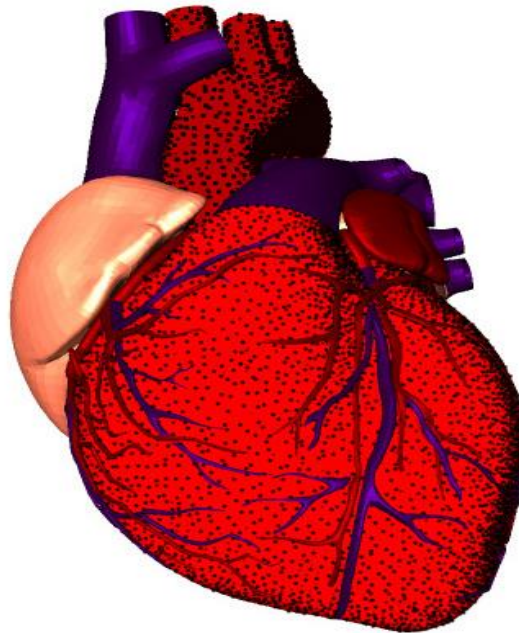


**Semester II Lecture 3.**

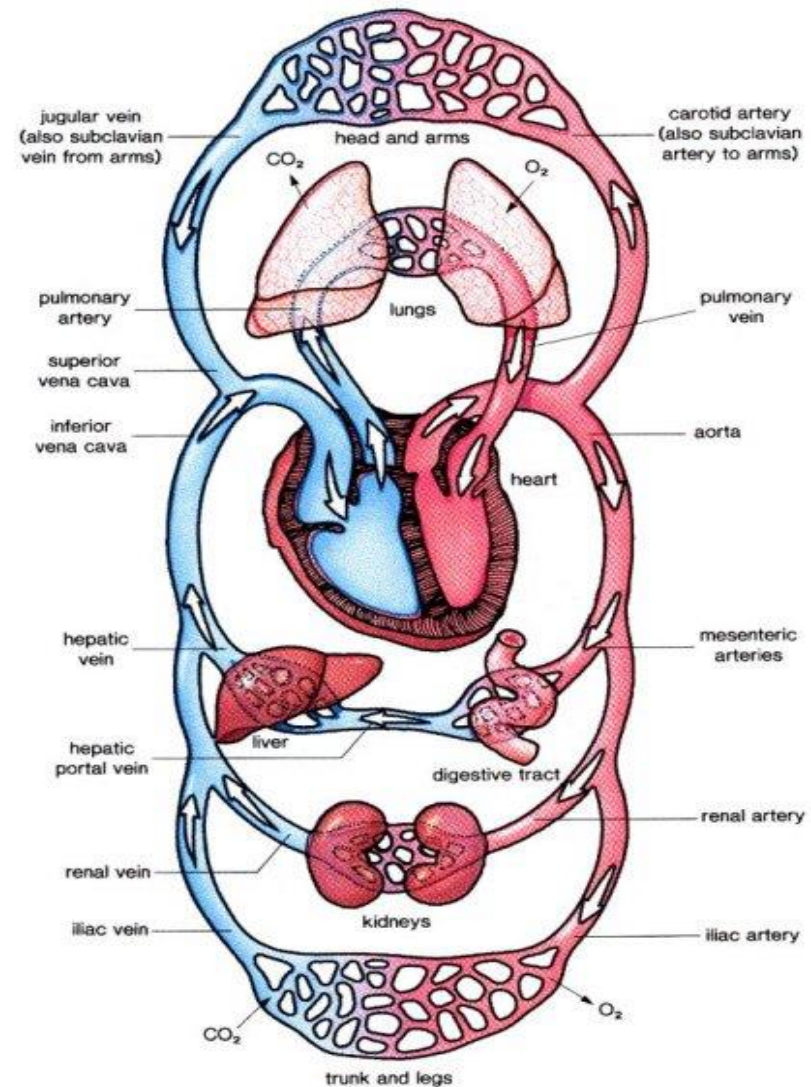
**Pathophysiology of heart. Heart failure.**

**Coronary heart disease**



# Functions of the circulatory system

- **Transport is the main function of circulatory system**
- **Stabilization of arterial pressure**
- **circulatory system delivers  $O_2$  and nutrients to the tissues**
- **circulatory system carries waste products to the kidneys and other excretory organs**

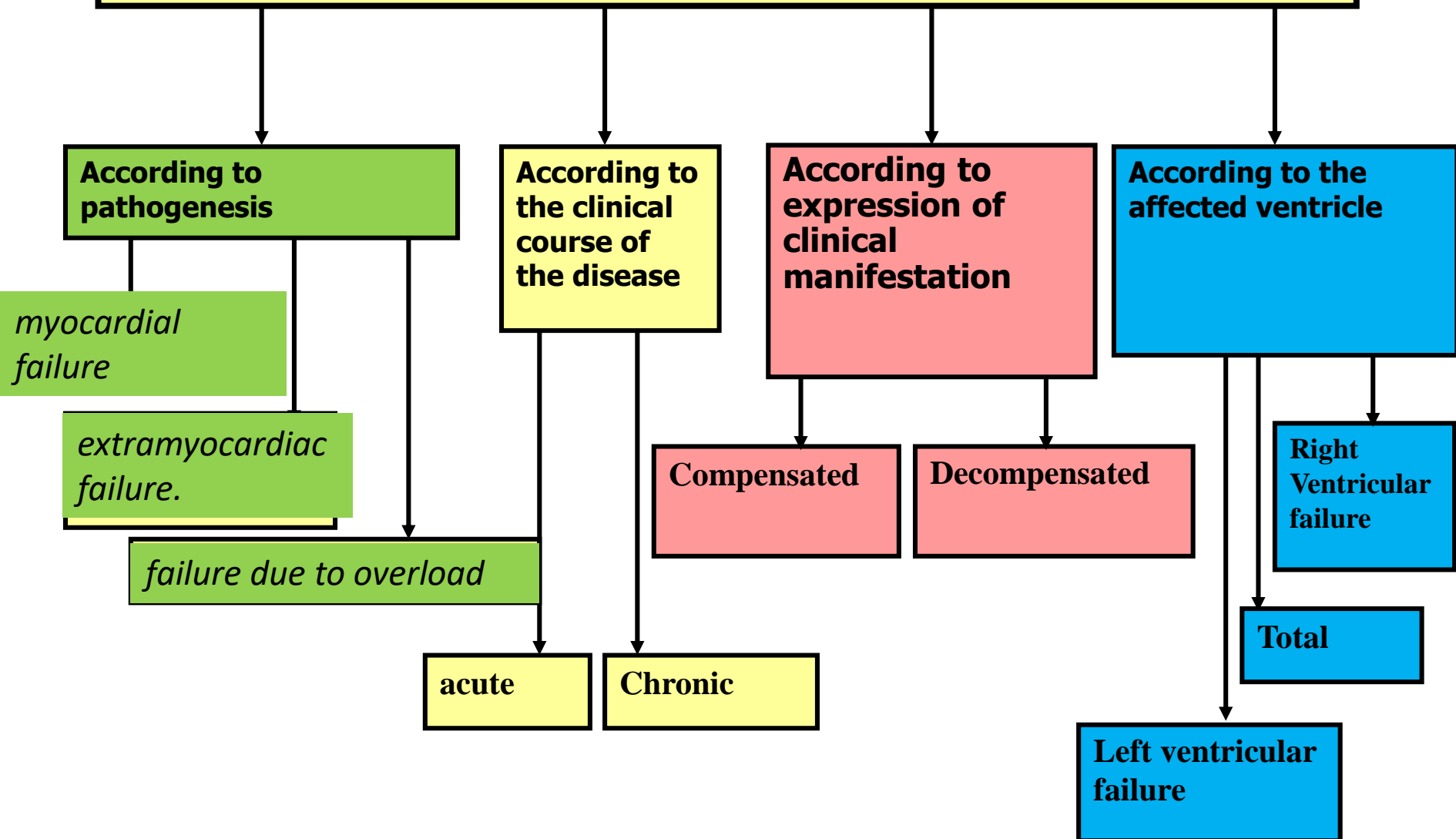


Pathological state in which the circulatory system can not satisfy the requirements of organs and tissues with a needed amount of blood is called *circulatory failure*.

It can be due to **heart failure**, **vascular failure** or both heart and vascular system failure.

