PATHOLOGY OF CARDIOVASCULAR SYSTEM

ISCHEMIC HEART DISEASE, ANGINA & MYOCARDIAL INFARCTION

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REFERENCE: ROBBINS & COTRAN PATHOLOGY AND RUBIN'S PATHOLOGY

OBJECTIVES FOR ATHEROSCLEROSIS, ISCHEMIC HEART DISEASES (ANGINA AND MYOCARDIAL INFARCTION)

- Understand the pathogenesis and clinical consequences of atherosclerosis.
- Be able to discuss pathology and complications of ischemic heart diseases with special emphasis on myocardial infarction.
- Know how lifestyle modifications can reduce the risk of ischemic heart diseases.
- **Key principles to be discussed:**
- Risk factors of atherosclerosis.
- Pathogenesis of the fibro lipid atherosclerotic plaque.
- Clinical complications of atherosclerosis.
- Commonest sites for the clinically significant coronary atherosclerosis.
- Macroscopic and microscopic changes in myocardial infarction.
- Biochemical markers of myocardial infarction.
- Complications of myocardial infarction: immediate and late.

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ISCHEMIC HEART DISEASE/IHD (CORONARY HEART DISEASE)

- IHD = A group of closely related conditions/syndromes caused by an imbalance between the myocardial oxygen demand and blood supply. Usually caused by decreased coronary artery blood flow ("coronary artery disease")
- Four syndromes:
  - ✓Angina pectoris (chest pain).
  - ✓Acute myocardial infarction.
  - ✓Sudden cardiac death.
  - ✓Chronic ischemic heart disease with congestive heart failure.
- The most common cause if IHD is coronary artery atherosclerosis
- Less commonly it is due to vasospasm and vasculitis

EPIDEMIOLOGY OF ISCHEMIC HEART DISEASE (IHD):

- Peak incidence: 60y for males and 70y for females.
- Men are more affected than women.
- Contributing factors are same as that of atherosclerosis e.g.
  - Hypertension.
  - Diabetes mellitus.
  - Smoking.
  - High levels of LDL.
  - Genetic factors (direct or indirect).
  - Lack of exercise.

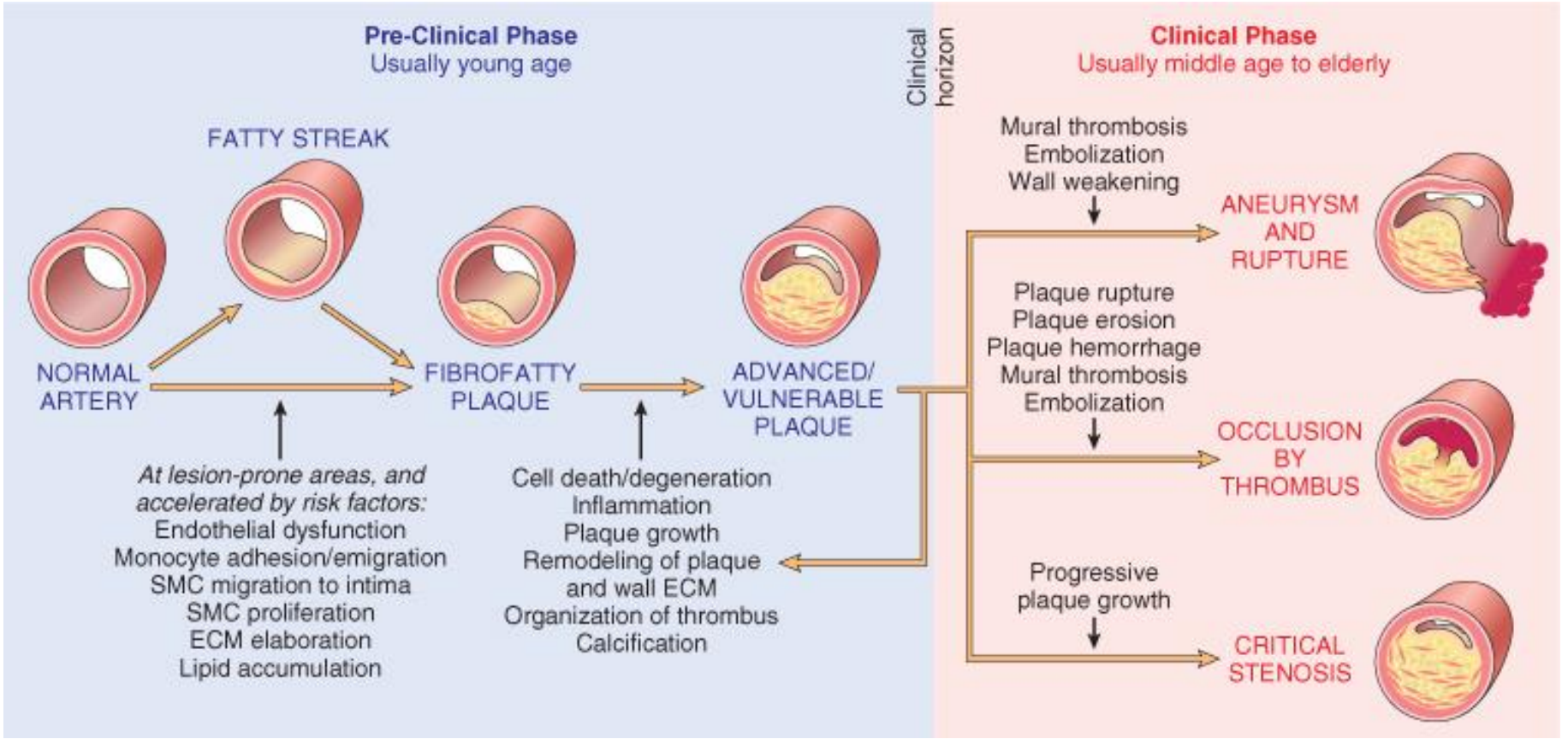
PATHOGENESIS OF IHD

1. Role of Critical stenosis or obstruction
2. Role of Acute Plaque Change
3. Role of Coronary Thrombus
4. Role of Vasoconstriction
5. Role of Inflammation

PATHOGENESIS OF IHD

1) **Role of Critical stenosis or obstruction:**

(>=75% of the lumen of one or more coronary arteries by atherosclerotic plaque).



PATHOGENESIS OF IHD

2) **Role of Acute Plaque Change**:

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

i. hemorrhage into the atheroma which will expand in volume.

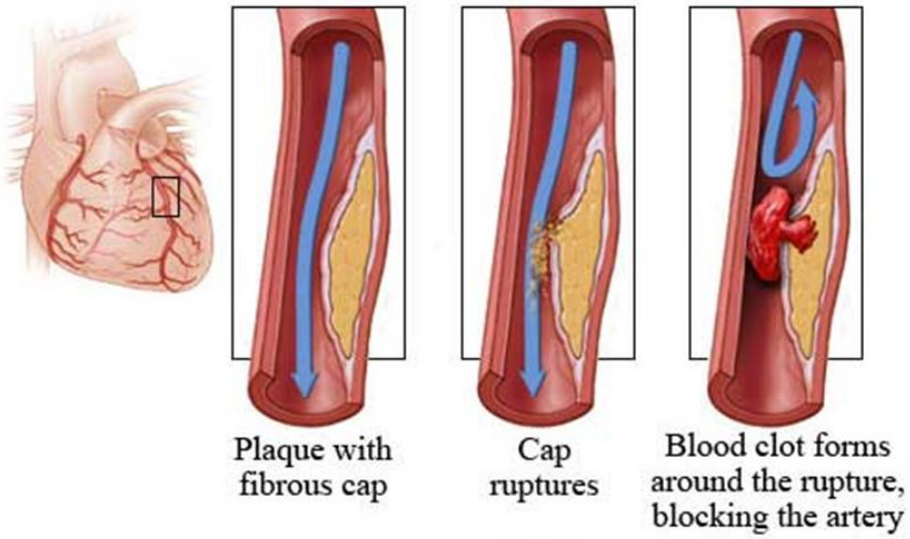
ii. exposure of the thrombogenic basement membrane just below the endothelial lining followed by thrombosis

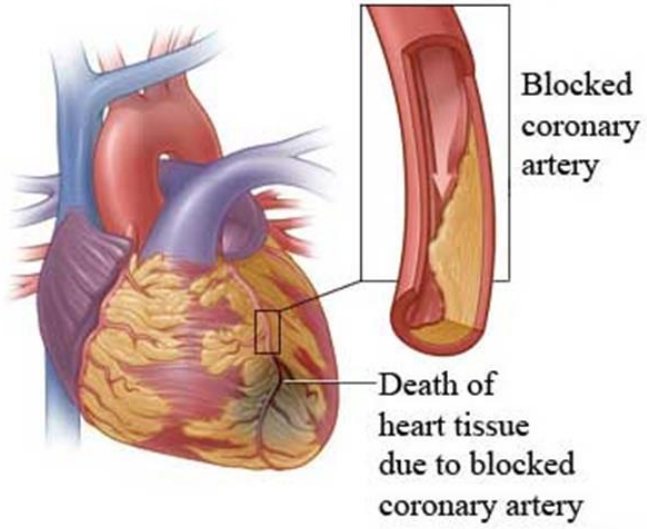
Acute plaque change can cause myocardial ischemia in the form of

