13. PATHOPHYSIOLOGY OF CVS DISEASE

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PATHOPHYSIOLOGY OF

- *ANGINA*
- *MYOCARDIAL INFARCTION*
- *ATHEROSCLEROSIS*
- *ARTERIOSCLEROSIS*

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13. PATHOPHYSIOLOGY OF CARDIOVASCULAR DISEASES

DEFINATION OF ISCHEMIA

"Ischemia is defined as inadequate blood supply (circulation) to a local area due to blockage of the blood vessels supplying the area."

INTRODUCRION

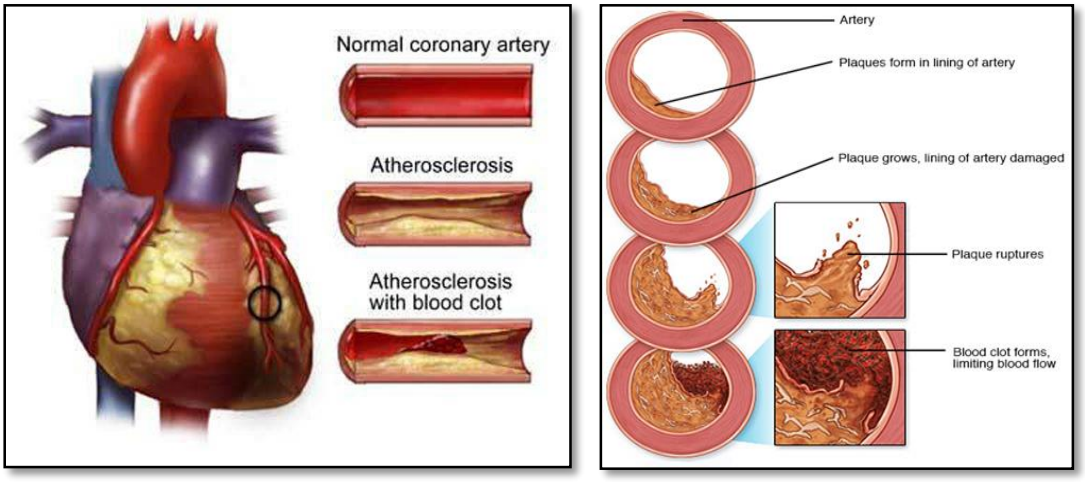
Ischemic means that an organ (e.g., the heart) is not getting enough blood and oxygen. Ischemic heart disease, also called coronary heart disease (CHD) or coronary artery disease.

It is the term given to heart problems caused by narrowed heart (coronary) arteries that supply blood to the heart muscle.

Although the narrowing can be caused by a blood clot or by constriction of the blood vessel, most often it is caused by buildup of plaque, called atherosclerosis.

When the blood flow to the heart muscle is completely blocked, the heart muscle cells die, which is termed a heart attack or myocardial infarction (MI).

Clinical presentations include silent ischemia, angina pectoris, acute coronary syndromes (unstable angina, myocardial infarction), and sudden cardiac death.



Coronary artery disease: Clinical manifestation and pathology

Clinical manifestations	Pathology
Stable angina	Ischaemia due to fixed athermanous stenosis of one or more coronary arteries
Unstable angina	Ischaemia caused by dynamic obstruction of a coronary artery due to plaque or erosion with superimposed thrombosis
Myocardial Infraction	Myocardial necrosis caused by acute occlusion of coronary artery due to plaque rupture or erosion with superimposed thrombosis
Heart failure	Myocardial dysfunction due to ischaemia or infraction
Arrhythmia	Altered conduction due to ischaemia or infraction
Sudden death	Ventricular arrhythmia, asystole or massive myocardial infraction

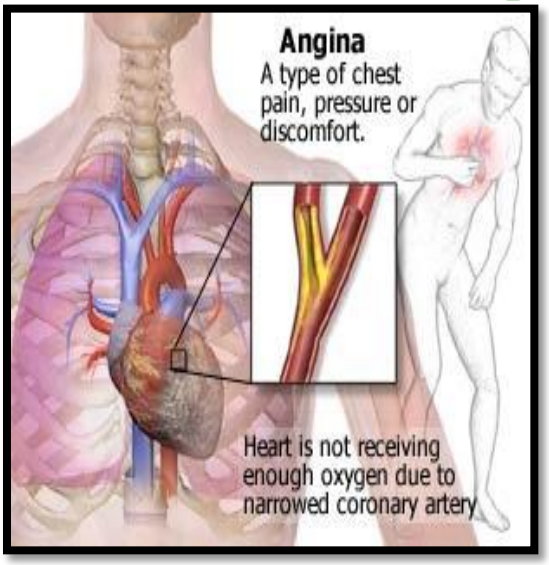
ANGINA PECTORIS

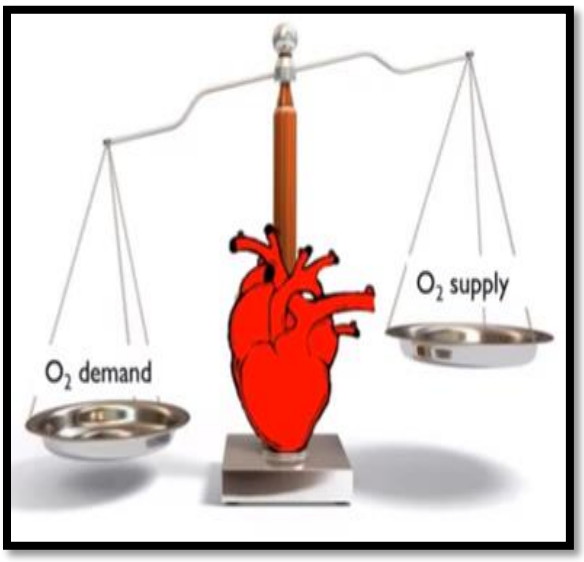
DEFINITION:

Angina pectoris is the result of myocardial ischemia caused by an imbalance between myocardial blood supply and oxygen demand.

Angina pectoris is a clinical syndrome usually characterized by episodes of pain or pressure in the anterior chest.

The cause is usually insufficient coronary blood flow which results in a decreased oxygen supply to meet an increased myocardial demand for oxygen in response to physical exertion or emotional stress.





