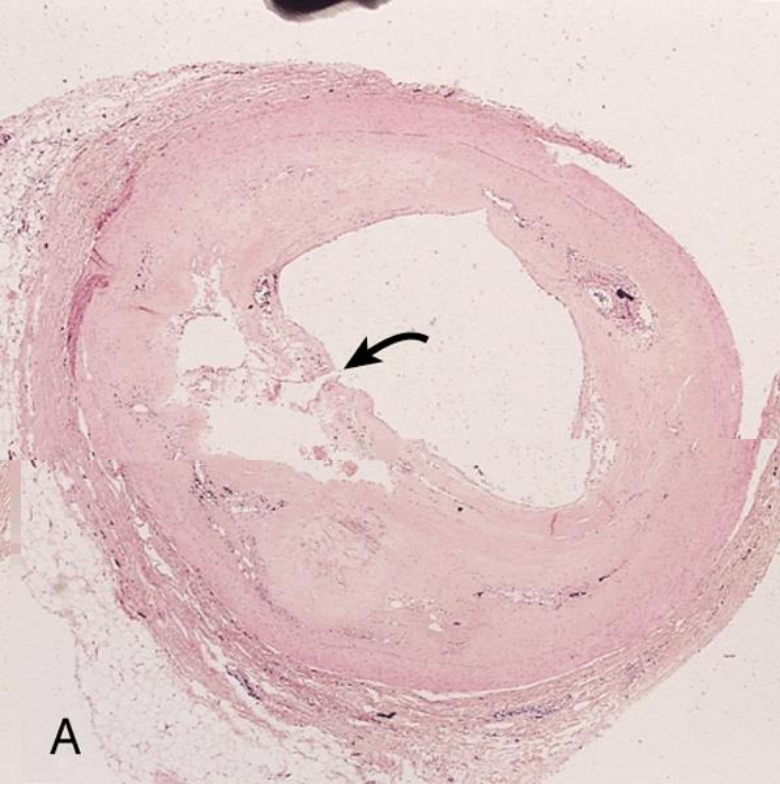
A. Plaque rupture without superimposed thrombus in a patient who died suddenly.

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

Pathogenesis of MI

- Myocardial necrosis begins within 20-30 minutes, mostly starting at the subendocardial region (less perfused, 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: 20-40 min

Types

1. **Transmural**
   Full thickness (>50% of the wall)
2. **Subendocardial**
   Inner 1/3 of myocardium