- **Heart failure (HF)** is a pathological state in which impaired cardiac function fails and can not satisfy the requirements of organs and tissues with a needed amount of blood
- *the failure of the heart as a pump leads to the **decrease in cardiac output**.*

# Classification of heart failure



# Reasons

## Failure due to overload

(results from great **volume** or **pressure** loads on the heart with normal myocardial contractivity).

### ***Volume overload occurs***

- in *incompetence of the heart valves*. In this case heart failure develops due to increased blood filling (**preload**) of the appropriate ventricle.
- in *increased venous return* (hypervolemia).

### ***Pressure overload occurs***

- In *systemic or pulmonary hypertension*
- *in stenosis of the aortic or pulmonary valves*. They cause pressure overload in the left or right ventricle. In these cases, heart failure develops due to an increased resistance to ejection of blood from the heart (**afterload**).

# *Pathogenesis of heart failure*

- There are **short-term and long-term** mechanisms of compensation which help the heart to compensate for its decreased pump function or increased work load.

**Short-term compensatory mechanisms  
of heart contractility function decreasing**

*Heterometric  
mechanism of  
compensation*

*Homeometric  
mechanism of  
compensation*

*Tachycardia*

*Chronoinotropic  
action of  
catecholamines*

*Increase:*  
- cardiac output  
- frequency of cardiac contractions

# *Heterometric mechanism of compensation*

- Heterometric mechanism comes into play at ***volume overload*** on the heart.
- It is called heterometric because an increase in the force of contraction of cardiac muscle is based on an increase in length of muscle.
- It was stated by **Starling** that the force of contraction depends on the degree to which cardiac muscle is stretched during diastole.



# *Homeometric mechanism of compensation*

- Homeometric mechanism comes into play at ***pressure overload*** on the heart.
- It is called homeometric because the myocardial muscle fibers contract with greater strength at any given length.

## ***Tachycardia***

- An increase in a frequency of cardiac contractions allows the heart to maintain constancy of the cardiac output.

## ***Chronoinotropic action of catecholamines***

- Increased sympathetic activity accelerates the heart rate and myocardial contractility that help to maintain cardiac output.

# Long-term compensatory mechanism

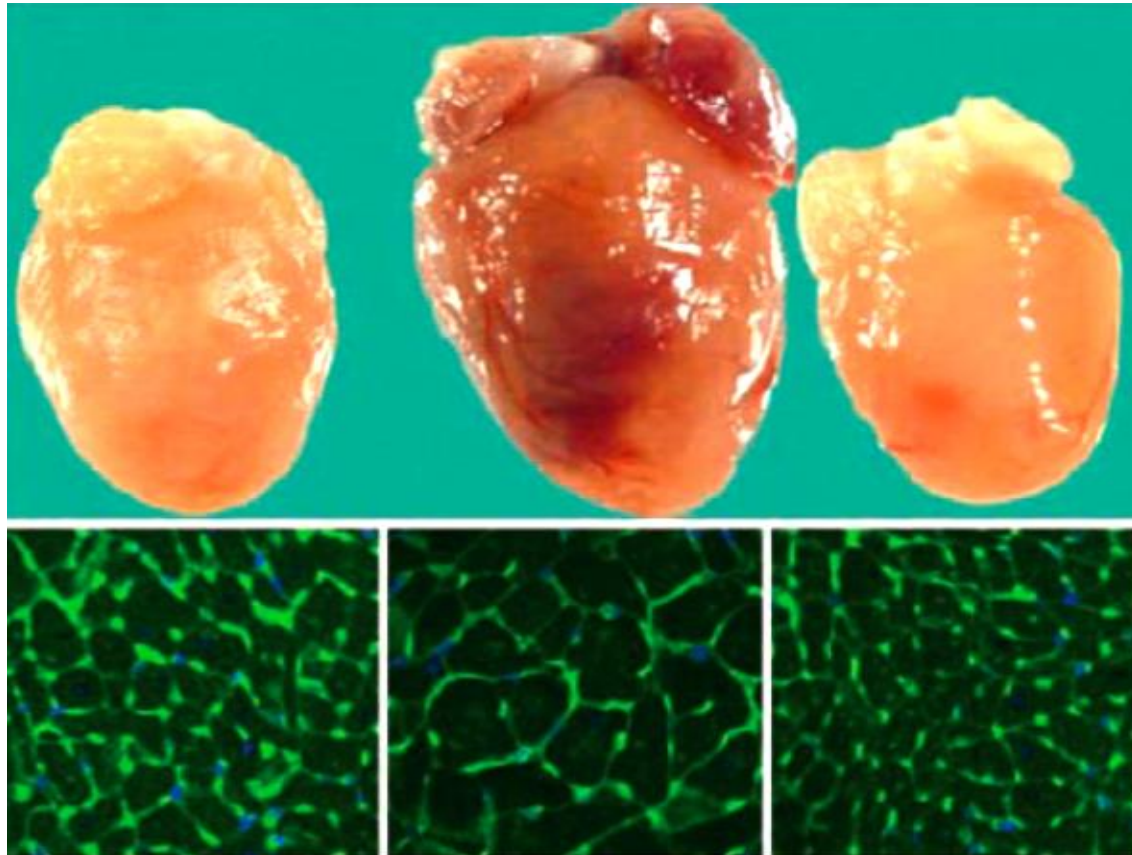
## *Hypertrophy of the heart muscle*

- Myocardial hypertrophy is a long-term compensatory mechanism.
- If increased functional requirements are made of the heart for a long time (e. g., in valve incompetence) the result is hypertrophy of the heart muscle, especially of the parts functioning under an increased load.
- Increase in work demands activation of the genetic apparatus of cardiomyocytes with resultant increase in protein synthesis.
- **Hypertrophy** increases the number of contractile elements with enlargement of cardiac myocytes as a means of increasing their contractile performance.
- **It** allows the heart to maintain the cardiac output.
- **Hypertrophy** of the heart is usually accompanied by a dilatation of the heart chambers.

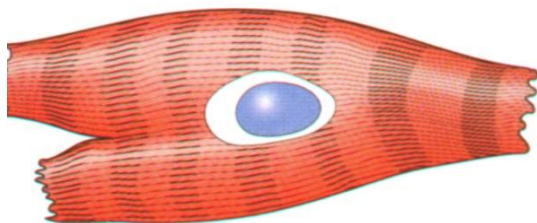
# ***Hypertrophy of the heart muscle***

Pathophysiological process that occurs in overload of the heart (or its parts), what causes the increasing in heart weight by the increasing of a cardiomyocyte mass and volume.

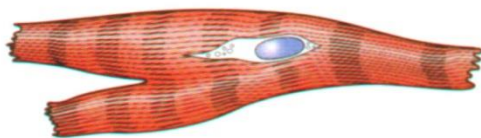
**Result: heart stable adaptation to load**