SYMPTOMS

- Angina symptoms include chest pain and discomfort, possibly described as pressure, squeezing, burning or fullness.
- Also have pain in arms, neck, jaw, shoulder or back.
- Other symptoms that may have with angina include:
  - Dizziness
  - Fatigue
  - Nausea
  - Shortness of breath
  - Sweating

TYPES OF ANGINA

There are six main anginal syndromes:

1. Chronic stable angina
2. Nocturnal angina
3. Unstable angina
4. Variant angina (Prinzmetal's)
5. Decubitus angina
6. Syndrome X

1. Chronic stable angina

- ✓ Pain is provoked by physical exertion, especially after a meal, in cold weather or walking against the wind. The pain is often also aggravated by anger or excitement.
- ✓ The pain is relieved within 2-10 min by rest. Occasionally the pain will disappear even though exertion continues.
- ✓ Often angina will be precipitated by a predictable degree of exertion in a particular patient; the threshold for pain varies widely between patients.
- ✓ The severity of the symptoms is not closely related to the extent of coronary artery disease, indeed periods of ischaemia and myocardial infarction may be entirely painless.
- ✓ The pain is often more easily provoked in the morning.

2. Nocturnal angina

- ✓ Nocturnal angina wakes a patient from sleep and may be provoked by vivid dreams. Symptoms are commonest in the early hours of the morning when coronary artery tone is maximal.
- ✓ The patient often has critical coronary artery disease and hence usually suffers from exertional angina.
- ✓ Nocturnal angina may be associated with coronary artery spasm - Prinzmetal's angina.

3. Unstable angina

- ✓ Unstable angina is defined as recurrent episodes of angina on minimal effort or at rest. It may be the initial presentation of ischaemic heart disease, or it may represent the abrupt deterioration of a previously stable anginal syndrome.
- ✓ Unstable angina is also described as crescendo angina, preinfarction angina, and intermediate chest pain syndrome.
- ✓ Unstable angina is provoked more easily and persists for longer than stable angina. It may fail to respond to therapy. Pain is often associated with reversible ST segment depression on the ECG.
- ✓ Unless vigorously treated, 30% of patients will progress to myocardial infarction or death within 3 months.

4. Prinzmetal's angina or Variant Angina Pectoris

- ✓ This type of angina results from transmural myocardial ischemia caused by coronary artery spasm and may occur in patients with or without coronary atherosclerosis. Pain occurs principally at rest, usually unprovoked, but since coronary artery disease may coexist, pain may also be provoked by exercise.
- ✓ The pain may occur in a circadian manner, often in the early morning hours. The pain is associated with ST-segment elevation, in contrast to typical angina pectoris.
- ✓ Often sub clinical (painless) episodes occur with ST- segment elevations, often associated with arrhythmias, or bundle branch block.
- ✓ This is angina caused by focal spasm of angiographically normal coronary arteries.
- ✓ In about 75% of patients there is also atherosclerotic coronary artery obstruction.
- ✓ In cases where there is atherosclerotic obstruction the vasospasm occurs near the stenotic lesion.

5. Decubitus angina

- ✓ Decubitus angina occurs when the patient lies down.
- ✓ It is usually a complication of cardiac failure due to the strain on the heart resulting from the increased intravascular volume.
- ✓ Patients usually have severe coronary artery disease.

6. Syndrome X (angina)

- ✓ Syndrome X comprises: Symptoms and signs of angina
- ✓ Radiologically normal coronary arteries
- ✓ Positive exercise test
- ✓ Syndrome X may be due to Microvascular disease.

Classification of angina by Canadian Cardiovascular society (CCS)

Class I	Ordinary activity does not cause angina such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.
Class II	Slight limitation of ordinary activity. Angina on walking or climbing stairs rapidly, walking or stair climbing after meals, or in cold, wind or under emotional stress, or only during the first few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
Class III	Marked limitation of ordinary physical activity. Angina on walking one to two blocks[a] on the level or one flight of stairs in normal conditions and at a normal pace.
Class IV	Inability to carry on any physical activity without discomfort' – angina syndrome may be present at rest'.

13. PATHOPHYSIOLOGY OF CARDIOVASCULAR DISEASES

ETILOGY & PATHOPHYSIOLOGY

Angina pectoris is most commonly caused by myocardial ischaemia which results from a mismatch between myocardial blood flow (supply) and oxygen demand.

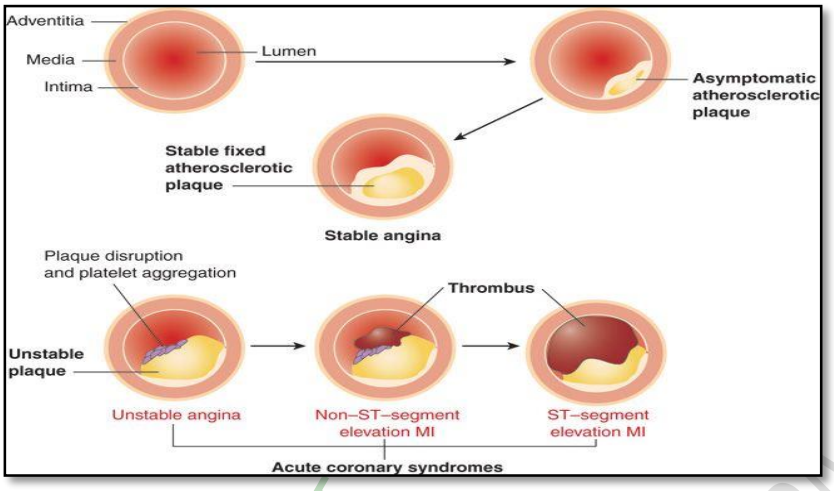
- **Atherosclerosis**:- Restriction of myocardial blood flow usually results from atherosclerotic narrowing of an epicardial (surface) coronary artery
- **Endothelial dysfunction:-** Abnormal vasodilatation or even vasoconstriction resulting from impaired endothelial function are also important mechanisms.
- Use of vasoconstricting drugs (eg, cocaine, nicotine) and emotional stress also can trigger coronary spasm.

I] Atherosclerotic narrowing of coronary artery

Mechanisms of atherosclerosis

- ✓ The pathophysiology of atherosclerosis, development of symptomatic angina and subsequent, acute coronary syndrome (ACS) is well characterized. The earliest visible atherosclerotic lesion appears to be the fatty streak.
- ✓ Many of these fatty streaks progress to become advanced atherosclerotic plaques. The earliest detectable *physiological* manifestation of atherosclerosis is reduced production of the endothelium-dependent vasodilator, nitric oxide (NO).

- **Coronary atherosclerosis** is often irregularly distributed in different vessels but typically occurs at points of turbulence.
- As the atheromatous plaque grows, the arterial lumen progressively narrows, resulting in ischemia (often causing angina pectoris). The degree of stenosis required to cause ischemia varies with oxygen demand.
- Occasionally, an atheromatous plaque ruptures or splits. Reasons are unclear but probably relate to plaque morphology, plaque calcium content, and plaque softening due to an inflammatory process.
- Rupture exposes collagen and other thrombogenic material, which activates platelets and the coagulation cascade, resulting in an acute thrombus, which interrupts coronary blood flow and causes some degree of myocardial ischemia.
- The consequences of acute ischemia, collectively referred to as acute coronary syndromes (ACS), depend on the location and degree of obstruction and range from unstable angina to transmural infarction to sudden death.