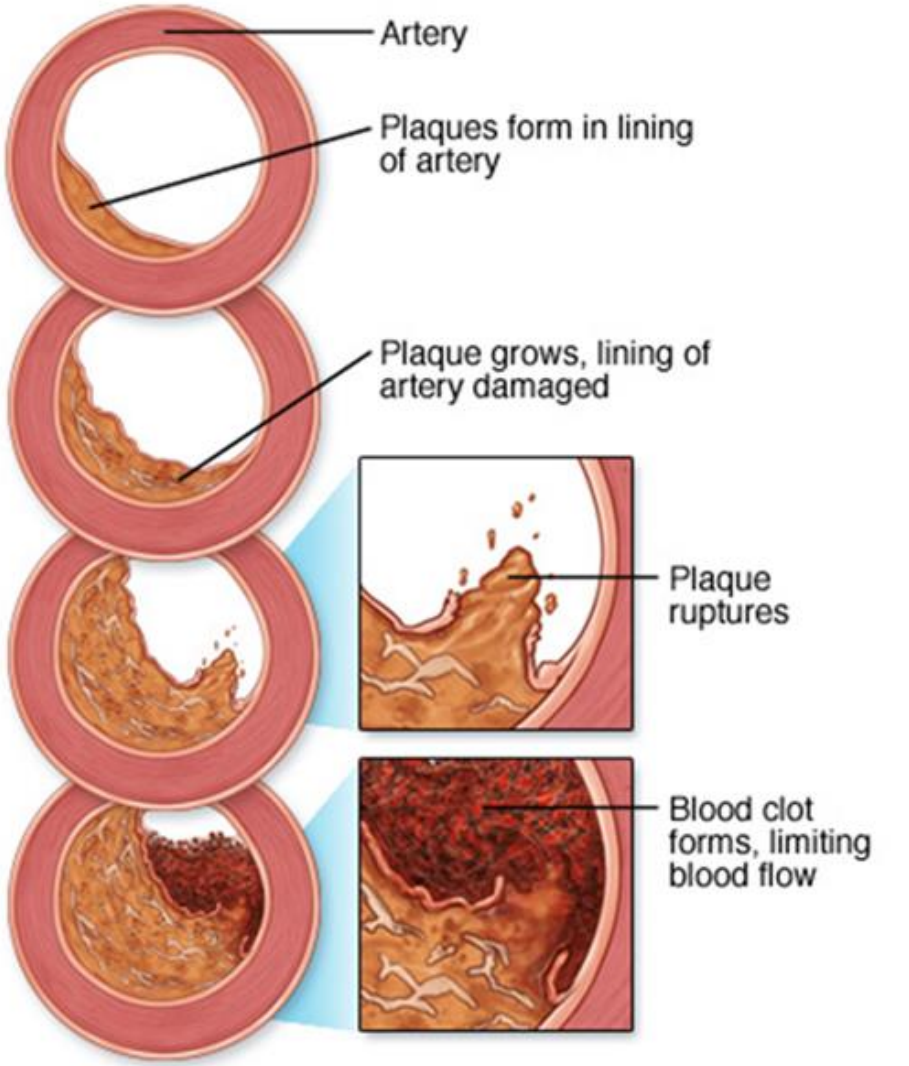
a. unstable angina

b. acute myocardial infarction

c. and (in many cases) sudden cardiac death.







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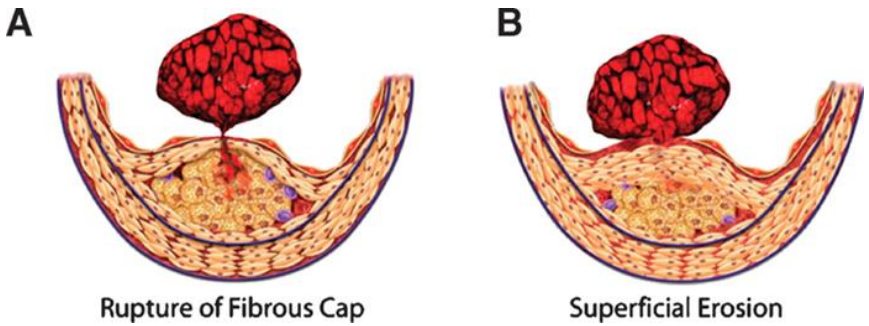

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PATHOGENESIS OF IHD

3**) Role of Coronary Thrombus:**

- thrombus superimposed on a disrupted partially occluding plaque can convert the plaque to either
  i. A total occlusion leading to acute transmural MI or sudden death.
  ii. Or a partial/incomplete/subtotal occlusion leading to unstable angina, acute subendocardial infarction, or sudden death.
- Thrombus in coronary artery can also embolize.

4) **Role of Vasoconstriction:**

- Vasoconstriction reduces lumen size and can therefore potentiate plaque disruption.

5) **Role of Inflammation:**

- Inflammatory processes play important roles at all stages of atherosclerosis.

PATHOGENESIS OF IHD

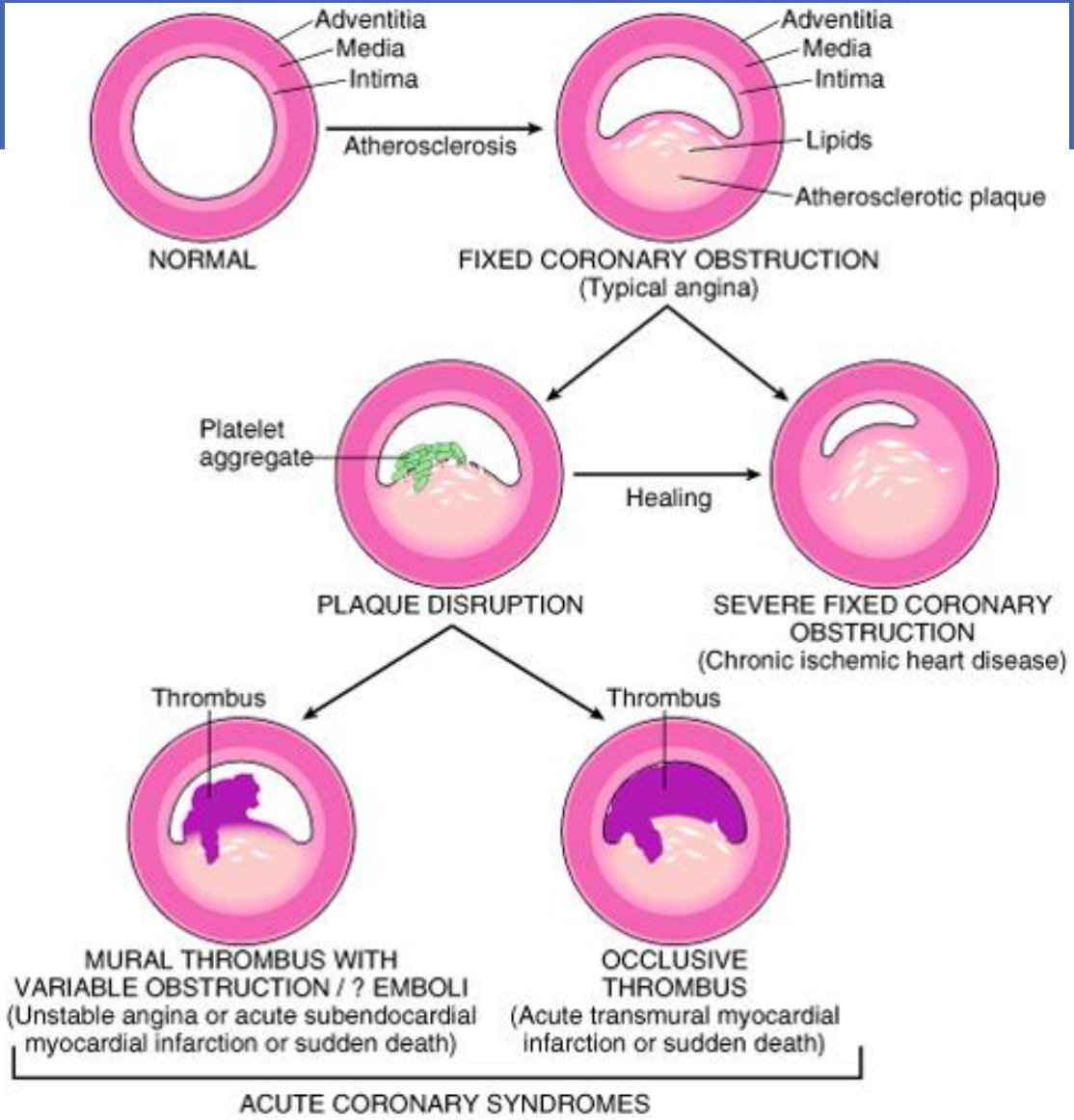
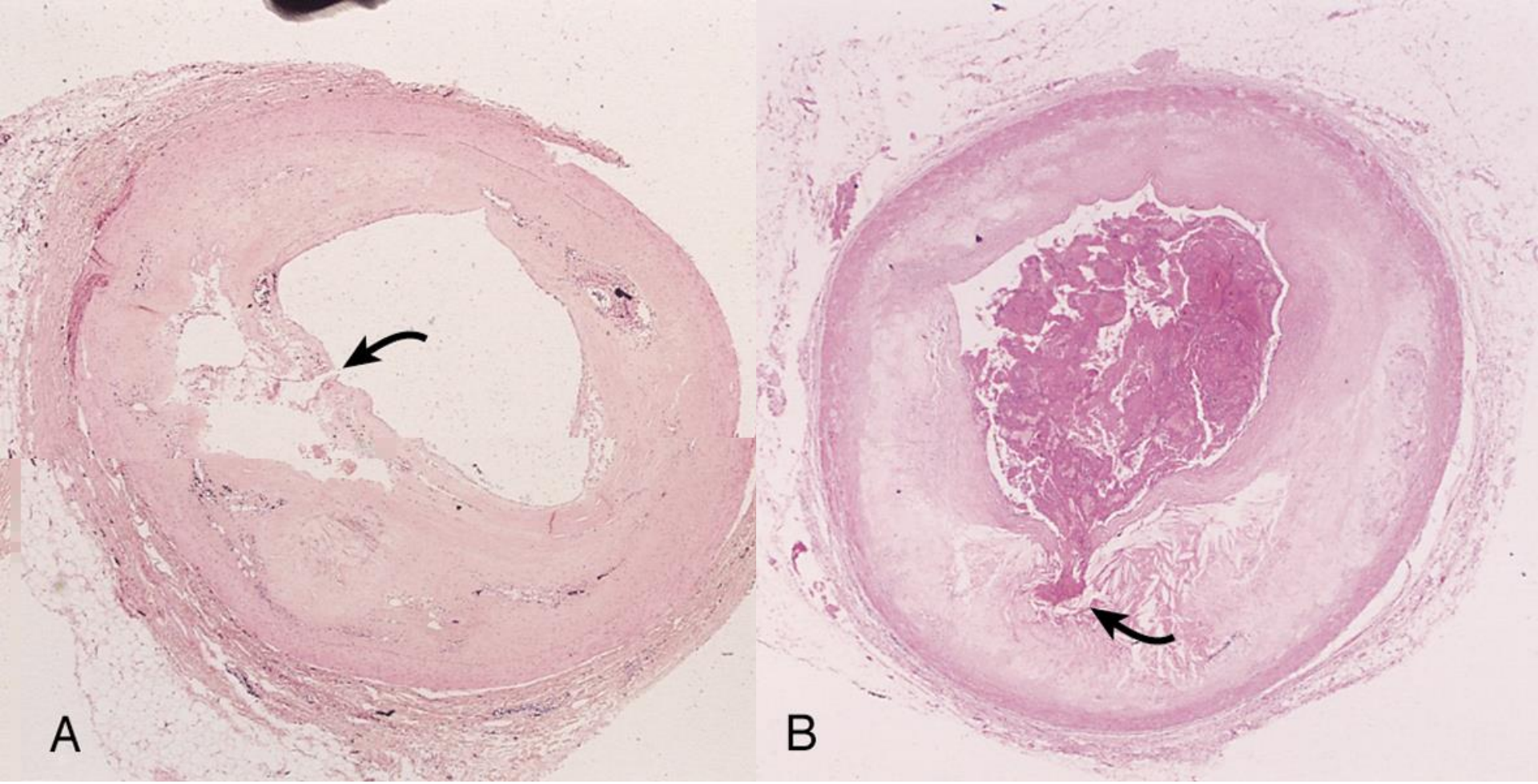