# Hypertrophy



гіпертрофія кардіоміоциту

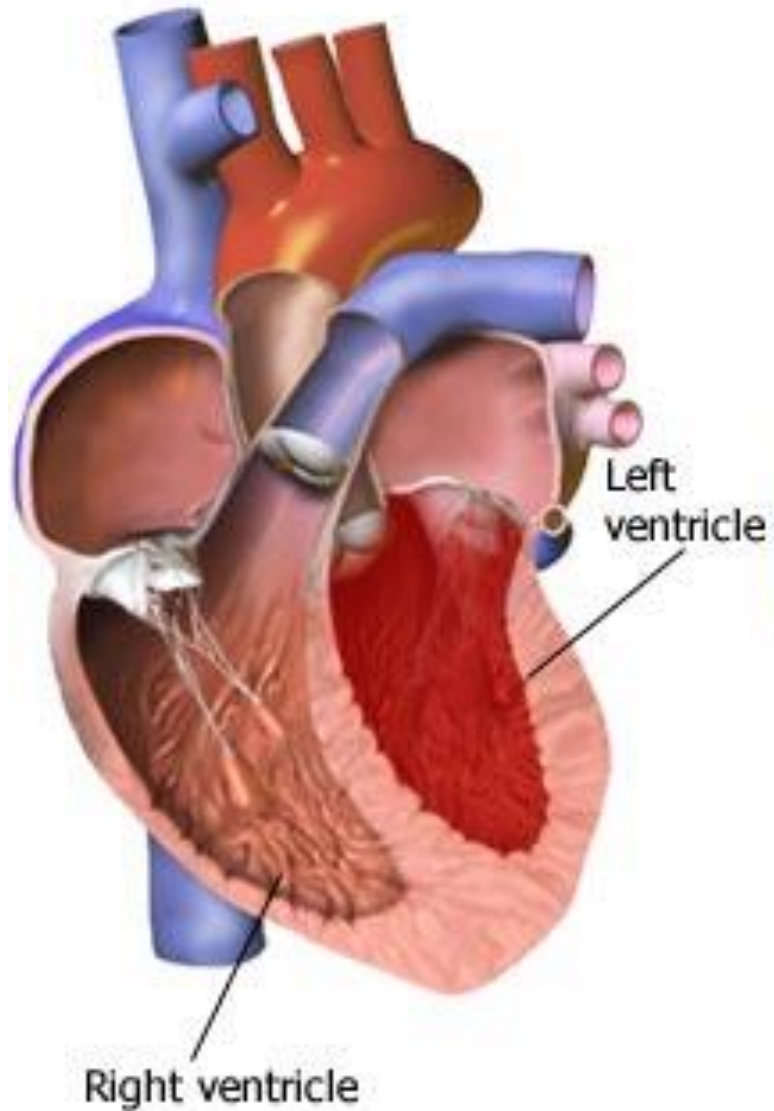


норма



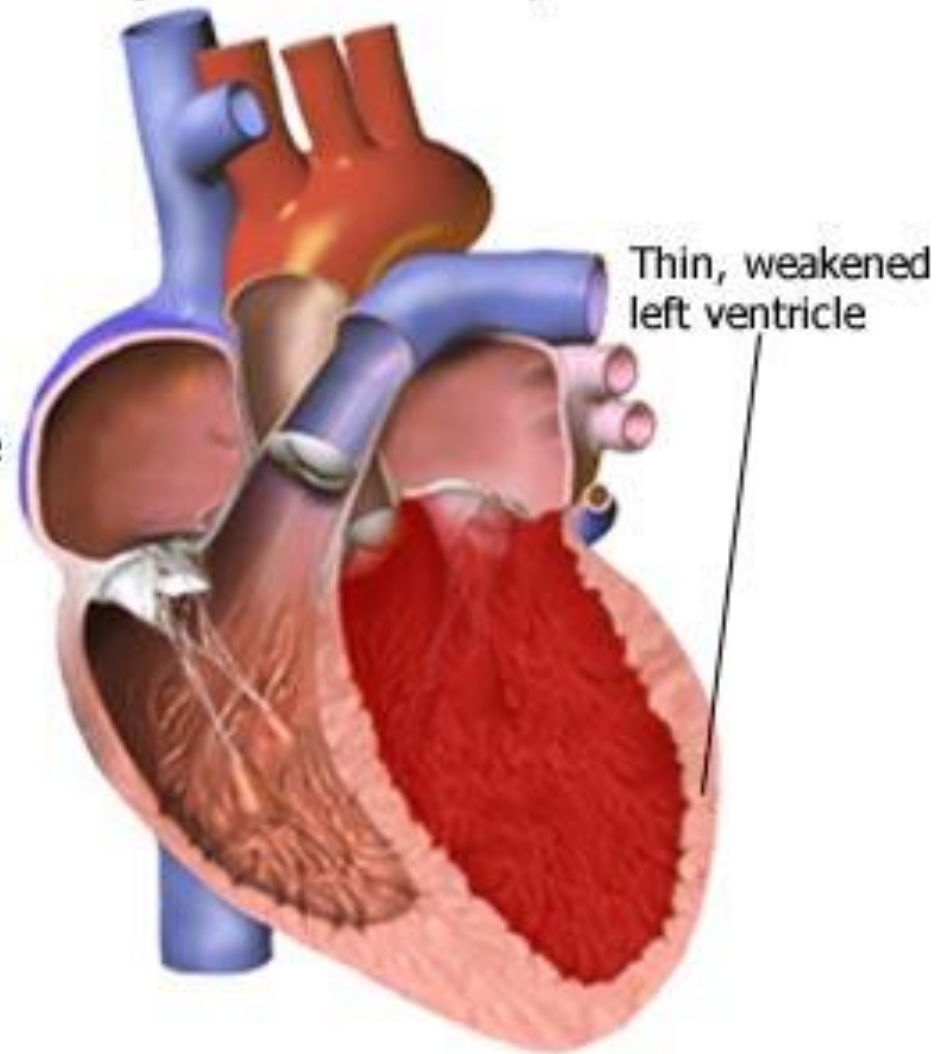


## Normal



## Enlarged Heart

A type of cardiomyopathy. An enlarged heart is a sign that the heart may be overworked.





The X-Ray on the left shows a normal heart.

On the right, the heart is enlarged.

**Cardiomegaly/ventricular remodeling** occurs as heart overworked > changes in size, shape, and function of heart after injury to left ventricle. Injury due to acute myocardial infarction or due to causes that inc. pressure or volume overload as in *Heart failure*

Hypertrophy of the heart may be physiologic and pathologic.

**Physiologic hypertrophy or — athlete's heart** is the normal response to regular, intense exercise which results in increased synthesis of contractile proteins and enlargement of cardiomyocytes. In this type of hypertrophy, an increase in the heart's muscle mass is balanced by growth of all constituents of the heart (vessels, nerves, mitochondria, ribosome and others).

**Pathologic hypertrophy** develops as a result of pathologic processes in the heart. It is due to increased filling of the heart or greater resistance to blood ejection.

In this type of hypertrophy in contrast to physiologic one, an increase in a mass of the heart muscle isn't balanced by a growth of apparatus of cardiomyocytes energetic and plastic provision. As a result the myocardium suffers from energy and nutrition deficiency that **leads to its dystrophy in time.**



# Signs of hypertrophy

## Sick person

1. Continuous heart load
2. Heart hypertrophy is inadequate to body weight
3. Decrease of capillaries amount in weight unit
4. Inadequate activity of MCh
5. Decrease of nervous structures amount in weight unit

**Heart insufficiency is compensated by the hypertrophy (bigger heart mass).**

## Sportsman

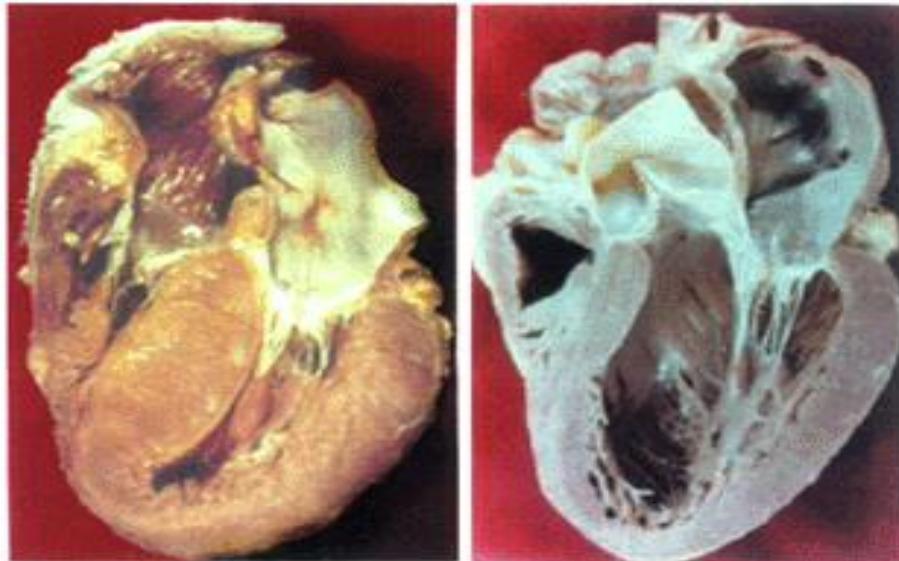
1. There are periods of heart load and restoring
2. Heart hypertrophy is adequate to body weight
3. Increase of capillaries amount in weight unit
4. Adequate activity of MCh
5. Increase of nervous structures amount in weight unit

**Heart insufficiency, which is compensated by the hypertrophy, increases of heart muscles contraction power and speed one.**