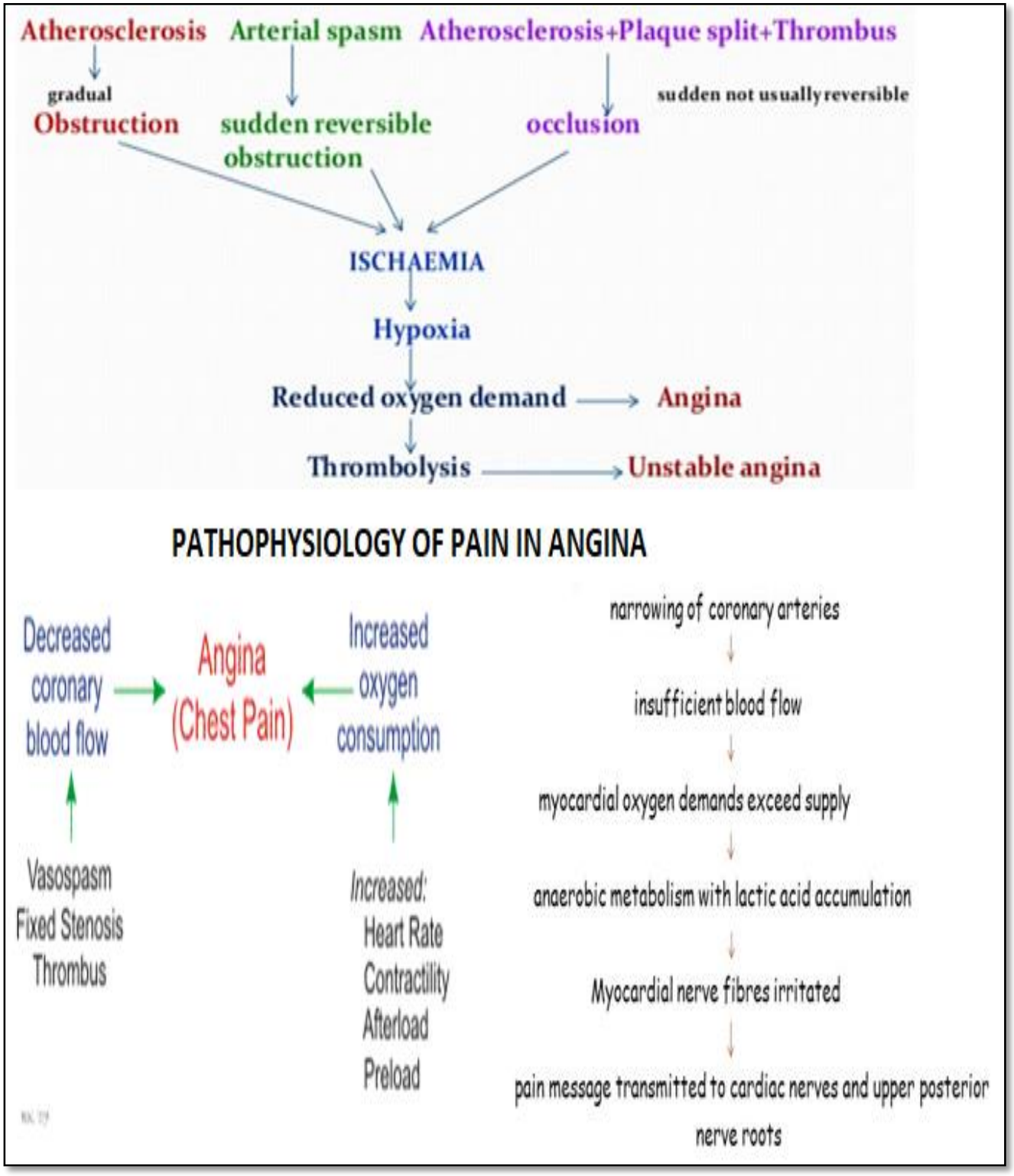


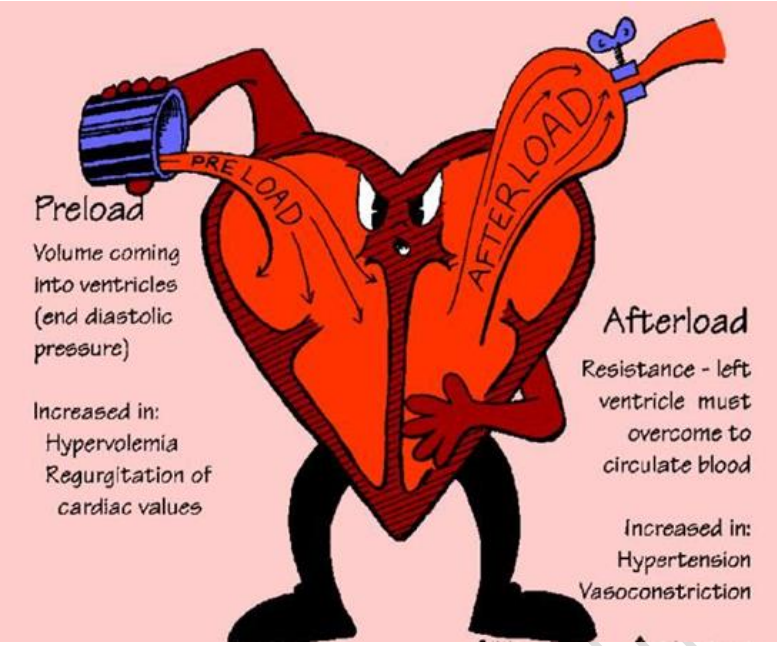
II] Coronary artery spasm

- ✓ **Coronary artery spasm** is a transient, focal increase in vascular tone, markedly narrowing the lumen and reducing blood flow; symptomatic ischemia (variant angina) may result. Marked narrowing can trigger thrombus formation, causing infarction or life-threatening arrhythmia. Spasm can occur in arteries with or without atheroma.is a transient, focal increase in vascular tone, markedly narrowing the lumen and reducing blood flow; symptomatic ischemia (variant angina) may result. Marked narrowing can trigger thrombus formation, causing infarction or life-threatening arrhythmia. Spasm can occur in arteries with or without atheroma.
  - **In arteries without atheroma,** basal coronary artery tone is probably increased, and response to vasoconstricting stimuli is probably exaggerated. The exact mechanism is unclear but may involve endothelial cell abnormalities of nitric oxide production or an imbalance between endothelium-derived contracting and relaxing factors.
  - **In arteries with atheroma,** the atheroma causes endothelial dysfunction, possibly resulting in local hypercontractility. Proposed mechanisms include loss of sensitivity to intrinsic vasodilators (eg, acetylcholine) and increased production of vasoconstrictors (eg, angiotensin II, endothelin, leukotrienes, serotonin, thromboxane) in the area of the atheroma. Recurrent spasm may damage the intima, leading to atheroma formation.