Diagram from Robbins



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.

ISCHEMIC HEART DISEASE

Four closely related conditions/syndromes that come under IHD are:

1. Angina pectoris (chest pain).
2. Acute myocardial infarction (MI).
3. Sudden cardiac death.
4. Chronic ischemic heart disease with congestive heart failure.

ANGINA PECTORIS

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).*
- 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 i.e. duration and severity is not sufficient for infarction
- There are three types of angina pectoris:

(1) Stable or typical angina

(2) Unstable or crescendo angina

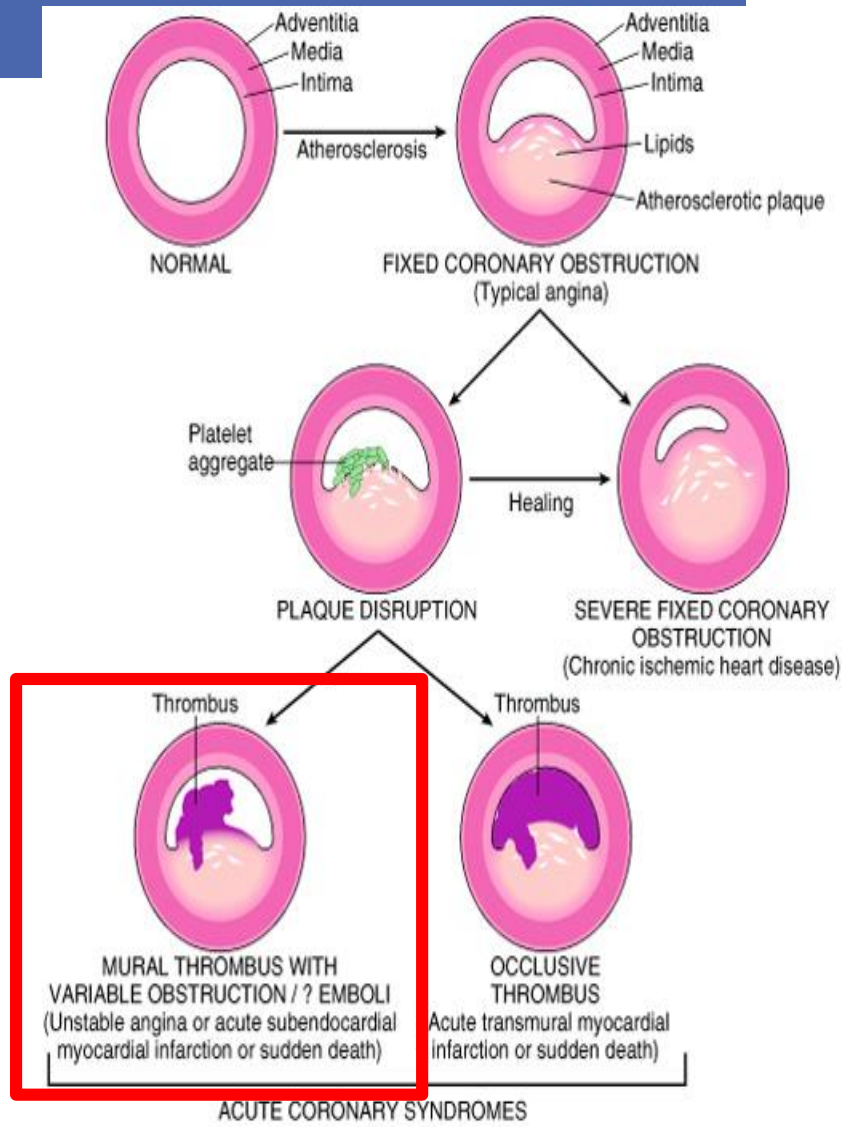
(3) Prinzmetal or variant angina

STABLE ANGINA/ TYPICAL ANGINA

- **Stable angina/ typical angina is** the most common form of angina. It is caused by atherosclerotic disease with usually ≥70% to 75% narrowing of lumen i.e. (critical stenosis or fixed chronic stable stenosis).
- This reduction (due to ≥ 70% stenosis) of blood flow in 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.

UNSTABLE OR CRESCENDO ANGINA

- It is an unstable and progressive condition.
- 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.



PRINZMETAL VARIANT ANGINA:

- is an uncommon pattern of episodic angina that occurs at rest and is due to coronary artery spasm.
- Prinzmetal angina generally responds promptly to vasodilators, such as nitroglycerin and calcium channel blockers.
- Not related to atherosclerotic disease
- The etiology is not clear.

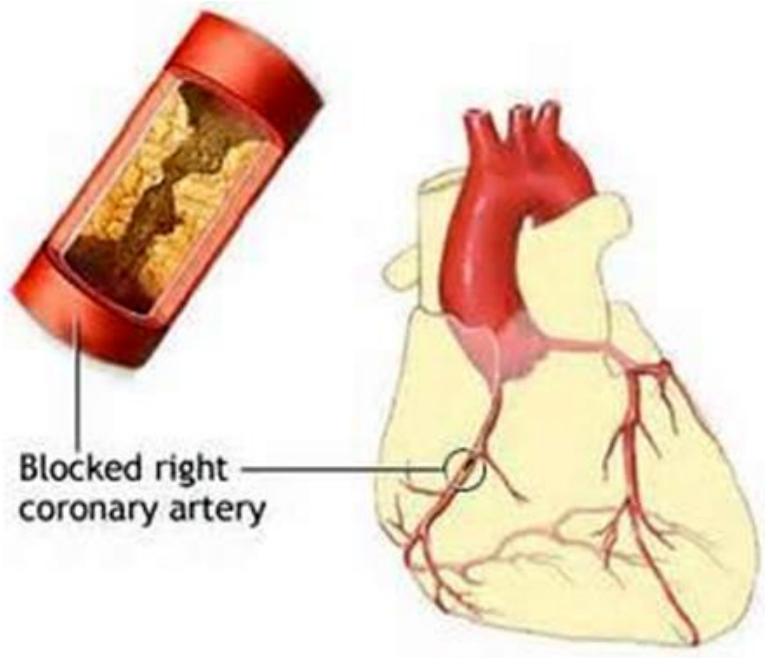
ANGINA PECTORIS. SUMMARY

- Intermittent chest pain caused by transient, reversible ischemia
- **Typical (stable) angina**
  - pain on exertion
  - fixed narrowing of coronary artery
- **Unstable (pre-infarction) angina**
  - increasing pain with less exertion
  - plaque disruption and thrombosis
- **Prinzmetal (variant) angina**
  - pain at rest
  - coronary artery spasm of unknown etiology