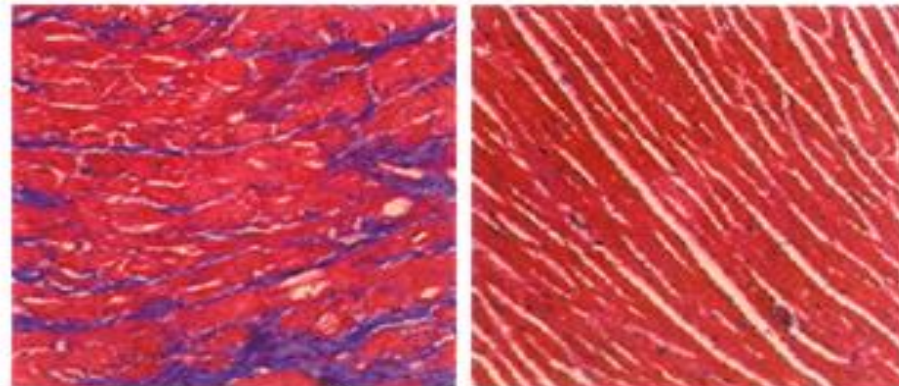
## Decompensation

**CARDIOSCLEROSIS – a consequence of myocardial hypertrophy**

A



B



HCM

Normal

# (stage of decompensation) symptoms



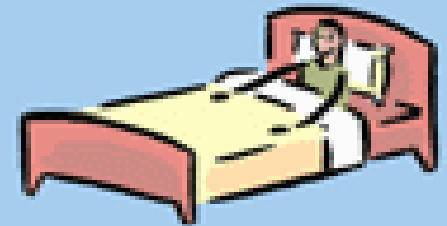
*Shortness  
of breath*



*Swelling of  
feet & legs*



*Chronic lack  
of energy*



*Difficulty sleeping  
at night due to  
breathing problems*



*Swollen or tender  
abdomen with  
loss of appetite*



*Cough  
with frothy  
Sputum*



*Increased  
urination  
at night*



*Confusion and/or  
impaired memory*

## Myocardium failure

(results from decreased myocardial contractility caused by a *primary damage to myocardium*).

- It may be due to:
- -*alterations in the conductive system of the heart - arrhythmical form*
- -*alterations in myofibers - cardiomyopathic form.*

Causes of the myocardial failure include:

- Myocardium hypoxia or ischemia
- Infectional-toxical myocardium damage
- Metabolism disorder (avitaminosis)
- Nervous-trophical and hormonal influences on the organism
- Coronary artery diseases

## *Extramyocardiac heart failure*

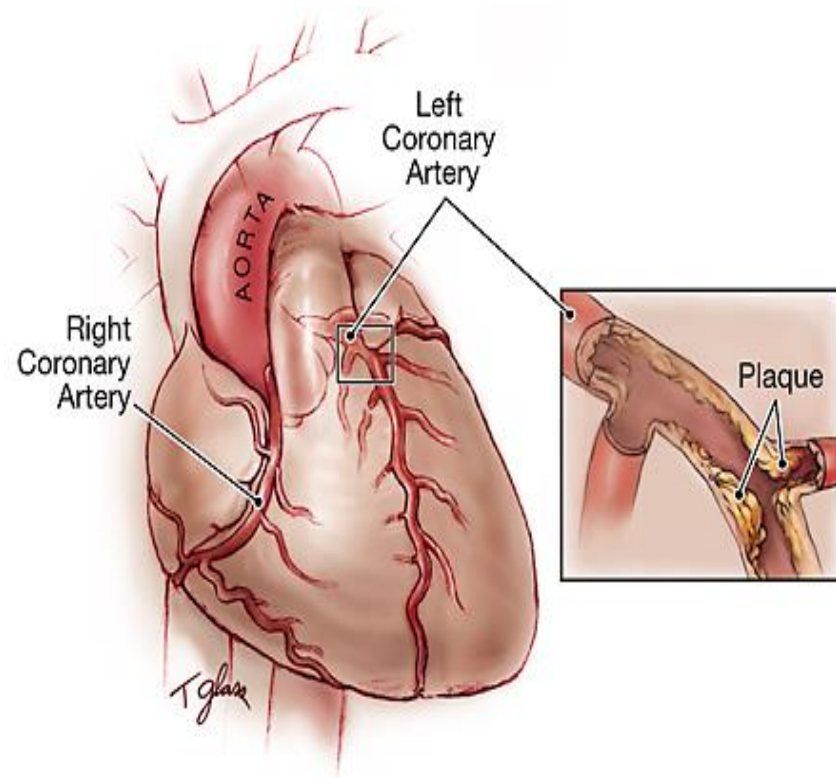
- conditions that restrict diastolic filling (e.g., in pericarditis or hemorrhages into the pericardium);
- conditions that decrease venous return of blood to the heart (hypovolemia, collapse).

## **Coronary artery disease**

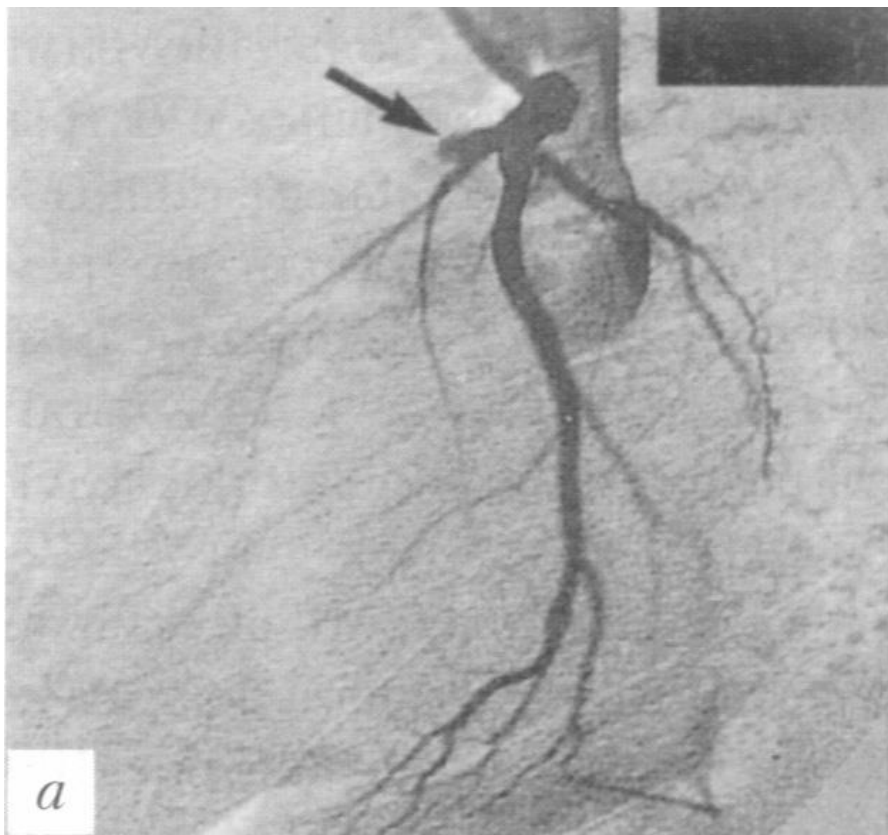
**Coronary insufficiency** - a pathological process characterized by increased myocardial demand in oxygen and metabolic substrates over their inflow in the coronary arteries.