III] Use of vasoconstricting drugs (eg, cocaine, nicotine) and emotional stress also can trigger coronary spasm.

PATHOPHYSIOLOGY OF ANGINA





CONCEPT OF PRELOAD AND AFTERLOAD

COMPLICATIONS

- The primary threat of angina is the higher probability of being exposed to cardiac arrest if not detected and diagnosed in time.
- Any form of angina if left ignored and untreated can lead to a heart attack at any stage thereafter.
- According to doctors, unstable angina and variant angina demand strict changes in lifestyle and immediate medication to curb the chance of a cardiac arrest.

MYCARDIAL INFRACTION

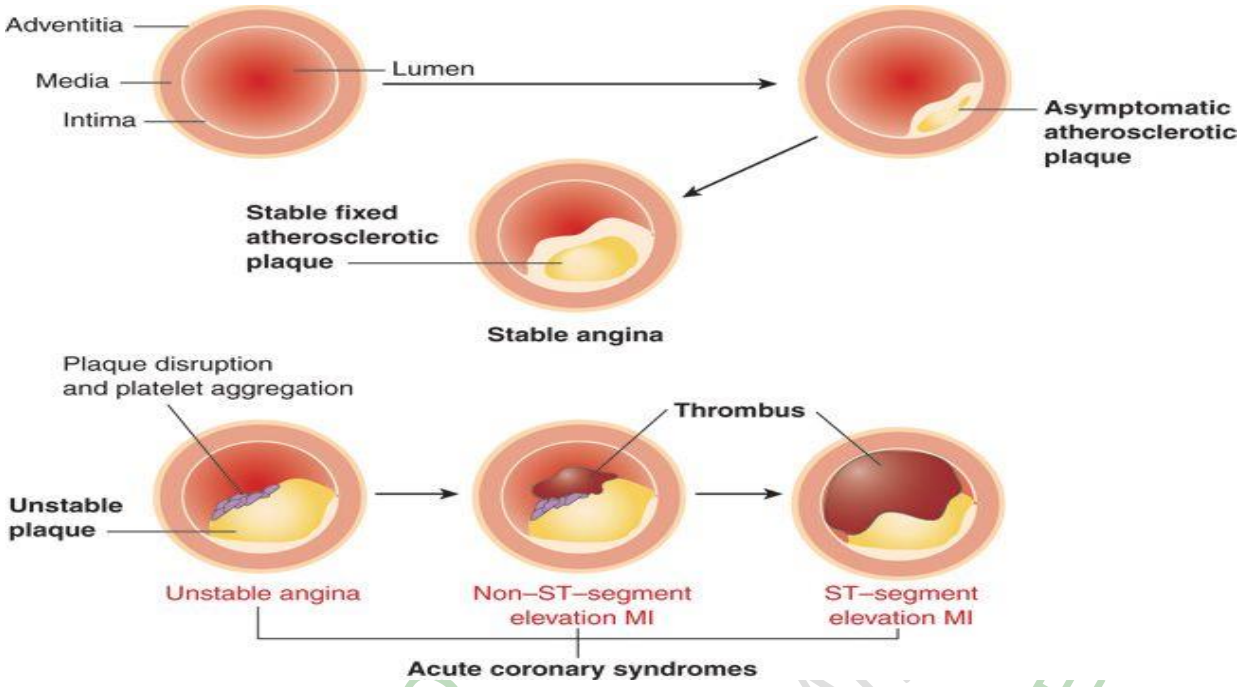
DEFINITION:

"Myocardial infarction (MI) refers to tissue death (infarction) of the heart muscle (myocardium). It is a type of acute coronary syndrome, which describes a sudden or short-term change in symptoms related to blood flow to the heart"

OR

"Myocardial infarction (MI) is the irreversible death (necrosis) of heart muscle secondary to prolonged lack of oxygen supply (ischemia)".

- This is usually the result of a blockage in one or more of the coronary arteries. A blockage can develop due to a buildup of plaque, a substance mostly made of fat, cholesterol, and cellular waste products.
- Unlike other causes of acute coronary syndromes, such as unstable angina, a myocardial infarction occurs when there is cell death, as measured by a blood test for biomarkers (the cardiac protein troponin or the cardiac enzyme CK-MB).
- When there is evidence of an MI, it may be classified as an
- ST elevation myocardial infarction (STEMI) or
- Non-ST elevation myocardial infarction (NSTEMI) based on the results of an ECG.
- The phrase "heart attack" is often used non-specifically to refer to a myocardial infarction and to sudden cardiac death.
- An MI is different from—but can cause—cardiac arrest, where the heart is not contracting at all or so poorly that all vital organs cease to function, thus causing death. It is also distinct from heart failure, in which the pumping action of the heart is impaired. However, an MI may lead to heart failure.



ETIOPATHOGENESIS

- The etiologic role of severe coronary atherosclerosis (more than 75% compromise of lumen) of one or more of the three major coronary arterial trunks in the pathogenesis of about 90% cases of acute MI is well documented by autopsy studies as well as by coronary angiographic studies.
- A few notable features in the development of acute MI are as under:

1. **Myocardial ischaemia**

   Myocardial ischaemia is brought about by one or more of the following mechanisms:
   - ✓ **Diminised coronary blood flow** e.g. in coronary artery disease, shock.
   - ✓ **Myocardial demand** e.g. in exercise, emotions.
   - ✓ **Hypertrophy of the heart without simultaneous increase of coronary blood flow** e.g. in hypertension, valvular heart disease.

2. **Role of platelets**
   - ✓ Rupture of an atherosclerotic plaque exposes the subendothelial collagen to platelets which undergo aggregation, activation and release reaction.
   - ✓ These events contribute to the build-up of the platelet mass that may give rise to emboli or initiate thrombosis.

3. **Acute plaque rupture**
   - ✓ Acute complications in coronary atherosclerotic plaques in the form of superimposed coronary thrombosis due to plaque rupture and plaque haemorrhage is frequently encountered in cases of acute MI:

   I. **Superimposed coronary thrombosis**
   - Due to disruption of plaque is seen in about half the cases of acute MI.
   - Infusion of intracoronary fibrinolysins in the first half an hour of development of acute MI in such cases restores blood flow in the blocked vessel in majority of cases.