Morphologic Changes in Myocardial Infarction

Time	Gross changes	Microscopic changes
0-4h	None	None
4-12h	Mottling تبقع	Coagulation necrosis
12-24h	Mottling	More coagulation necrosis; neutrophils come in
1-7 d	Yellow infarct center	Neutrophils die, macrophages come to eat dead cells
1-2 w	Yellow center, red borders	Granulation tissue
2-8 w	Scar	Collagen
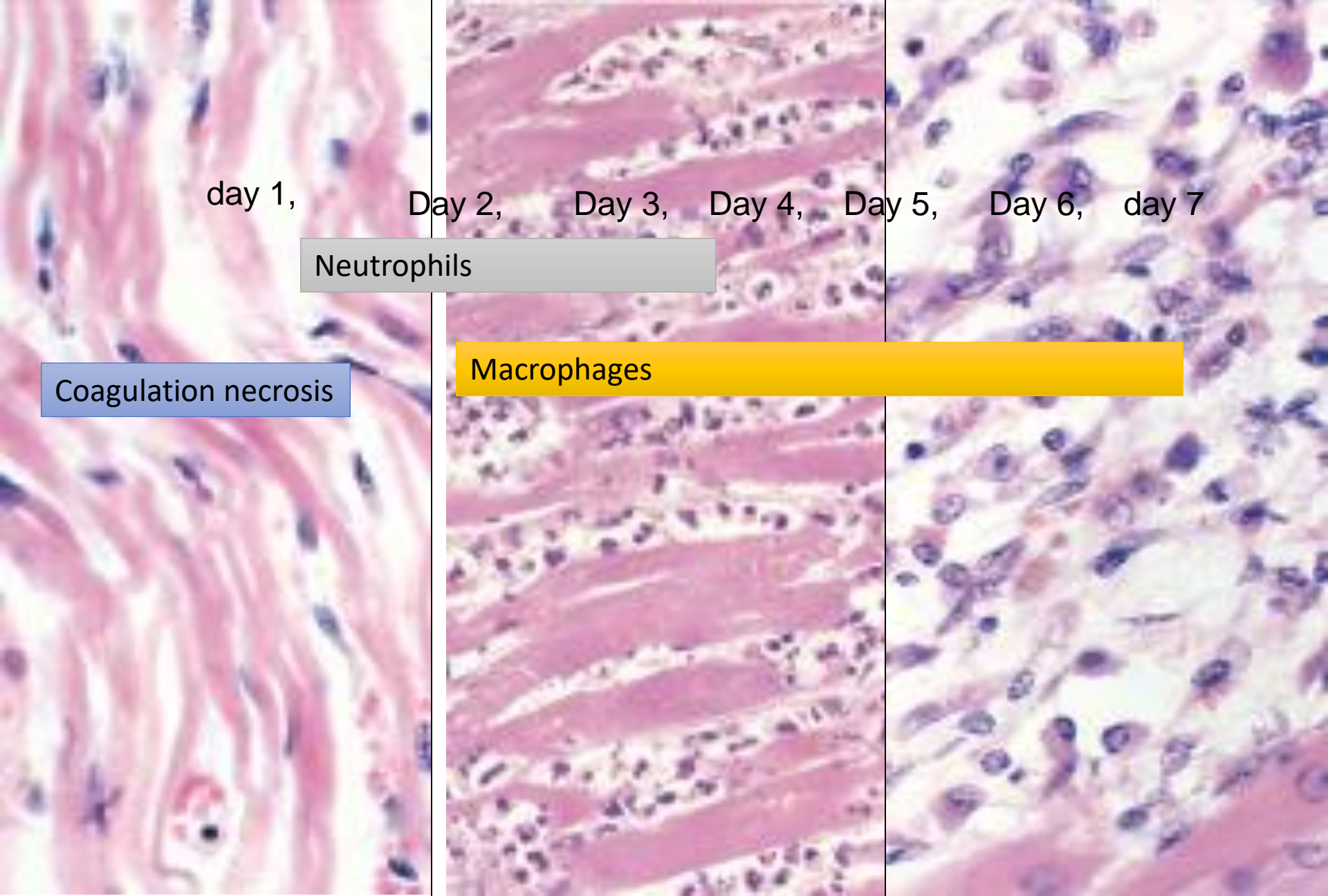
day 1,   Day 2,   Day 3,   Day 4,   Day 5,   Day 6,   day 7

Neutrophils

Coagulation necrosis

Macrophages

MI: day 1, day 3, day 7

2 weeks — Granulation tissue

1 month — collagenous scar

Myocardial Infarction: 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 in massive MI(>40%of lt. ventricle).

▶ ECG shows typical findings of ischemia.

shock is low blood perfusion to tissues

Ischemic Heart Disease
# Laboratory evaluation

1. Troponins: **best marker**, TnT, TnI (more specific).
   - TnI and TnT are not normally detectable in the circulation
   - After acute MI both troponins become detectable after 2 to 4 hours, peaks at 48 hours. Their levels remain elevated for 7 to 10 days

2. CK-MB is the **second best mar**ker:
   - It begins to rise within 2 to 4 hours of MI, peaks at 24 to 48 hours and returns to normal within approximately 72 hours

3. Lactate dehydrogenase (LD)… LD1.
   - Rise 24 hrs,   peaks 72 hrs, persists 72 hrs.

Troponins are regulatory proteins ((troponin C, troponin I, and troponin T) that are integral to muscle contraction

Creatine kinase (CK) —is an enzyme expressed by various tissues and cell types 3 isoypes CK-MM, CK-BB and CK-MB. [M: musle B brain]

A **lactate dehydrogenase** (**LDH** or **LD**) is an enzyme found in nearly all living cells [LDH-1— heart RBC, brain].