# ETHIOLOGY

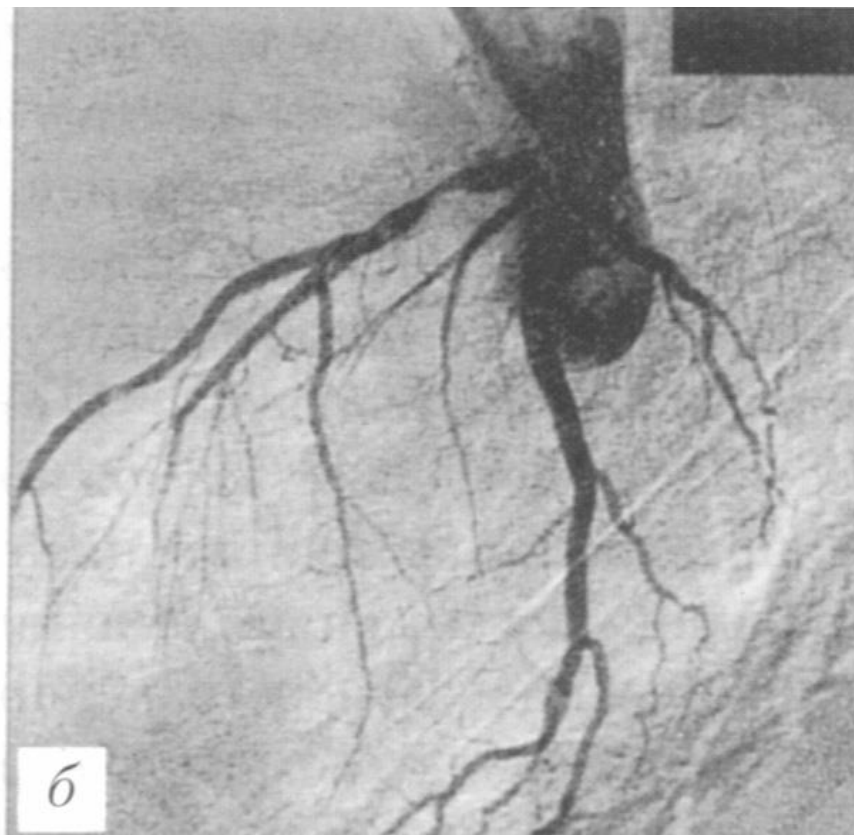
- **Atherosclerosis of the coronary arteries** (in 90-95 % died people at section was found)
- **Trombosis of the coronary arteries** :
  - \*at the 4 stage of atherosclerosis
  - \*arterial hypertension (because it causes blood coagulation hyperactivity)
- **Trombembolism** (septic endocarditis, thrombus lyses)
- **Spasm of the coronary arteries**



# ***КОРОНАРОГРАФІЯ - СТЕНОЗ КОРОНАРНОЇ АРТЕРІЇ***



***Стеноз лівої  
коронарної артерії  
(меіжшлуночкова гілка)***



***Після ангіопластики –***



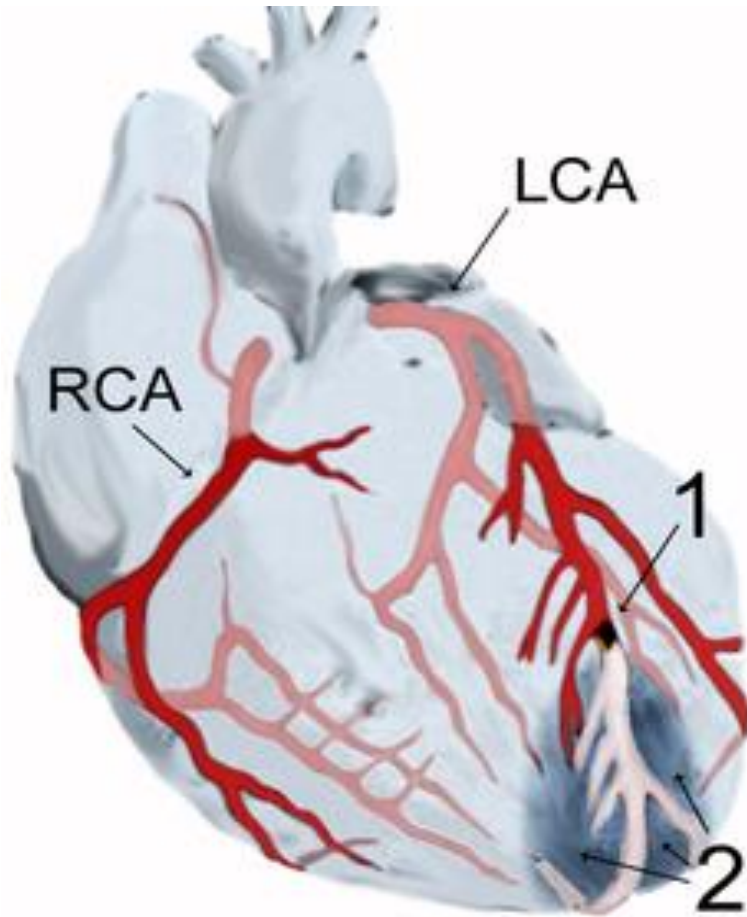
**Ischemic (coronary) heart disease** – multifactorial disease characterized by absolute or relative insufficiency of myocardial perfusion due to violation of coronary arteries

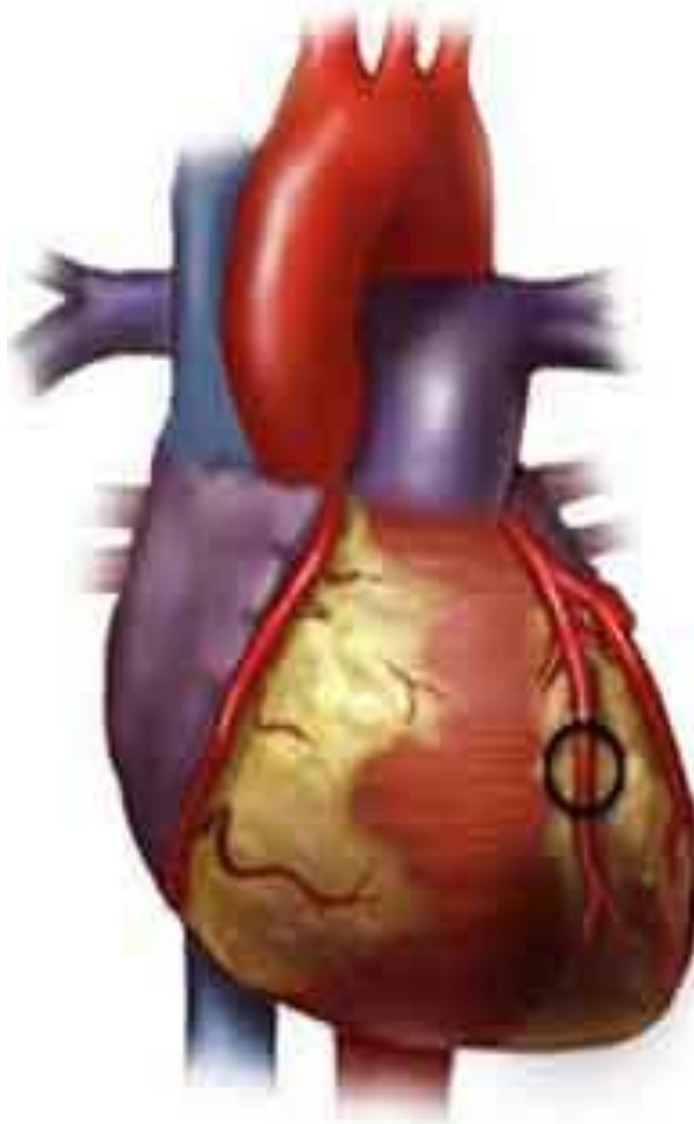
## **Clinical forms**

1. Angina
2. Myocardial infarction
3. Cardiosclerosis
4. Sudden coronary death

# Myocardial infarction

If the blood flow is completely blocked then a myocardial infarction (heart attack) occurs.





Normal coronary artery



Atherosclerosis



Atherosclerosis  
with blood clot



# Initial mechanisms

## 1. Increase of the atherosclerotic plaque size:

**Vessel narrowing---ischemia---necrogenic ATP deficit**

**vessels narrowing on 95 % (“critical stenosis”) causes ATP deficit (less than 40-60 %) which results in cardiomyocytes necrosis**

# Initial mechanisms

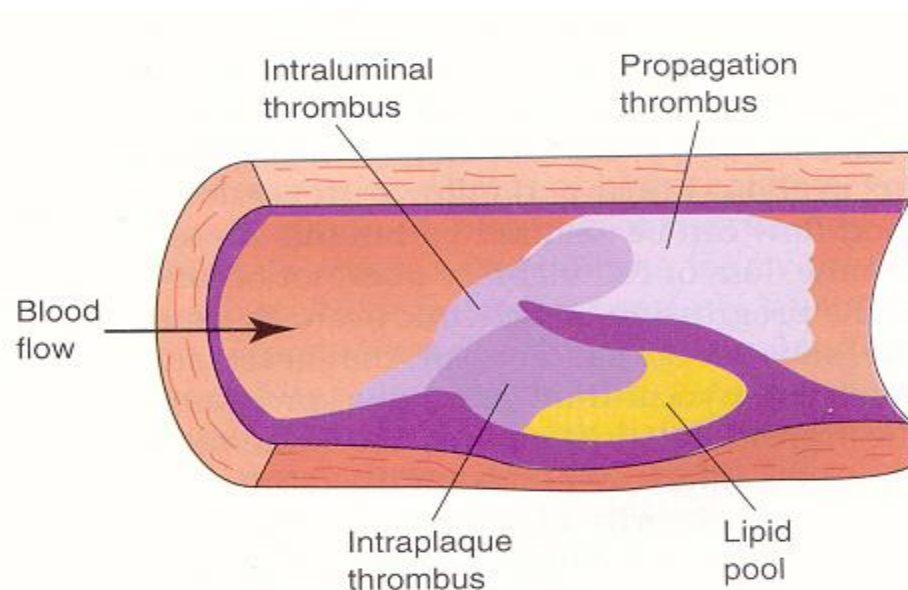
## 2. Increase of injured vessel sensitivity to vasospastic effects