MYOCARDIAL INFARCTION (MI)

MYOCARDIAL INFARCTION (MI)

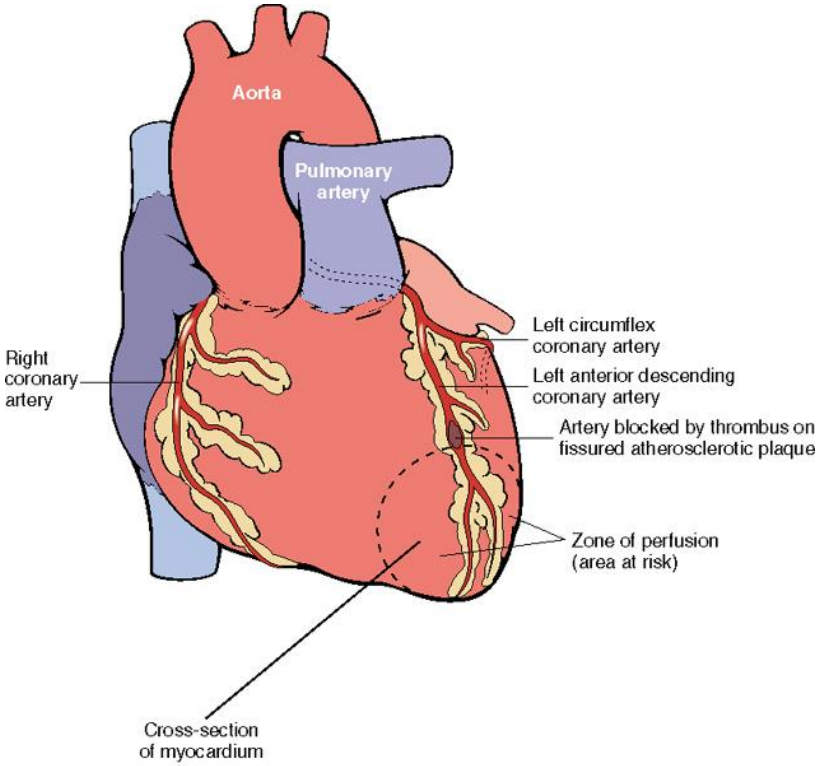
- Definition: MI, also known as "heart attack," is the death of cardiac muscle (coagulative necrosis) resulting from ischemia.
- Risks are the same as those of coronary atherosclerosis.



THE COMMONLY AFFECTED CORONARY VESSEL IN MI

In persons with right dominant coronary artery heart (90% of population) the commonly affected blood vessels are:

- Left anterior descending artery (40-50%)
- Right coronary artery (30-40%)
- Left circumflex artery (about 20%)



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 usually occur:

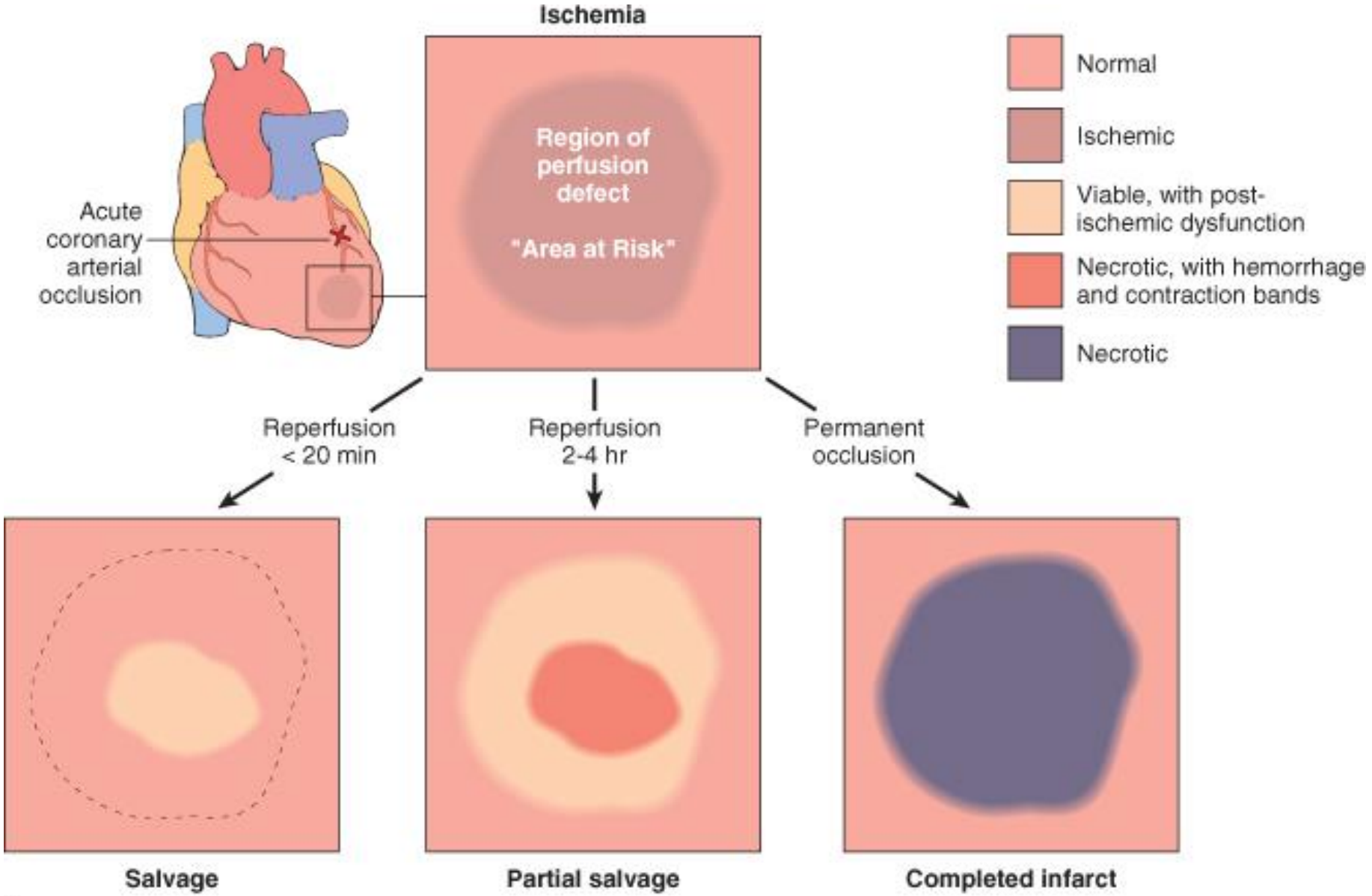
1. Acute plaque change (sudden change in the structure of an atheromatous plaque e.g. disruption, ulceration, rupture or intraplaque hemorrhage).
2. Exposure of the thrombogenic subendothelial basement membrane resulting in thrombus formation.
3. Frequently within minutes, the thrombus evolves to completely occlude the lumen of the coronary vessel.

PATHOGENESIS OF MI

- Severe ischemia lasting at least 20 to 40 minutes causes *irreversible* injury and myocardial necrosis on the ultrastructural level (on electron microscopy).

- Myocardial necrosis mostly starts in the sub-endocardial region (because it is less perfused and has high intramural pressure).

- The full size of the infarct is usually determined within 3-6 hours of the onset of severe myocardial ischemia. During this period, lysis of the thrombus by treatment with streptokinase or tissue plasminogen activator, may limit the size of the infarct. So any intervention in this time frame can potentially limit the final extent of necrosis.