   II. **Intramural haemorrhage**

- It is found in about one-third cases of acute MI.
- Plaque haemorrhage and thrombosis may occur together in some cases.

4. Non-atherosclerotic causes

✓ About 10% cases of acute MI are caused by non-atherosclerotic factors such as coronary vasospasm, arteritis, coronary ostial stenosis, embolism, thrombotic diseases, and trauma.

5. Transmural *versus* subendocardial infarcts

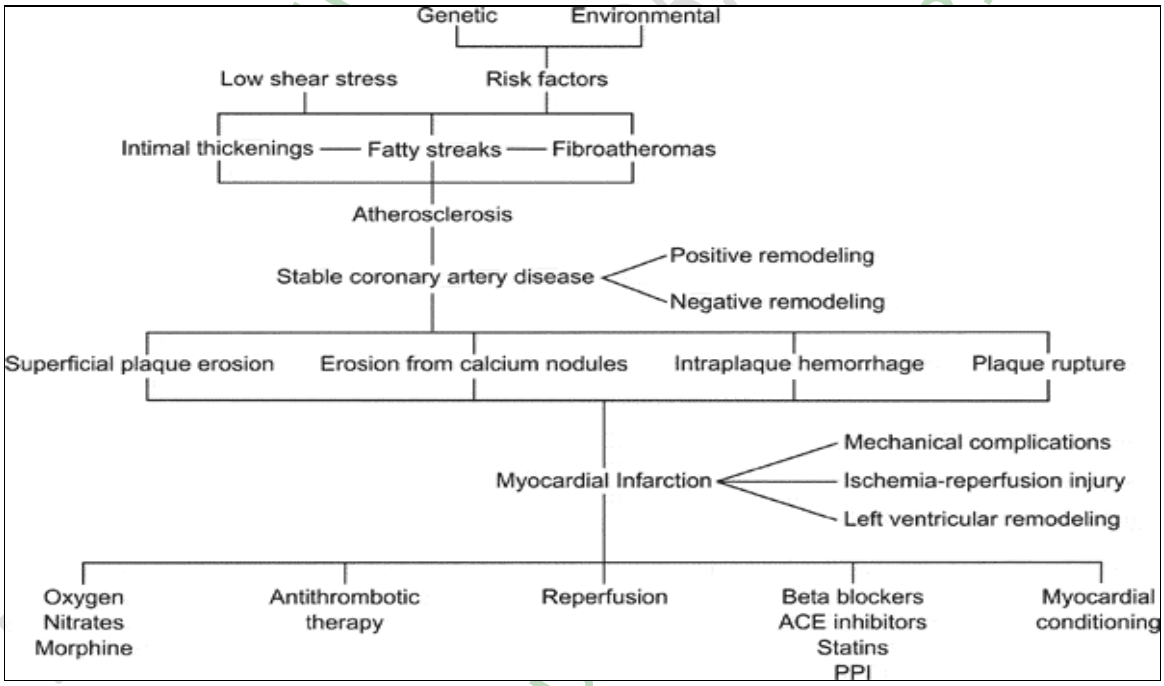
✓ There are some differences in the pathogenesis of the *transmural infarcts* involving the full thickness of ventricular wall and the *subendocardial (laminar) infarcts* affecting the inner subendocardial one-third to half. **II**

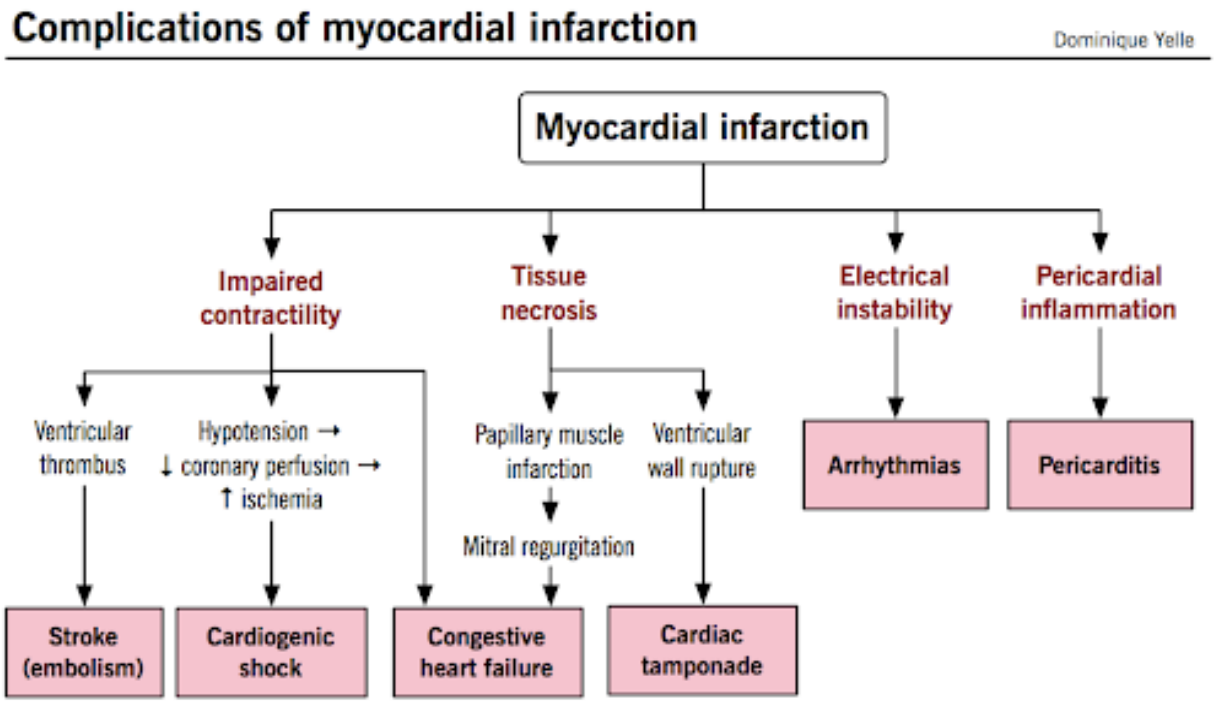
I. Transmural (full thickness) infarcts

- Are the most common type seen in 95% cases.
- Critical coronary narrowing (more than 75% compromised lumen) is of great significance in the causation of such infarcts.

II. Subendocardial (laminar) infarcts

- It have their genesis in reduced coronary perfusion due to coronary atherosclerosis but without critical stenosis (not necessarily 75% compromised lumen), aortic stenosis or haemorrhagic shock.





ATHEROSCLEROSIS

"**Atherosclerosis**: disease of large and medium-sized arteries characterized by endothelial dysfunction, vascular inflammation and accumulation of lipids, cholesterol, calcium and cellular debris within the intima of the vessel wall".