Blood levels of myoardial proteins (times elevated over the reference limit)

Troponin I

Troponin T

MB

CKMB

Time since onset of symptoms
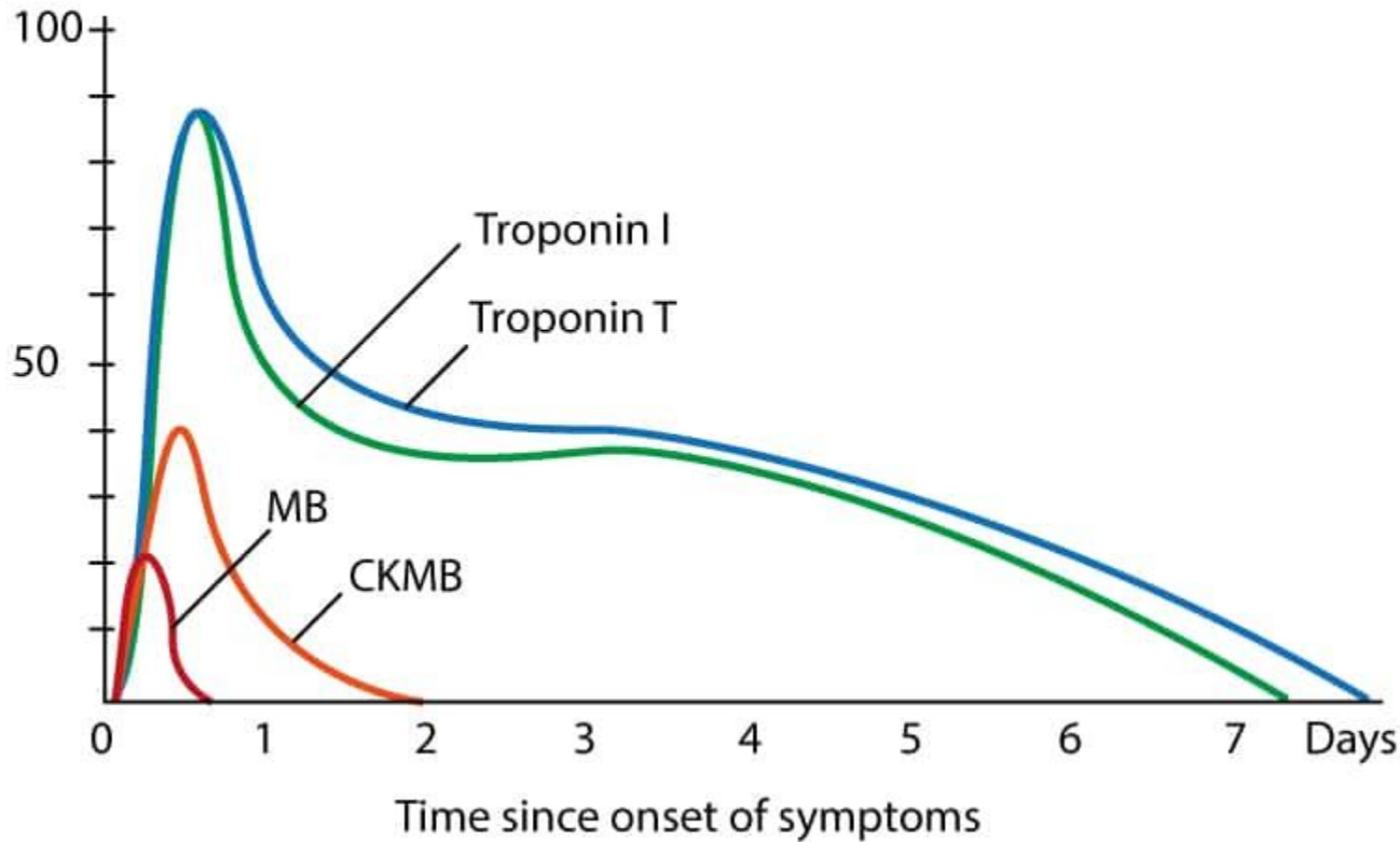
Myocardial Infarction: Outcomes or complications

- No complications in 10-20%.
- 80-90% experience one or more of the following complications:
  1. Cardiac arrhythmia (75-90%). Many patients have conduction disturbances and myocardial irritability following MI, which undoubtedly are responsible for many of the sudden deaths. Sudden coronary death can occur due to ventricular arrhythmia.
  2. Left ventricular failure with mild to severe pulmonary edema (60%).
  3. Cardiogenic shock (10%).