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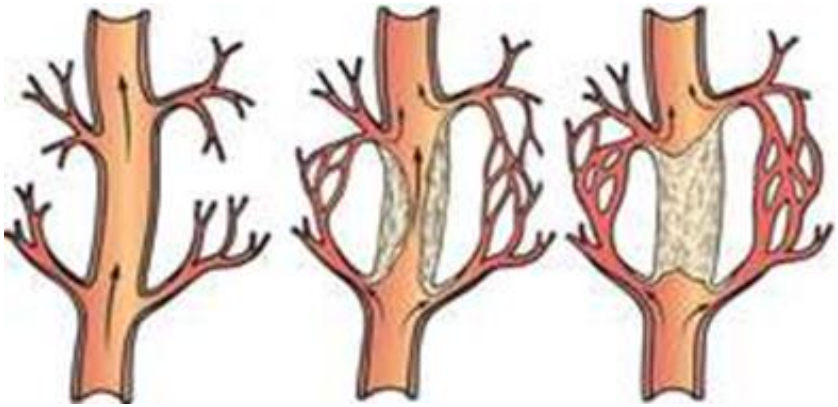
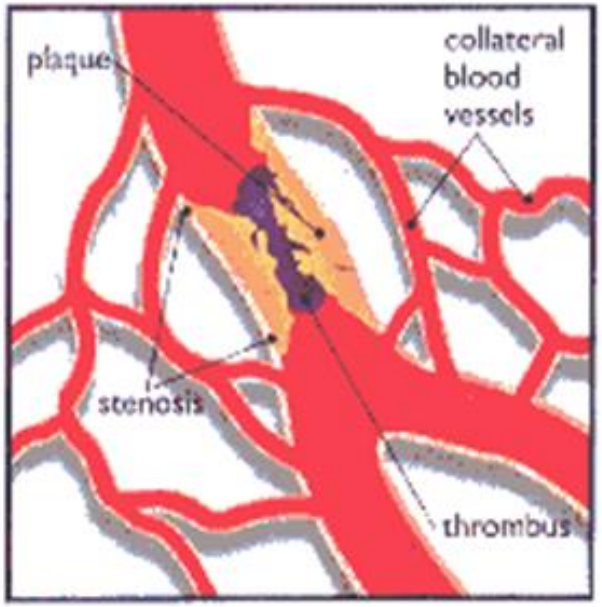
PATHOGENESIS OF MI

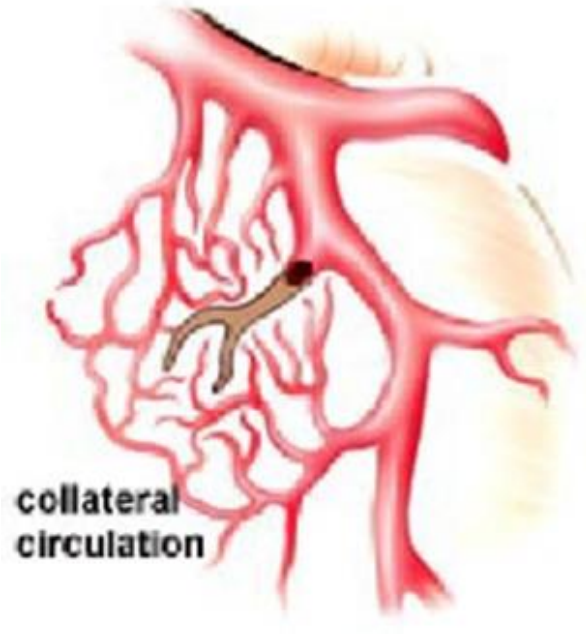
The precise location, size, and specific morphologic features of an acute myocardial infarct depend on:

1. The location, severity, and rate of development of coronary atherosclerotic obstructions
2. The size of the area supplied by the obstructed vessels
3. The duration of the occlusion
4. The oxygen needs of the myocardium at risk
5. The extent of collateral blood vessels
6. Other factors, such as blood vessel spasm, alterations in blood pressure, heart rate, and cardiac rhythm.
7. In addition reperfusion may limit the size of the infarct.

COLLATERAL CIRCULATION







ISCHEMIC HEART DISEASE
MI TYPES AND MORPHOLOGY

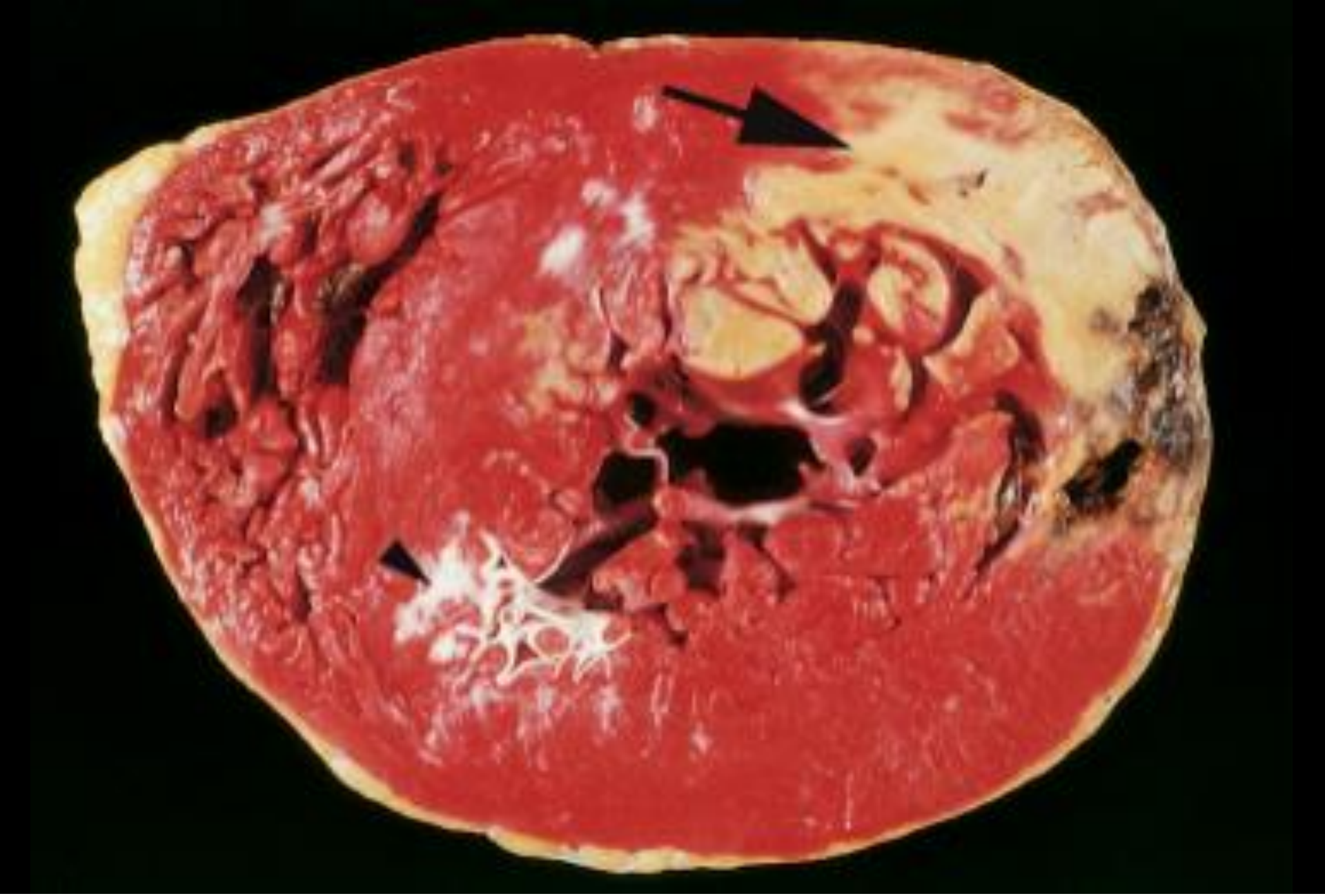
- **TYPES:**
  - **Transmural:** Full thickness (>50% of the wall)
  - **Subendocardial:** Inner 1/3 of myocardium
- **MORPHOLOGY:**
  - Begins with coagulative necrosis and inflammation (initially mainly neutrophils and later macrophages).
  - Followed by formation of granulation tissue.
  - Heals by formation of a fibrous scar.