STAGES OF PLAQUE DEVELOPMENT

1. FATTY STREAK

- Earliest visible lesions that appear as areas of yellow discoloration on artery's inner surface; blood flow is not yet impeded at this stage
- Central to this process is **endothelial dysfunction**, which allows entry and modification of lipids in the vessel subintima; these lipids then serve as pro-inflammatory mediators.

Endothelial dysfunction

- Triggered by injury to the arterial endothelium
  - ✓ Exposure to physical forces, e.g. shear stress
  - ✓ Chemical irritants and toxins
    - Increased production of reactive oxygen species (ROS) in cigarette smoking, elevated circulating low density lipoprotein (LDL) levels and diabetes
- Resulting activated state sets the stage for subsequent development of atherosclerosis

Lipoprotein entry and modification

- Accumulation of lipoprotein particles in the intima
  - ✓ Increased endothelial permeability allows for entry of LDL into the vessel intima
  - ✓ LDL binds to proteoglycans in the extracellular matrix and becomes trapped
- Chemical modification of lipoproteins

- ✓ Oxidation – by local ROS derived from endothelial cells or macrophages that penetrate the vessel wall
- ✓ Glycation – in diabetic patients with sustained hyperglycemia

❖ Modified LDL has antigenic and pro-inflammatory properties and contributes to leukocyte recruitment and foam cell formation

Leukocyte recruitment

❖ Modified LDL induces local pro-inflammatory cytokine elaboration (e.g. IL-1, TNF-α) by endothelial and Smooth muscle cells [SMCs]

❖ Cytokines promote increased expression of:

- ✓ Adhesion molecules (e.g. VCAM-1, ICAM-1, E-selectin, P-selectin)–bind leukocytes
- ✓ Chemoattractant molecules – direct leukocyte migration into the vessel intima

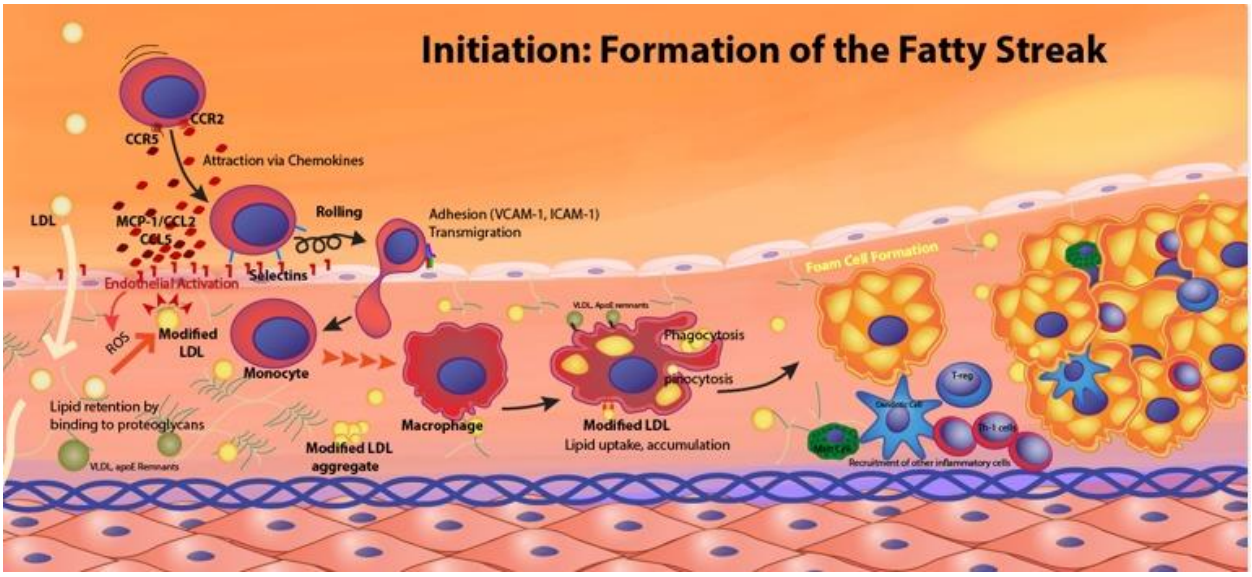
❖ Monocytes, and to a lesser extent T lymphocytes, are attracted to the vessel wall

Foam cell formation

❖ Upon entering the intima, monocytes differentiate into phagocytic macrophages and upregulate their expression of scavenger receptors in response to local macrophage colony-stimulating factor (M-CSF)

❖ Scavenger receptors mediate the uptake of modified LDL into macrophages

❖ Macrophages develop into foam cells which produce additional cytokines that perpetuate the process of atherosclerotic plaque formation



2. PLAQUE PROGRESSION

❖ Thickening of the intima due to migration of Smooth Muscle Cells from the media to the intima, proliferation of SMCs and extracellular matrix production

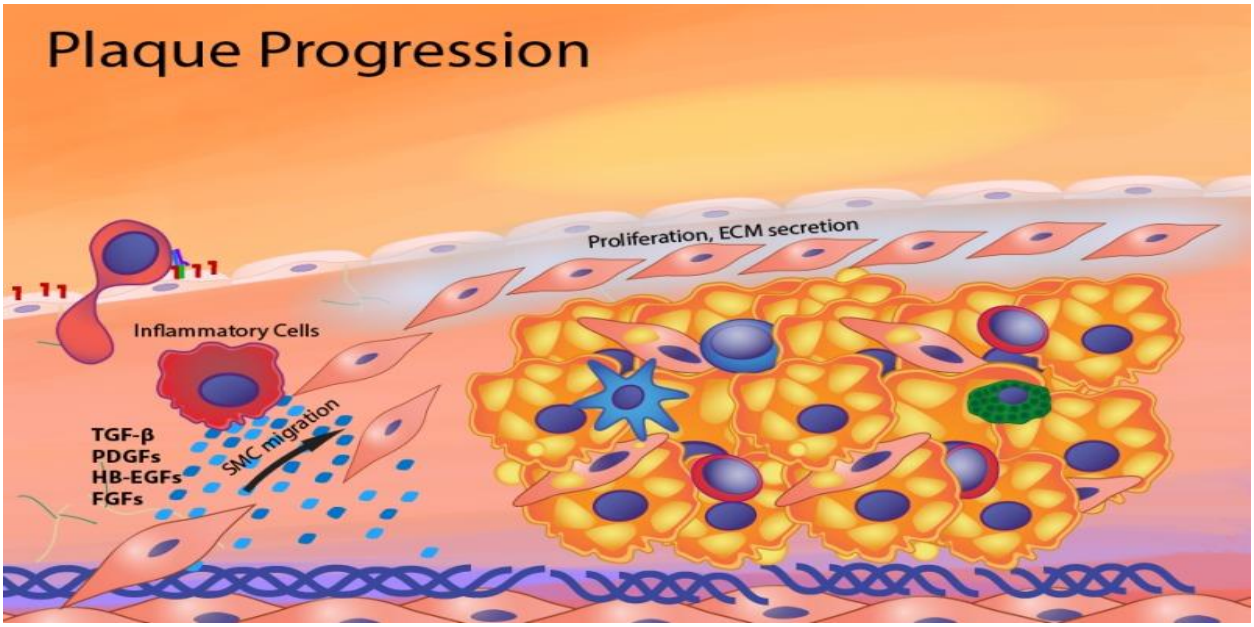
- ✓ Foam cells, activated platelets and endothelial cells release cytokines & growth factors (e.g. TNF-α, IL-1, FGF) that stimulate SMC migration and proliferation
- ✓ SMC activation & cytokine release and maintains inflammation in the lesion