Damage of endothelium -----  
decrease of NO-synthetase activity----  
decrease of NO concentration  
(which is powerful vasodilator)

# Initial mechanisms

## 3. Thrombosis

- Anticoagulants blood activity decrease  
(heparin is used for activation of lipoprotein lipase at hyperlipoproteinemia)
- Decreased antithrombotic properties of the injured endothelium



# Myocardial infarction

Ischaemical necrosis of the myocardial tissue,  
which is resulted from coronary blood supply  
insufficiency

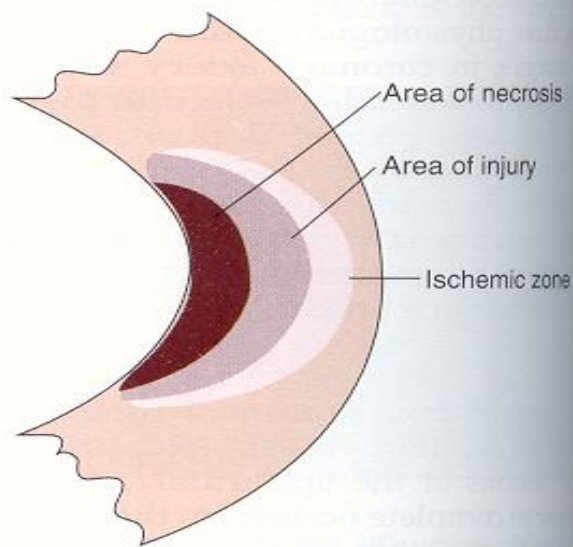


Figure 19–11 ■ ■ ■  
Areas of tissue damage after myocardial infarction.

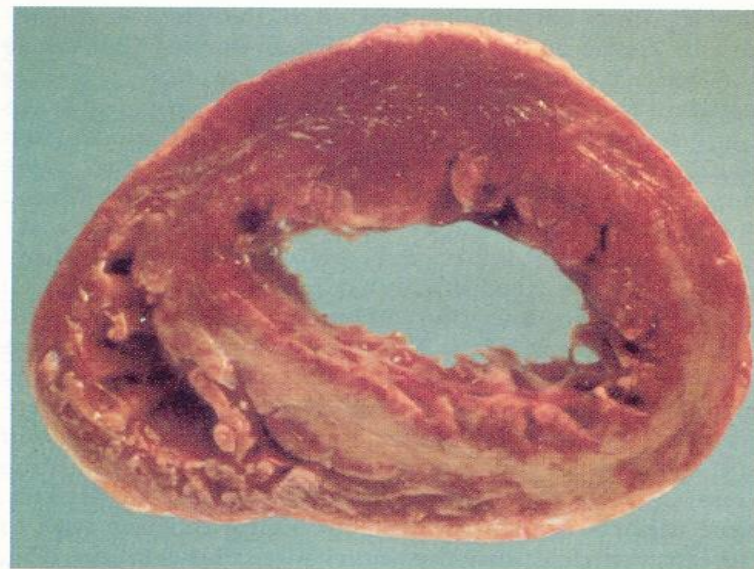


Figure 19–10 ■ ■ ■  
Acute myocardial infarct. A cross-section of the ventricles of a man who died a few days after the onset of severe chest pain shows a transmural infarct in the posterior and septal regions of the left ventricle. The necrotic myocardium is soft, yellowish, and sharply demarcated.

## Changes in cardiomyocytes based on myocardial ischemia duration

**Few  
seconds**

Initial ANP  
decreasing

**1-2 min**

Decreasing of  
heart contractility  
function

**≈ 10 min**

ANP decreasing  
≈ 50%

**≈ 20 min**

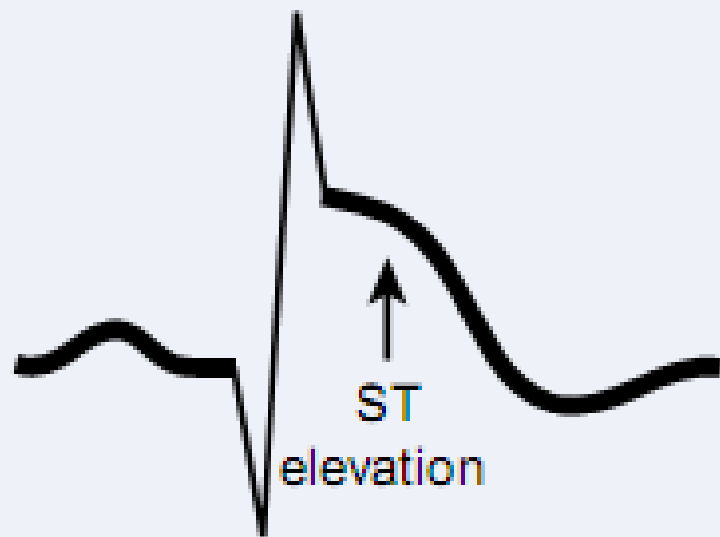
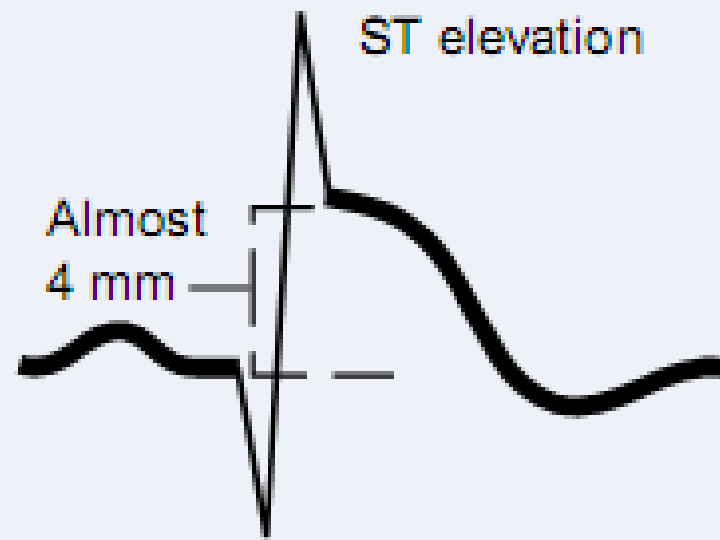
ANP decreasing  
≈ 90%

**30-40 min**

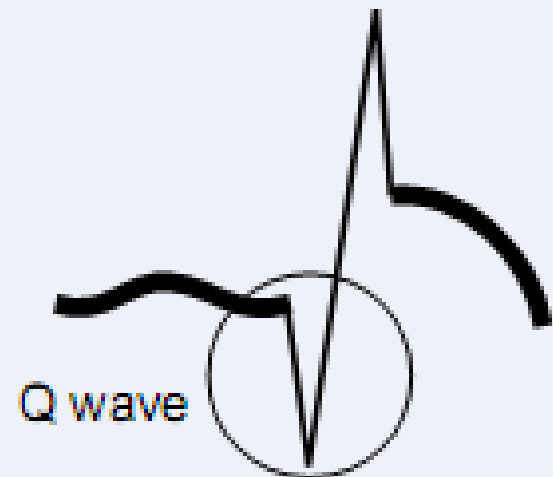
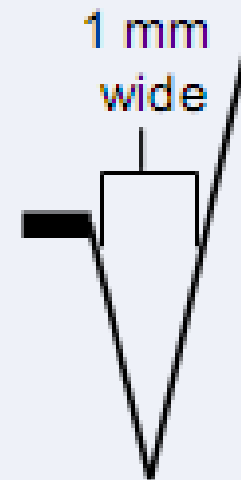
Damage and  
necrosis of  
cardiomyocytes