Summarized morphologic Changes in myocardial Infarction

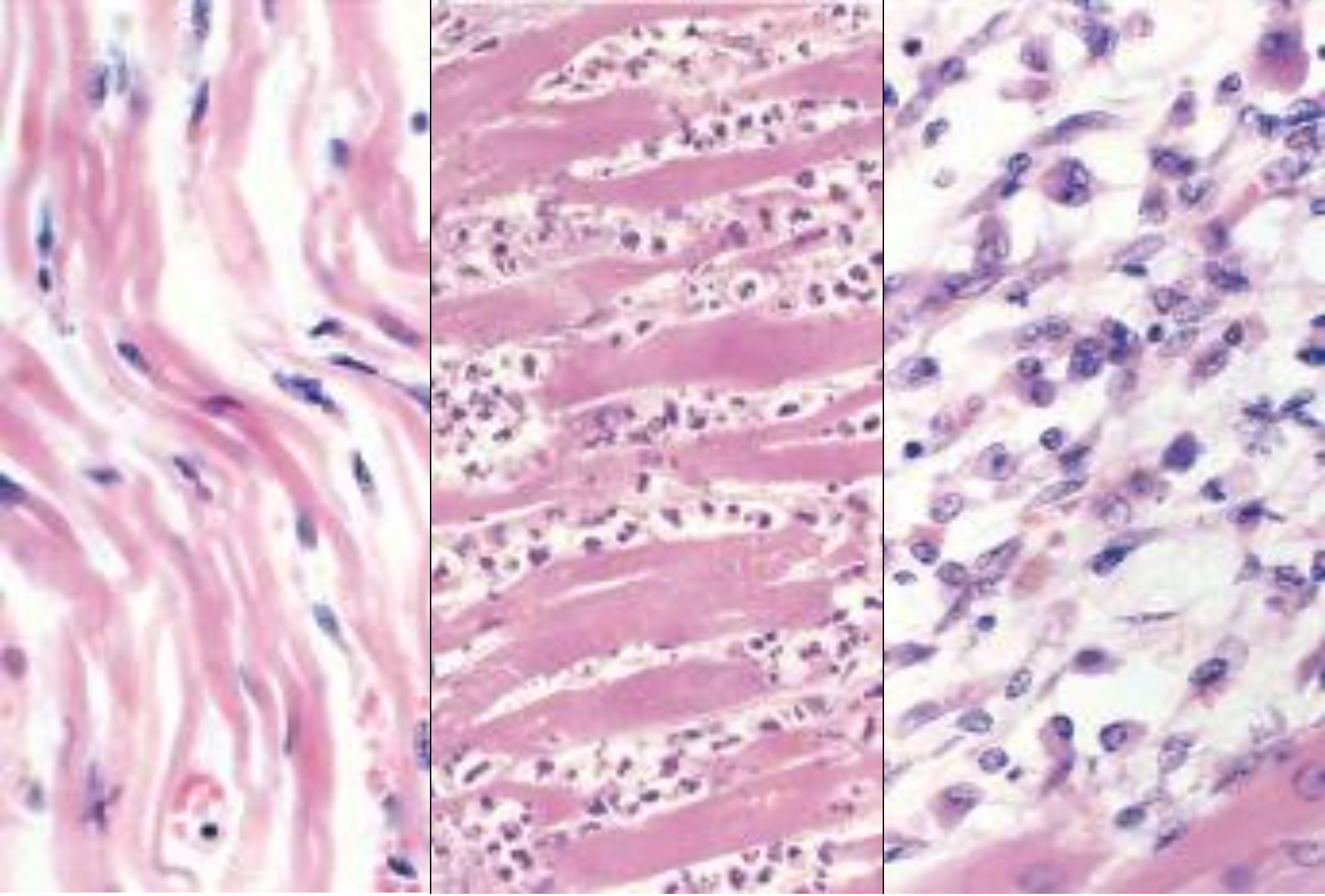
Time	Gross changes	Microscopic changes
0-4h	None	None
4-12h	Mottling	Coagulation necrosis
12-24h	Mottling	More coagulation necrosis; neutrophils come in
1-7 d	Yellow infarct center	Neutrophils die, macrophages come to eat dead cells
1-2 w	Yellow center, red borders	Granulation tissue
2-8 w	Scar	Collagen

Time	Gross Features	Light Microscope	Electron Microscope
REVERSIBLE INJURY			
0–½ hr	None	None	Ralaxation of myofibrils; glycogen loss; mitochondrial swelling
IRREVERSIBLE INJURY			
½–4 hr	None	Usually none; variable waviness of fibers at border	Sarcolemmal disruption; mitochondrial amorphous densities
4–12 hr	Dark mottling (occasional)	Early coagulation necrosis; edema; hemorrhage	
12–24 hr	Dark mottling	Ongoing coagulation necrosis; pyknosis of nuclei; myocyte hypereosinophilia; marginal contraction band necrosis; early neutrophilic infiltrate	
1–3 days	Mottling with yellow-tan infarct center	Coagulation necrosis, with loss of nuclei and striations; brisk interstitial infiltrate of neutrophils	
3–7 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	
7–10 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	
10–14 days	Red-gray depressed infarct borders	Well-established granulation tissue with new blood vessels and collagen deposition	
2–8 wk	Gray-white scar, progressive from border toward core of infarct	Increased collagen deposition, with decreased cellularity	
>2 mo	Scarring complete	Dense collagenous scar	

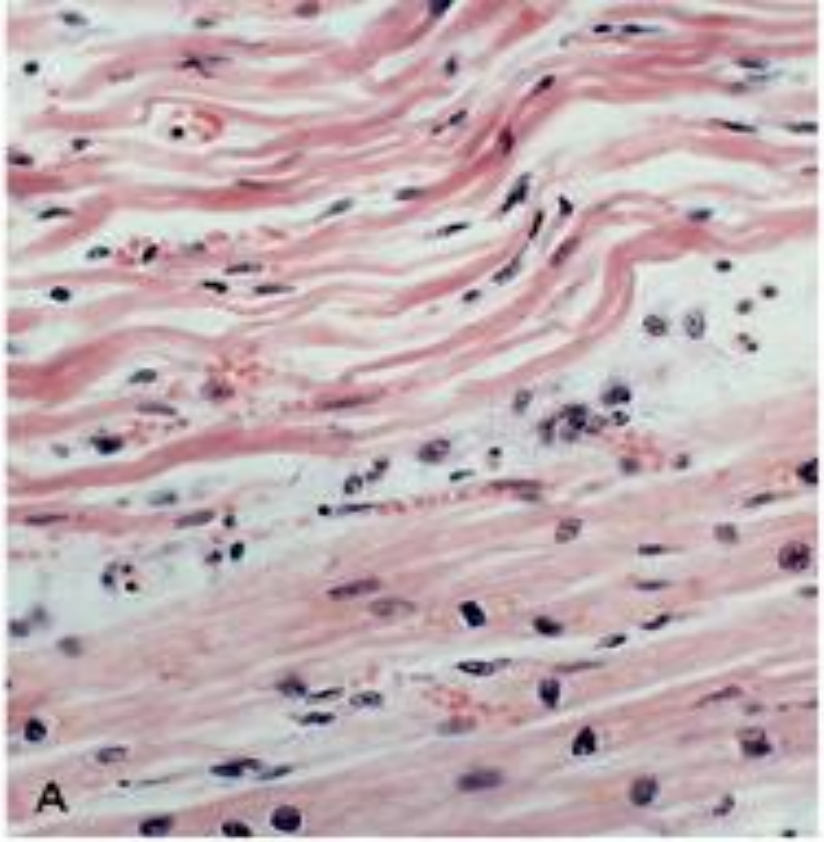
DETAILED TIME SCALE (ADDITIONAL INFORMATION)