❖ Fatty streak evolves into a fibrofatty lesion

❖ Calcification can occur at later stages and fibrosis continues

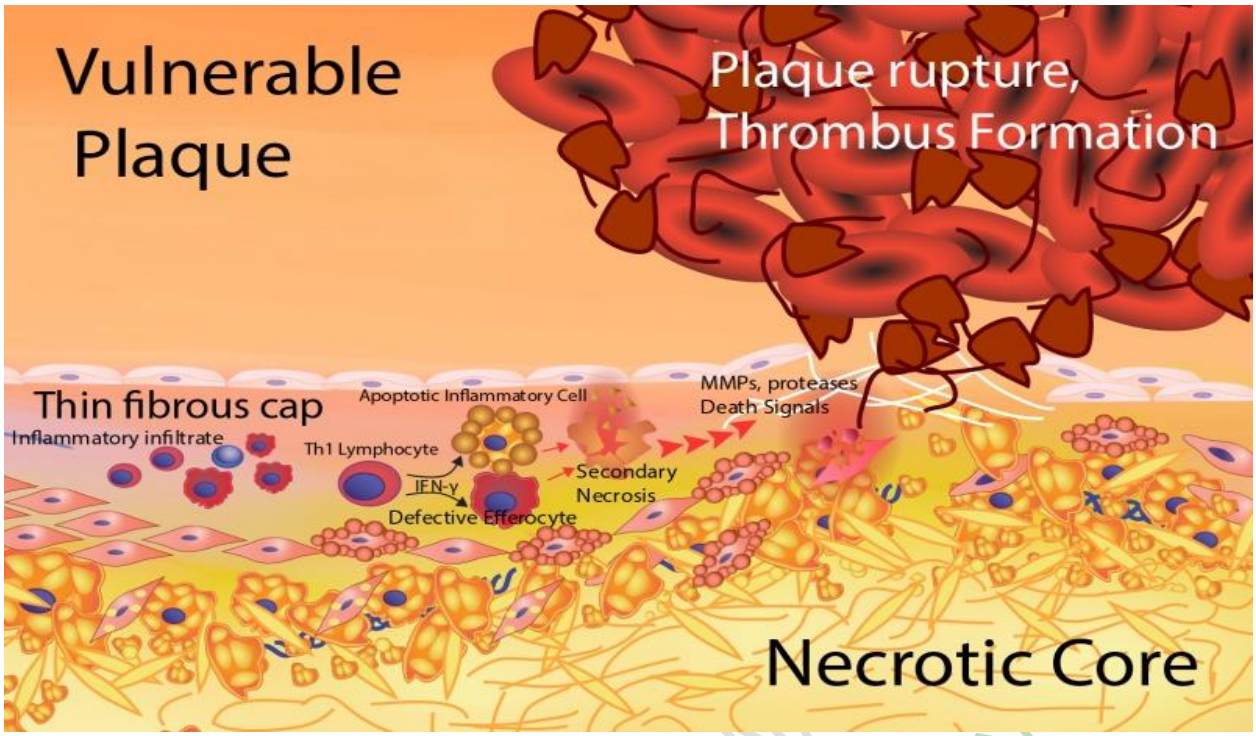
❖ Apoptosis of SMCs yields a relatively acellular fibrous capsule that surrounds a lipid-rich core

- Late plaque growth can significantly restrict the vessel lumen and impede perfusion
  - ✓ Flow-limiting plaques can lead to tissue ischemia and cause symptoms such as angina pectoris or claudication