# ECG in MI

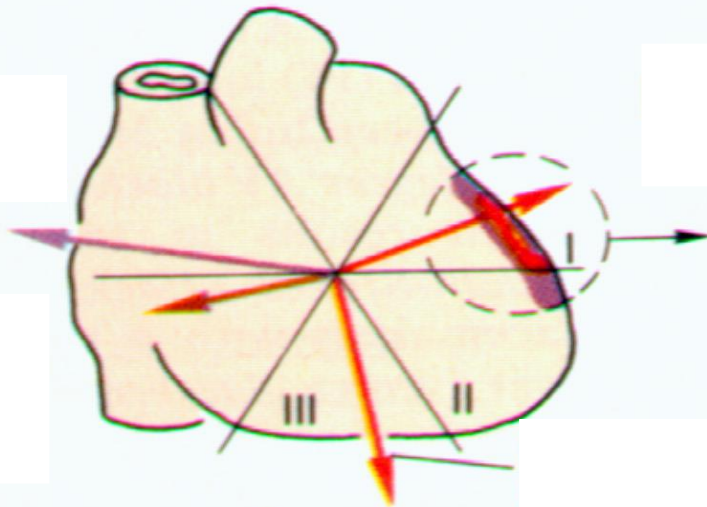


A



B

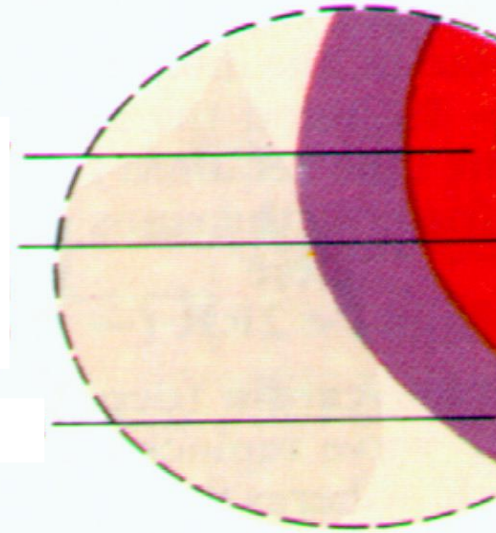
# MI



Damage

Necrosis

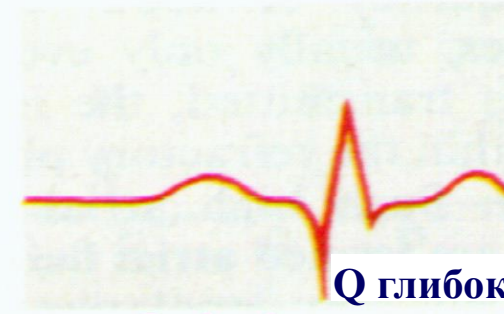
Ishaemia



1. Acute IM (hours)

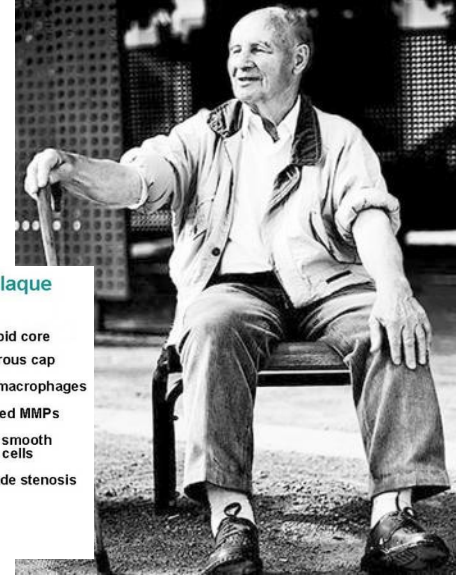


2. Days - weeks

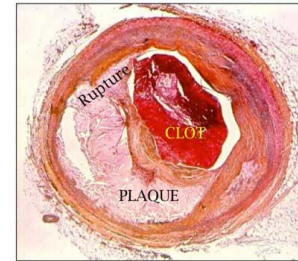


3. Months - years

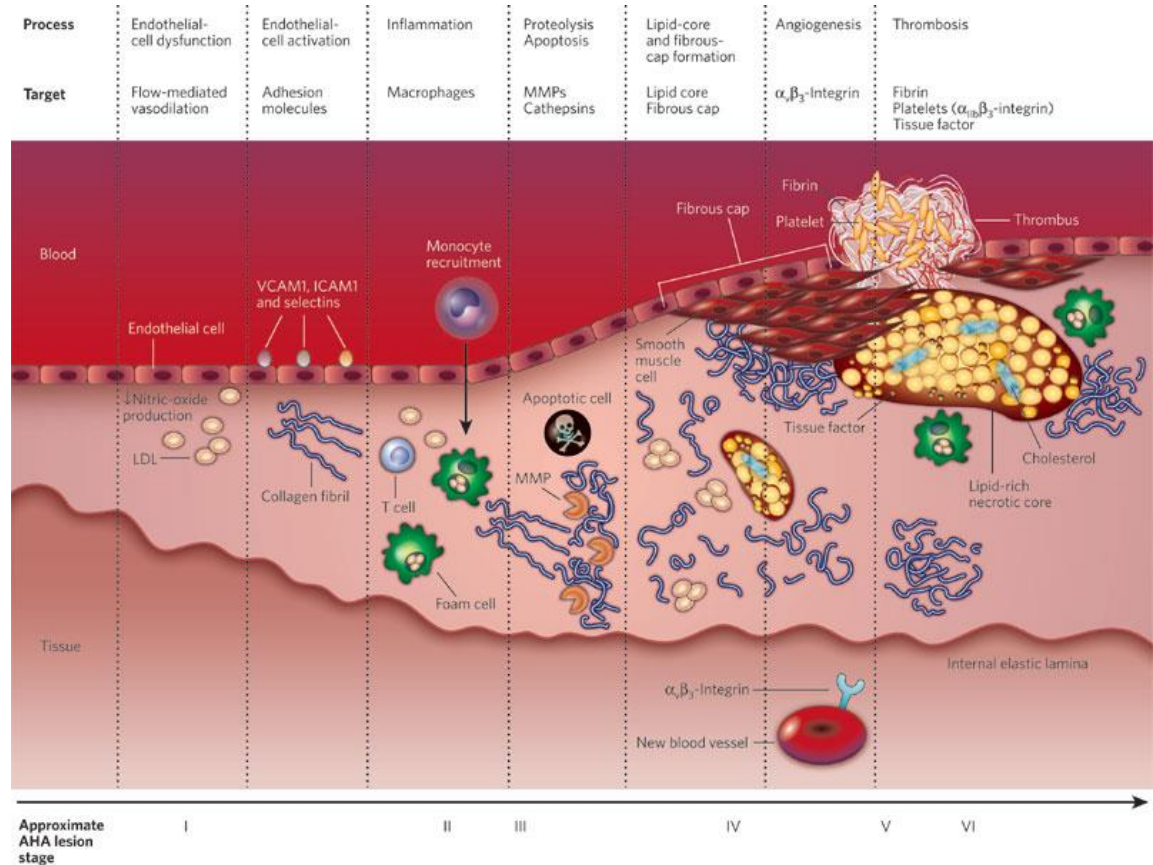
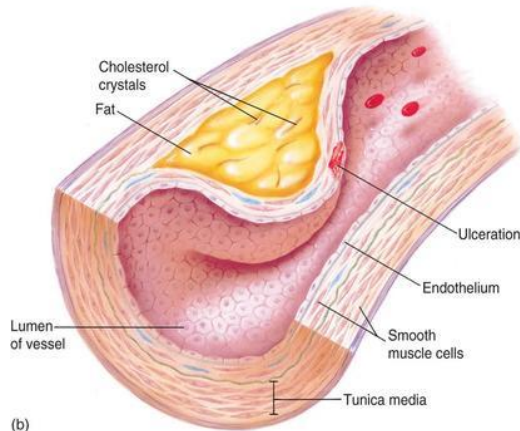
**Atherosclerosis** is the variable combination of changes in arteries intimae, which consists of focal accumulation of lipids, complicated carbohydrates, blood substances, fibrous tissue and calcium, and associated with changes in media (WHO definition)



The vulnerable atherosclerotic plaque



large lipid core  
thin fibrous cap  
rich in macrophages  
increased MMPs  
poor in smooth muscle cells  
low-grade stenosis



## *Morphological changes*

- ***Infiltration*** of the vessel intima by native or modified lipoproteins of the blood plasma. Lipid deposition is an early event in atherogenesis. Lesions occur primarily within the tunica intima. Excessive capture of lipids by macrophages and infiltration of the arterial wall with macrophages containing low-density lipoproteins. Transformation of macrophages into foam cells, which are the base of lipid stain formation. It leads to endothelial injury. Lipid capture by smooth muscle cells.
- ***Proliferation*** is local irritation and multiplication of histiocytes, fibroblasts and smooth muscle cells of vessels, which capture lipids.
- ***Degeneration*** and destruction of the intima and vascular wall. Destruction of foam cells, their lysis, fragmentation of fibrous structures. Formation of lipid stains.
- ***Sclerotization*** (calcification) of vessels. The lumen of the atherosclerotically changed vessels narrows as a result of atherosclerotic plaque formation.