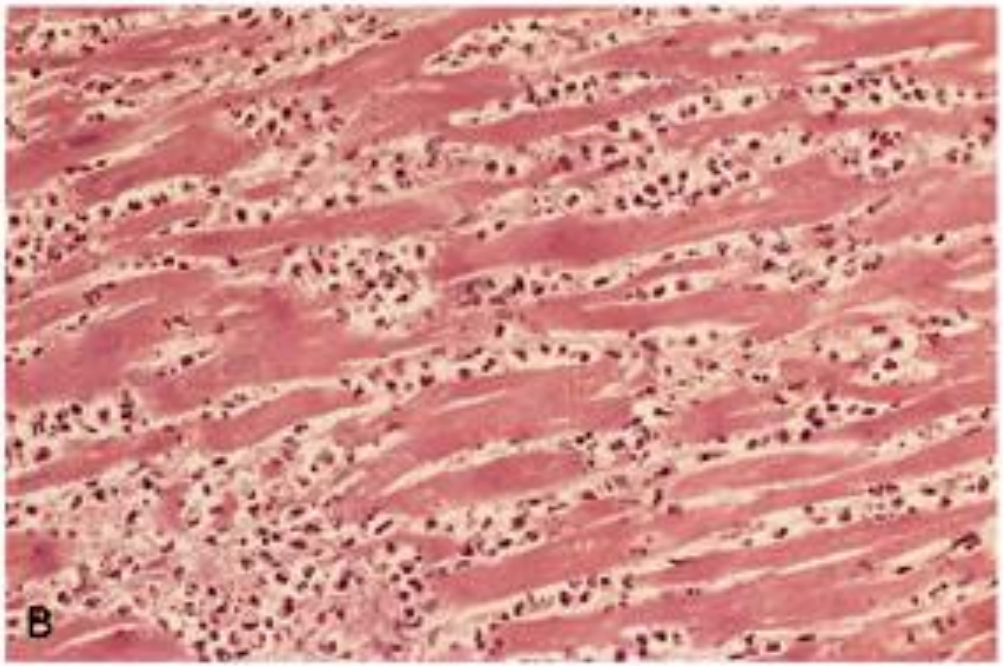


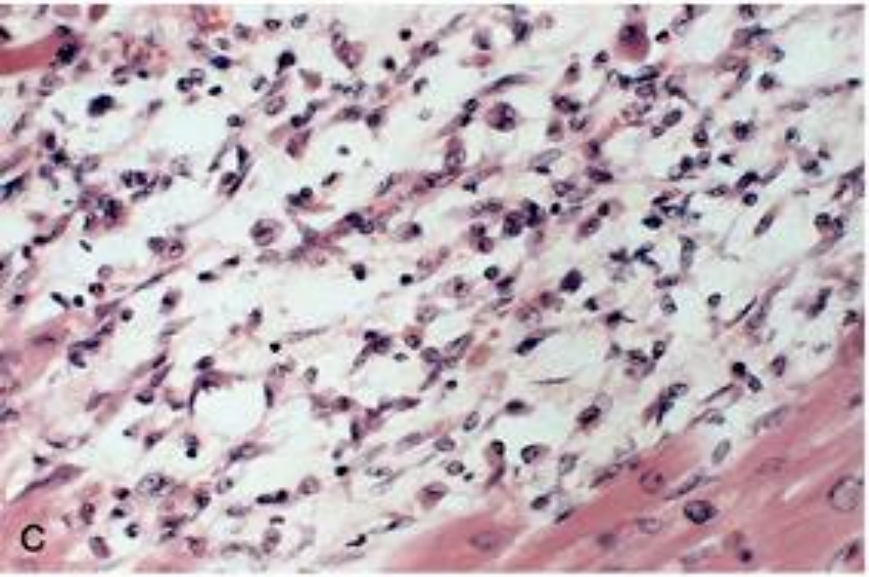
Acute Myocardial Infarction



MI: day 1, day 3, day 7







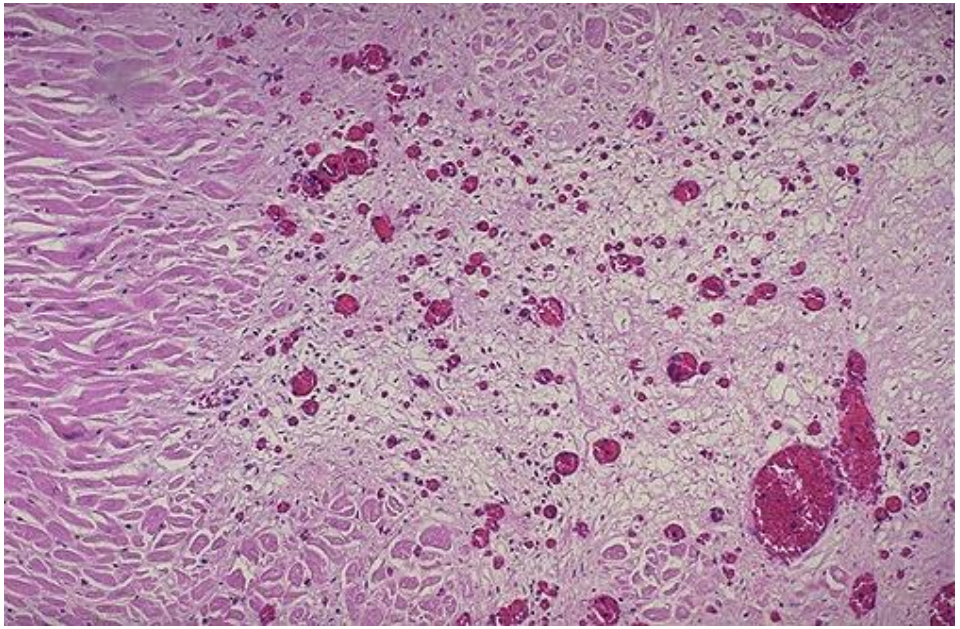
Microscopic features of myocardial infarction.

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. Nearly complete removal of necrotic myocytes by phagocytosis (approximately 7 to 10 days).

Granulation tissue approximately 3 weeks post MI



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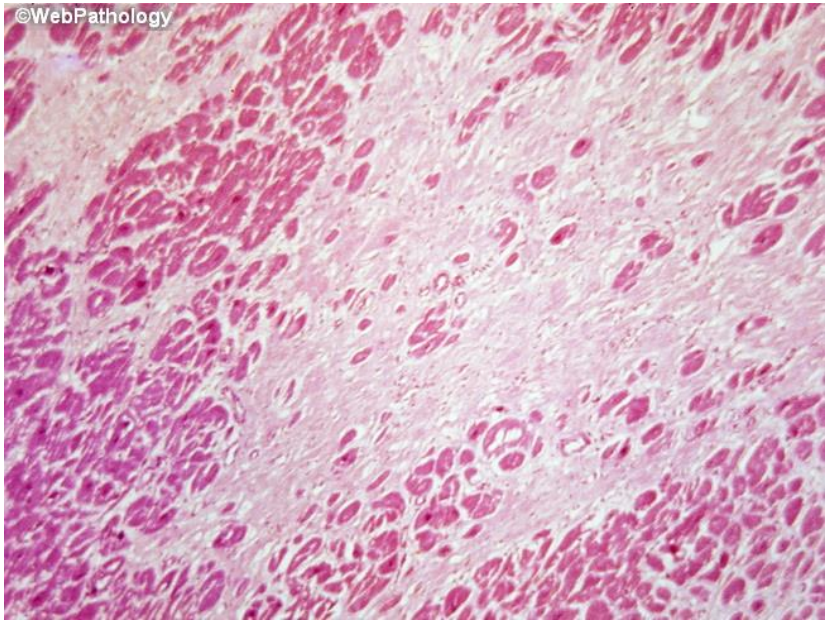
Healed MI with replacement of the necrotic fibers by dense collagenous scar. Residual cardiac muscle cells are present



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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.
  - No pain in 20-30% of patients (diabetics, hypertensive, elderly).
- Pulse is rapid and weak.
- Diaphoresis (sweating)
- Dyspnea.
- Cardiogenic shock can be seen in massive MI (when >40% of lt. ventricle is affected).
- ECG shows typical findings of ischemia.

ISCHEMIC HEART DISEASE LABORATORY EVALUATION

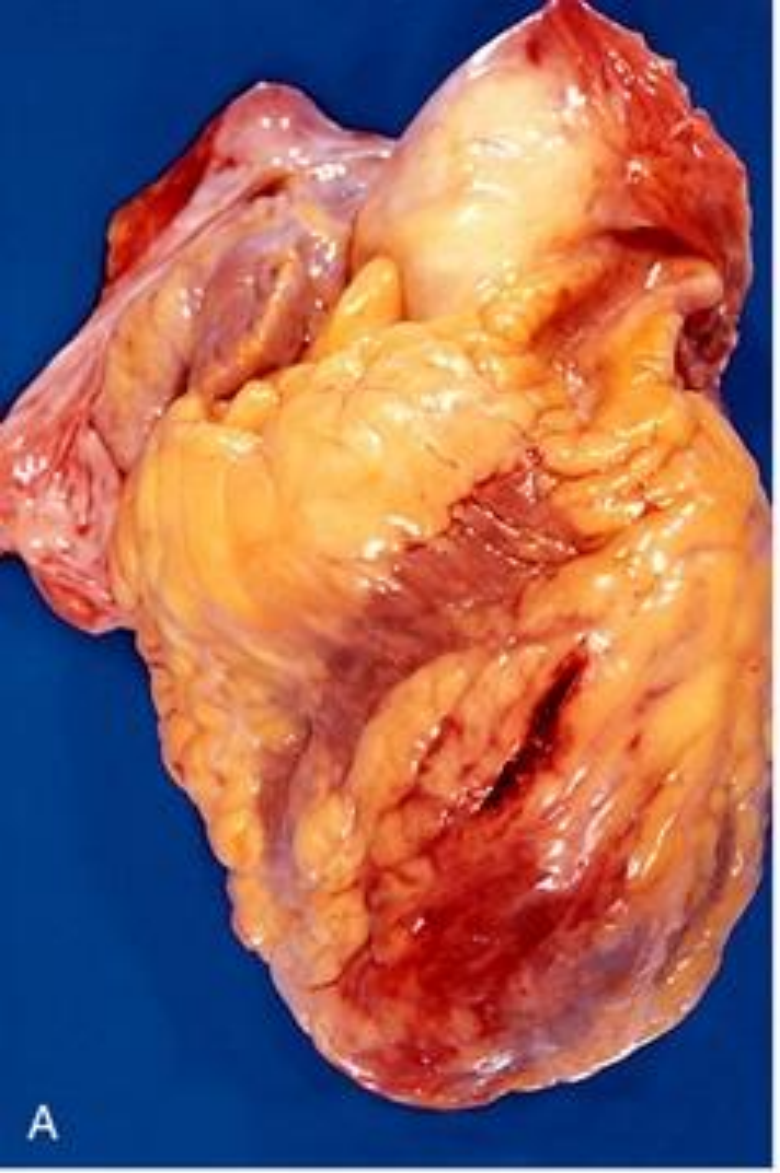
1. Troponins: **best marker**, TnT, TnI (more specific).
   - TnI and TnT are not normally detectable in the circulation
   - After acute MI both troponins become detectable after 2 to 4 hours, peaks at 48 hours. Their levels remain elevated for 7 to 10 days
2. CK-MB is the **second best mar**ker:
   - It begins to rise within 2 to 4 hours of MI, peaks at 24 hours and returns to normal within approximately 72 hours
3. Lactate dehydrogenase (LD):
   - Rise 24 hrs, peaks 72 hrs, gradually disappears in 5 to 14 days.