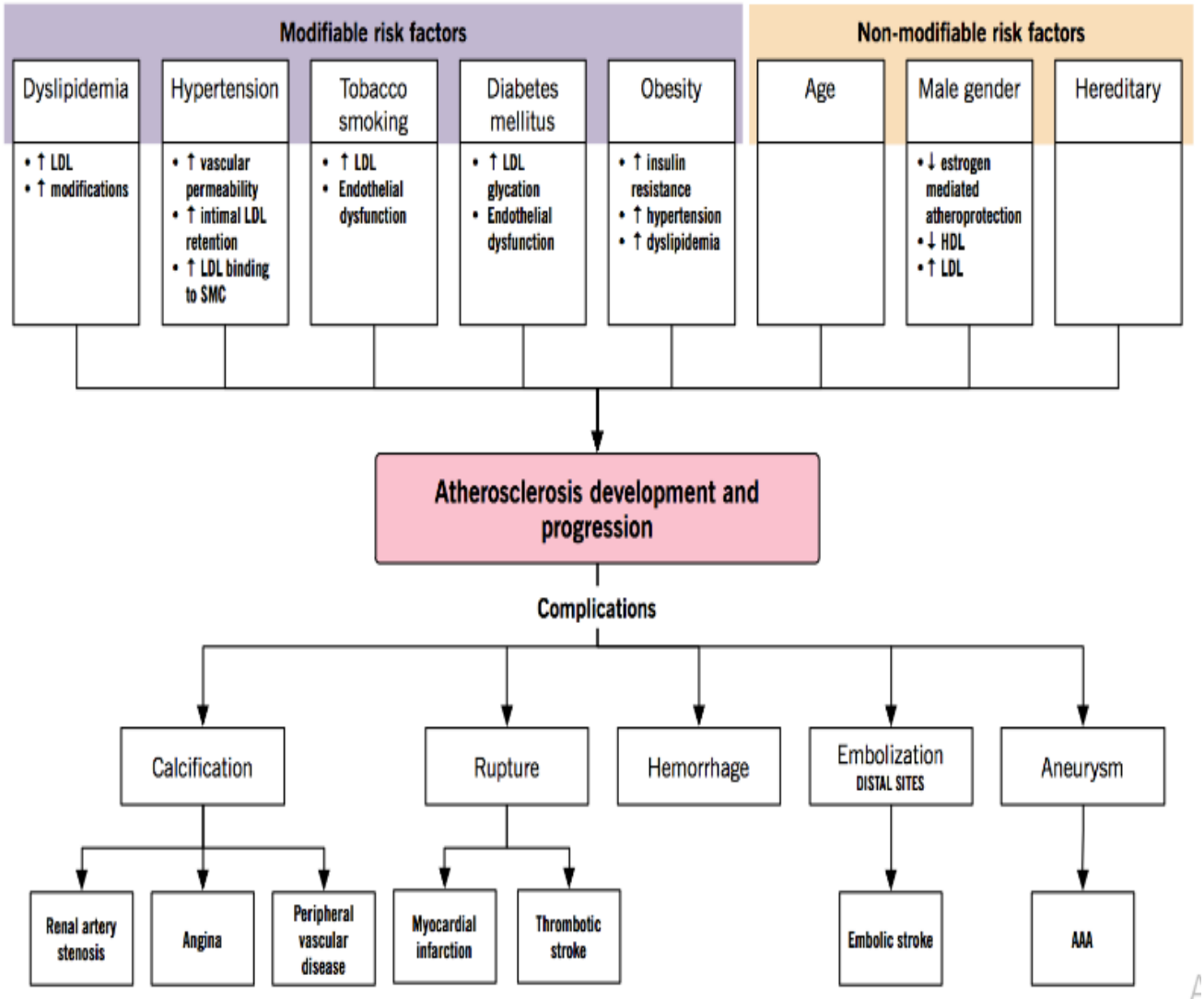
3. PLAQUE DISRUPTION

- Fibrous cap integrity depends on net extracellular matrix metabolism
  - SMCs synthesize constituents of the fibrous cap such as collagen and elastin
  - Foam cells synthesize proteolytic enzymes including collagen-degrading matrix metalloproteinases
- Over time hemodynamic stresses and degradation of extracellular matrix increase the risk of fibrous cap rupture
- While plaques with thicker fibrous caps tend to cause more pronounced arterial narrowing, they have less propensity to rupture (stable plaques); conversely, thinner less obstructive plaques tend to be more fragile and rupture (vulnerable plaques)
- When the fibrous cap ruptures, pro-thrombotic molecules within the lipid core are exposed and can sometimes, but not necessarily, precipitate formation of an acute thrombus which occludes the arterial lumen
  - This is the underlying mechanism in most acute coronary syndrome



BIOLOGICAL MARKERS

- Homocysteine
  - ✓ High levels may promote oxidative stress, vascular inflammation and platelet adhesiveness
- Lipoprotein particle Lp(a)
  - ✓ Detrimental effect may be attributed to competition with normal plasminogen activity
- C-reactive protein and other markers of inflammation
  - ✓ Activates complement and contributes to a sustained inflammatory state

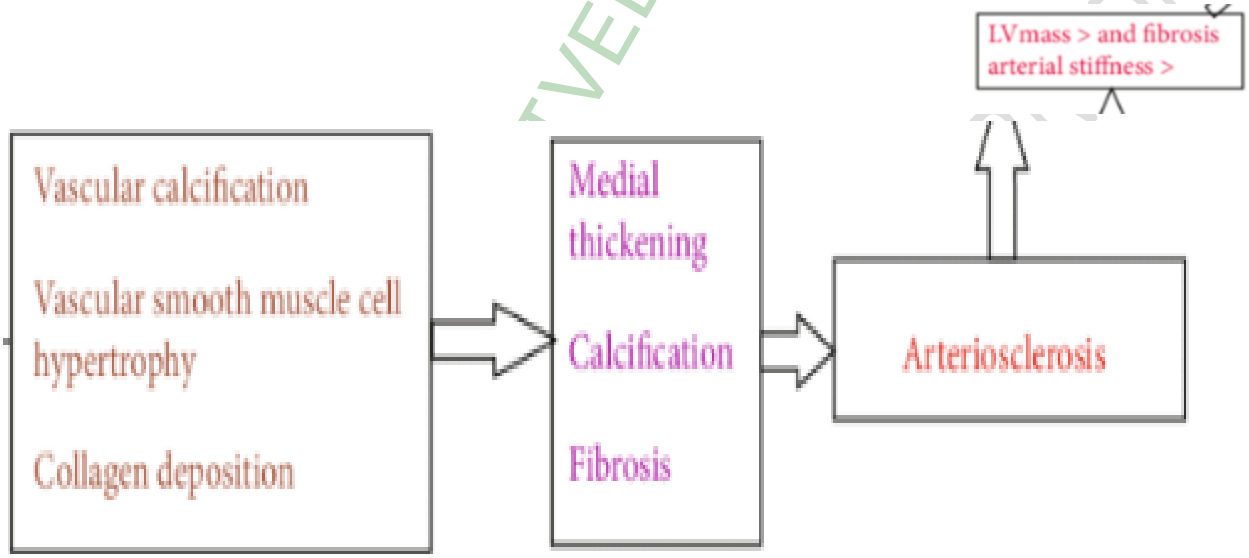


ARTERIOSCELROSIS

ARTERIOSCLEROSIS

Arteriosclerosis is a general term used to include all conditions with thickening and hardening of the arterial walls.

Arteriosclerosis occurs when the blood vessels that carry oxygen and nutrients from heart to the rest of body (arteries) become thick and stiff — sometimes restricting blood flow to organs and tissues. Healthy arteries are flexible and elastic, but over time, the walls in arteries can harden, a condition commonly called hardening of the arteries



The following morphologic entities are included under arteriosclerosis:

I. Senile arteriosclerosis
II. Hypertensive arteriolosclerosis
III. Mönckeberg's arteriosclerosis(Medial calcific sclerosis)
IV.Atherosclerosis

The last-named, atherosclerosis, is the most common and most important form of arteriosclerosis; if not specified, the two terms are used interchangeably with each other.

SENILE ARTERIOSCLEROSIS

- Senile arteriosclerosis is the thickening of media and intima of the arteries seen due to aging.
- The changes are nonselective and affect most of the arteries.
- These are possibly induced by stress and strain on vessel wall during life.

HYPERTENSIVE ARTERIOLOSCLEROSIS

- Hypertension is the term used to describe an elevation in blood pressure. Pathology of 3 forms of hypertension— systemic, pulmonary and portal.

MONCKEBERG'S ARTERIOSCLEROSIS (MEDIAL CALCIFIC SCLEROSIS)

- Mönckeberg's arteriosclerosis is calcification of the media of large and medium-sized muscular arteries, especially of the extremities and of the genital tract, in persons past the age of 50.
- The condition occurs as an age-related degenerative process, and therefore, an example of dystrophic calcification, and has little or no clinical significance. However, medial