Complications of MI

4. Myocardial rupture:

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.

Myocardial Infarction (MI), summary

- Necrosis of heart muscle caused by ischemia

- Most due to acute coronary artery thrombosis
  - irreversible injury/cell death in 20-40 minutes

- Prompt reperfusion can salvage myocardium

Salvage ينقذ

Myocardial Infarction (MI), summary

- ## Clinical features
  - Severe, crushing chest pain ± radiation
  - Not relieved by nitroglycerin, rest
  - Sweating, nausea, dyspnea
  - Sometimes no symptoms

- ## Laboratory evaluation
  - Troponins detected within 2-4 hours, remain elevated for a week.
  - CK-MB increases within 2-4 hours, returns to normal within 72 hours.

- ## Complications
  - contractile dysfunction
  - arrhythmias
  - rupture
  - chronic progressive heart failure

- ## Prognosis
  - depends on remaining function and perfusion
  - overall 1 year mortality: 30%
  - 3-4% mortality per year thereafter

Chronic ischemic heart disease

➢Progressive heart failure due to ischemic injury, either from:
- prior infarction(s) (most common)
- chronic low-grade ischemia

Ischemic Heart Disease
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

Understand the pathology, pathogenesis and clinical consequences of atherosclerosis.

pathology Cells, Extracellular matrix:, Lipid, fibrous cap

Pathogenesis   endothelial cell injury….dysfunction….smooth muscle immigration ……macrophages and smooth muscle
         engulf fat …… smooth muscle proliferation and collagen deposition

Complications

Arterial obstruction………ischemia

Embolization of plaque material…… ischemia

Weakening with rupture of the arterial wall …..aneurism and rupture of vessel

Be able to discuss pathology and complications of ischaemic heart diseases with special emphasis on myocardial infarction.

Pathology

MI

> 0-4 h No pathological findings
> 4-12h coagulation necrosis
> 12-1day neutrophils
> 1 day – 7 days less neutrophils and more macrophages
> 1 week-2 weeks granulation tissue
> 2 weeks – 8 weeks fibrosis

> 1.   Typical Angina
> 2.   Unstable angina
> 3.   Prinzmetal angina

Complications

MI

> Arrhythmia
> Left ventricular failure
> Cardiogenic shock
> Myocardial rupture
> Thromboembolism

Serum Troponins and CK MB

 ECG finding

1.   how lifestyle modifications can reduce the risk of atherosclerosis and ischaemic heart disease.

- A 68-year-old obese woman (BMI = 32 kg/m2) presents with substernal chest pain. Results of laboratory studies include an elevated WBC count (13,000/µL), CK-MB of 6.6 ng/mL, and troponin-I of 2.5 ng/mL. ECG confirms a myocardial infarction of the left ventricular wall. Which of the following mechanisms is most likely responsible for the myocardial infarction in this patient?

(A) Coronary artery thrombosis

(B) Coronary artery vasospasm

(C) Decreased collateral blood flow

(D) Deep venous thrombosis

(E) Paradoxical embolism

- **The answer is A: Coronary artery thrombosis.** Coronary artery thrombosis is the most common cause of acute myocardial infarction and is often secondary to rupture of an atherosclerotic plaque.

- **Diagnosis:** Myocardial infarction

- A study of atheroma formation leading to atherosclerotic complications evaluates potential risk factors for relevance in a population. Three factors are found to play a significant role in the causation of atherosclerosis: smoking, hypertension, and hypercholesterolemia. These factors are analyzed for their relationship to experimental models for atherogenesis. Which of the following events is the most important direct biologic consequence of these factors?

☐ (A) Endothelial injury and its sequelae

☐ (B) Conversion of smooth muscle cells to foam cells

☐ (C) Alterations of hepatic lipoprotein receptors

☐ (D) Inhibition of LDL oxidation

☐ (E) Alterations of endogenous factors regulating vasomotor tone

- **(A)** Atherosclerosis is thought to result from a form of endothelial injury and the subsequent chronic inflammation and repair of the intima. All risk factors, including smoking, hyperlipidemia, and hypertension, cause biochemical or mechanical injury to the endothelium. Formation of foam cells occurs after the initial endothelial injury. Although lipoprotein receptor alterations can occur in some inherited conditions, these account for only a fraction of cases of atherosclerosis, and other lifestyle conditions do not affect their action. Inhibition of LDL oxidation should diminish atheroma formation. Vasomotor tone does not play a major role in atherogenesis.