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%). Patients have conduction disturbances and myocardial irritability which can lead to sudden death especially in ventricular arrhythmia.
  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)

COMPLICATIONS OF MI

5. Thromboembolism (15-49%): the combination of myocardial abnormality in contractility (causing stasis) and endocardial damage (due to exposure of underlying thrombogenic basement membrane) can lead to cardiac thrombosis and embolism
6. Pericarditis
7. Infarct extension and expansion
8. Ventricular aneurysm in which the ventricle is dilated and the wall is thinned out.
9. External rupture of the infarct with associated bleeding into the pericardial space (hemopericardium).
10. Progressive late heart failure in the form of chronic IHD.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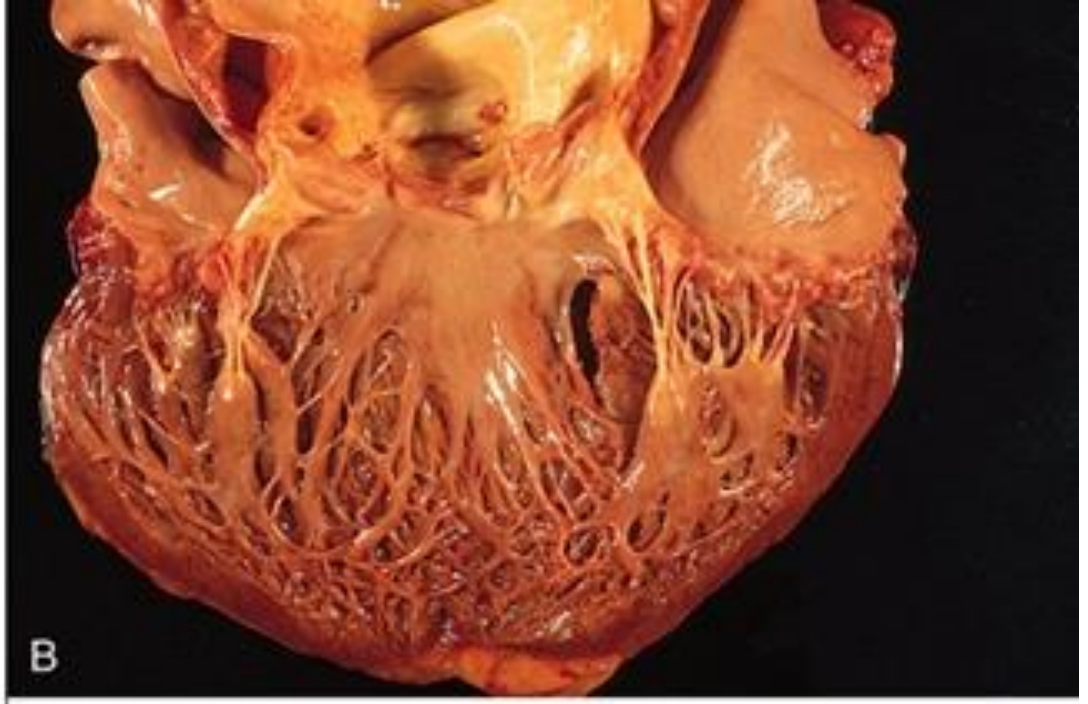
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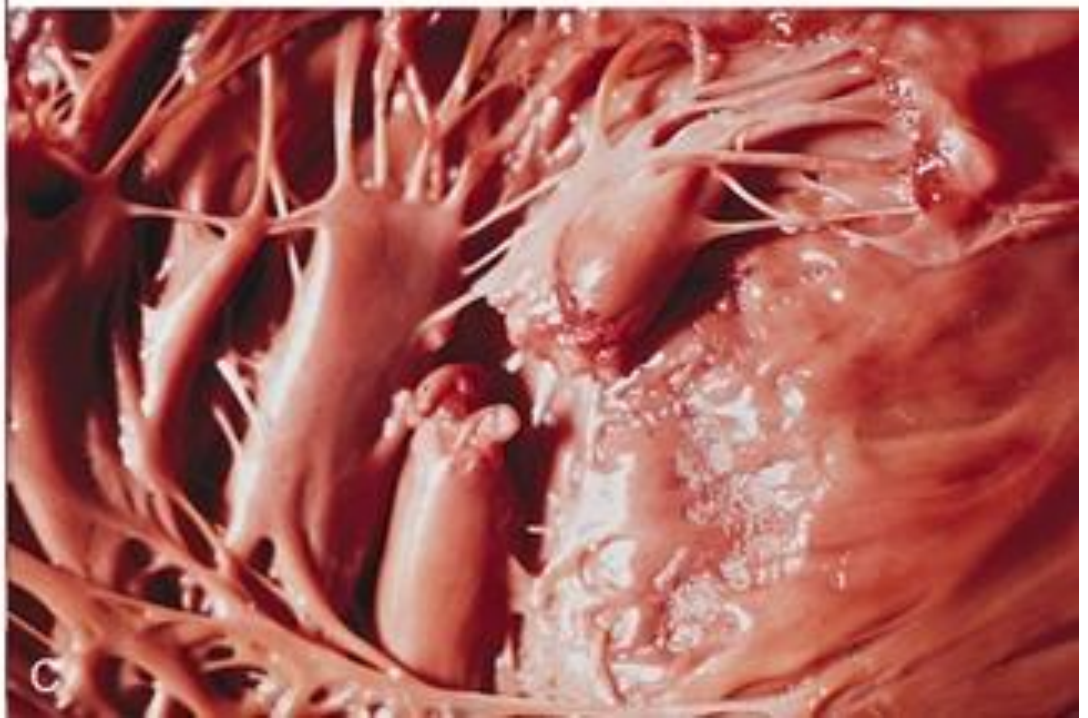
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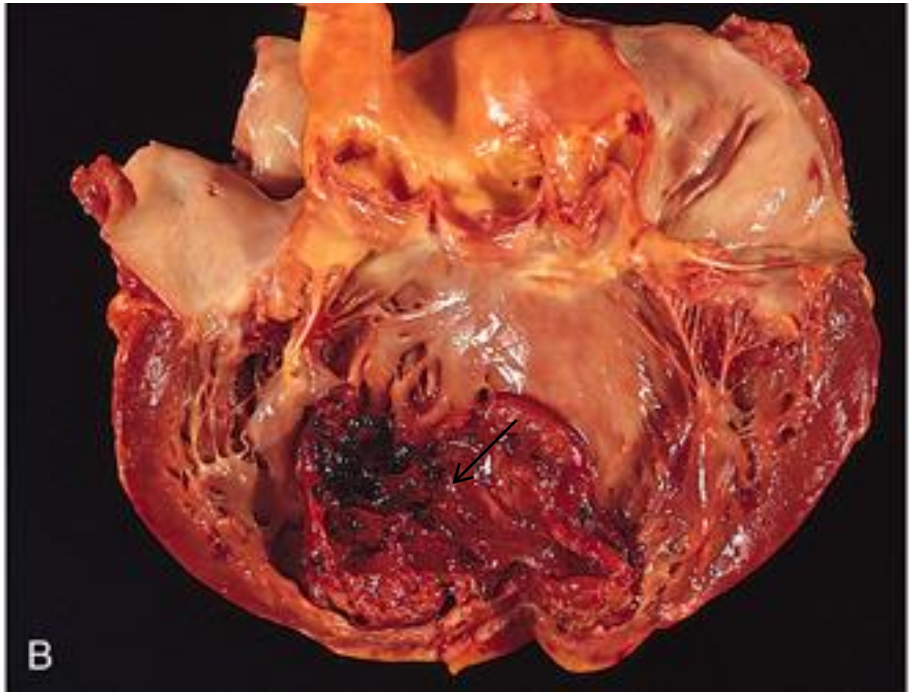
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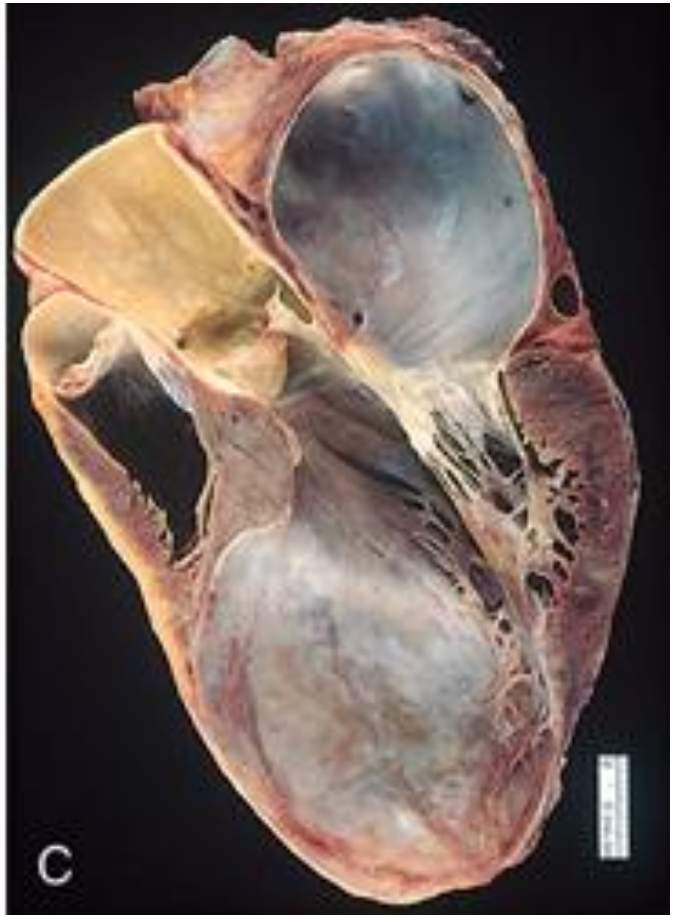
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MYOCARDIAL INFARCTION (MI), SUMMARY

- Necrosis of heart muscle caused by ischemia
- Mostly due to acute coronary artery thrombosis
  - sudden plaque disruption
  - platelets adhere
  - coagulation cascade activated
  - thrombus occludes lumen within minutes
  - irreversible injury/cell death in 20-40 minutes
- Prompt reperfusion can salvage myocardium

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 increase 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
&
SUDDEN CARDIAC DEATH

CHRONIC ISCHEMIC HEART DISEASE & SUDDEN CARDIAC DEATH

Chronic ischemic heart disease

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

Sudden cardiac death

- Definition: 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