- A 59-year-old man has experienced chest pain at rest for the past year. On physical examination, his pulse is 80/min and irregular. The figure shows the microscopic appearance representative of the patient's left anterior descending artery. Which of the following laboratory findings is most likely to have a causal relationship to the process illustrated?

- □ (A) Low Lp(a)

- □ (B) Positive VDRL

- □ (C) Low HDL cholesterol

- □ (D) Elevated platelet count

- □ (E) Low plasma homocysteine
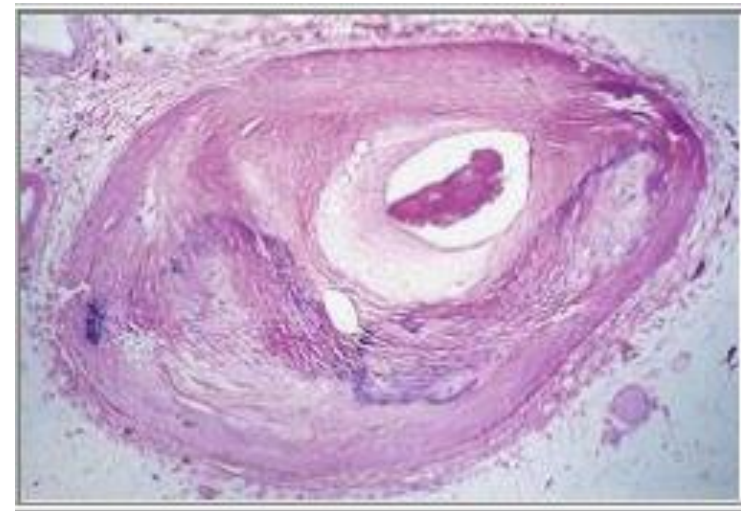
- **(C)** The figure shows an arterial lumen that is markedly narrowed by atheromatous plaque complicated by calcification. Hypercholesterolemia with elevated LDL and decreased HDL levels is a key risk factor for atherogenesis. Levels of Lp(a) and homocysteine, if elevated, increase the risk of atherosclerosis. Syphilis (positive VDRL test result) produces endarteritis obliterans of the aortic vasa vasorum, which weakens the wall and predisposes to aneurysms. Although platelets participate in forming atheromatous plaques, their number is not of major importance. Thrombocytosis can result in thrombosis or hemorrhage.

- A 60-year-old man has experienced angina on exertion for the past 6 years. A coronary angiogram performed 2 years ago showed 75% stenosis of the left anterior descending coronary artery and 50% stenosis of the right coronary artery. For the past 3 weeks, the frequency and severity of the anginal attacks have increased, and pain sometimes occurs even when he is lying in bed. Which of the following is most likely to explain these findings?

□ (A) Hypertrophy of ischemic myocardium with increased oxygen demands

□ (B) Increasing stenosis of right coronary artery

□ (C) Fissuring of plaque in left coronary artery with superimposed mural (partial) thrombosis

□ (D) Sudden complete thrombotic occlusion of right and left coronary arteries

□ (E) Reduction in oxygen-carrying capacity owing to pulmonary congestion

- **(C)** This patient has 75% stenosis of the left anterior descending branch of the coronary artery. This degree of stenosis prevents adequate perfusion of the heart when myocardial demand is increased, which occurs during exertion. The patient had angina on exertion. The patient has recently developed unstable angina, which is manifested by increased frequency and severity of the attacks and angina at rest. In most patients, unstable angina is induced by disruption of an atherosclerotic plaque followed by a mural thrombus and possibly distal embolization, vasospasm, or both.

- Hypertrophy of the heart is unlikely in this case because there is neither hypertension nor a valvular lesion.

- The remaining choices theoretically can give rise to a similar picture, but plaque disruption with mural thrombosis is the most common anatomic finding when the patient develops unstable angina.

- It is important to recognize this because unstable angina is a harbinger of myocardial infarction.

Prof. Ahmed alhumaidi