# ***Risk factors of atherosclerosis development***

**Atherosclerosis starts with damage or injury to the inner of an artery. The damage may be provoked by:**

- **1. Irreversible (endogenous) factors**
- Age (men over 40, women over 50 years)
- Gender (male, anti-sclerotic effect of estrogen)
- Genetic predisposition
- **2. Inverse (managed)**
- Smoking
- Hypertension
- Obesity
- Hyperlipidemia - Hypercholesterolemia and / or hypertriglyceridemia
- Hyperglycemia and diabetes mellitus
- Low levels of high density lipoprotein
- **3. Other possible factors**
- Low physical activity
- Emotional stress
- Intoxication, infection



# Pathogenesis of Atherosclerosis

## 1) Endothelial Injury

- ❑ Initial triggering event in the development of Atherosclerotic lesions
- ❑ Causes ascribed to endothelial injury include **mechanical trauma, hemodynamic forces, immunological and chemical mechanisms, metabolic agents like chronic hyperlipidemia, homocystine, circulating toxins from systemic infections, viruses, and tobacco products.**

# *Response-to-injury hypothesis*

## *2. Accumulation of lipoproteins*

- (mainly LDL and its oxidized forms) in the vessel wall. Low-density lipoprotein molecules (LDL) becoming oxidized (ldl-ox) by free radicals, particularly oxygen free (ROS). When oxidized LDL comes in contact with an artery wall, a series of reactions occur to repair the damage to the artery wall caused by oxidized LDL. Cholesterol can move in the bloodstream only by being transported by lipoproteins

# Disorders of lipid synthesis.

## Lipoprotein disorders

### Four main types of lipoproteins

- **Chylomicrons** – carry triglyceride from intestine to liver, skeletal muscle and adipose tissue.  
Chylomicrons are triglyceride rich lipoproteins appear in the blood after fat containing meal.
- **Very low density lipoproteins (VLDL)** – carry synthesized triglycerides from liver to adipose tissue.  
VLDL is triglyceride rich lipoprotein contains 10-15% of total serum cholesterol.



# Four main types of lipoproteins

- **Low density lipoproteins (LDL)** – transport cholesterol in the blood, carry cholesterol from liver to cells. 60-70% of total serum cholesterol contains in LDL.

## **Ranges of LDL:**

- **Optimal level** <100mg/dL – risk for coronary heart disease reduced.
- **High level** is >then 160 mg/dL (risk of atherosclerosis)

**High density lipoproteins (HDL)** – collect cholesterol from the tissue back to the liver. HDL carry 20-30% of total serum cholesterol.

Increased by exercise, wine, estrogen. Synthesis by the liver and small intestine

### **Functions:**

- Removes cholesterol from atherosclerotic plaques.

### **Ranges:**

- **High level** -  $>60$  g/dL
- **Low level** -  $<40$  g/dL

# The value of cholesterol

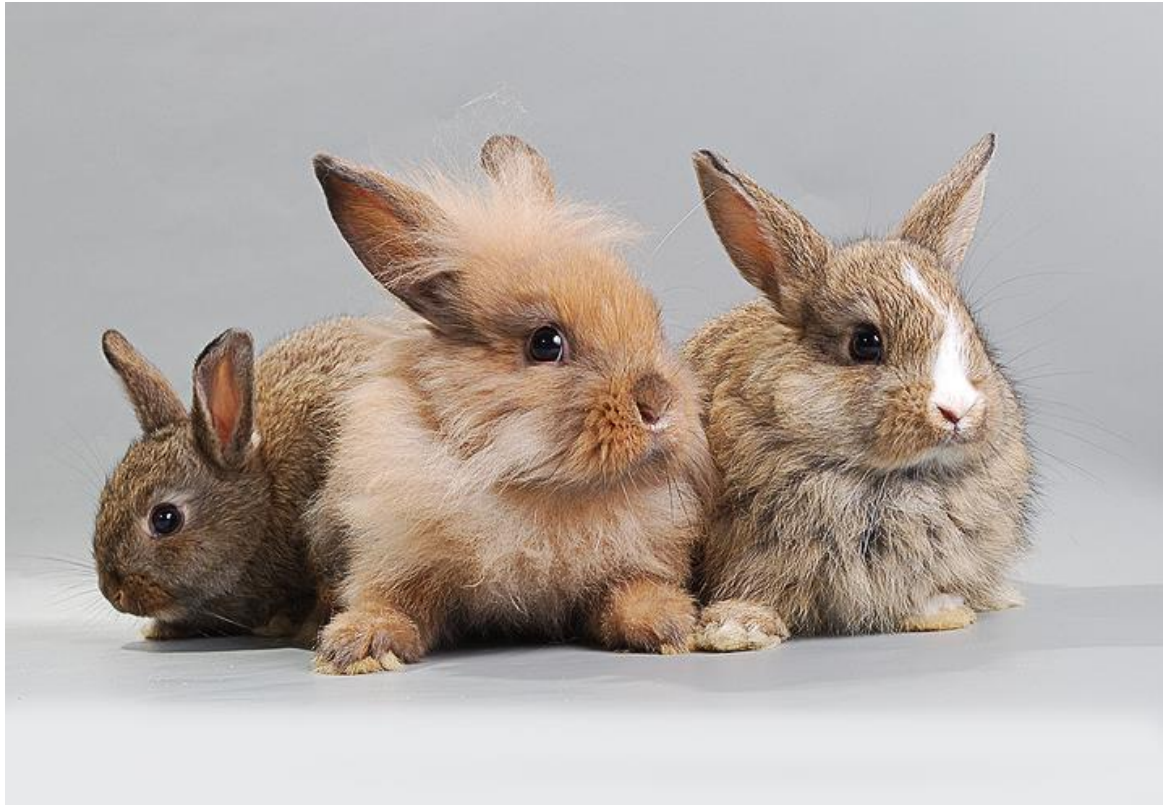
- 1. Necessary for maintaining of cell shape
- 2. Source of sex and steroid hormones
- 3. Source of bile acids
- 4. Necessary for growth of the organism and cell division

# Balance of cholesterol

One day in the human body

- 450 mg of cholesterol oxidized to bile acids
- 450 mg of cholesterol excreted with faeces
- 100 mg of cholesterol excreted with dermal fat
  
- 300 mg of cholesterol derived from food
- 700 mg of cholesterol is synthesized from acetyl-CoA in the cells of various organs, the highest in the liver and small intestine
  
- In adult is about 140 grams of cholesterol (93% is in the cells, 7% is transported in the form of LP mainly LDL in plasma).

**First experimental model of atherosclerosis was created on rabbits in 1913. Every day within 3-4 months A.Anichkov added 10 g of Cholesterol in rabbits ration.**



**“Atherosclerosis is impossible without cholesterol”.**

**A.N.Anichkov**

# Regulation of cholesterol contents

- Except the receptor-mediated cholesterol admission into the cell to regulate the content exists by removing cholesterol from the cell membrane surface. This is done by HDL.
- In blood this cholesterol undergoes etherification under influence of lecithin-cholesterol-acetyltransferase, is transported to the liver, where partially oxidized to bile acids.
- Normally, these two processes are balanced.

# PATHOGENESIS

**Macrophages have main role:**

- 1. Modified LDL stimulate macrophages activity**
- 2. They have “scavenger”-receptors so Cholesterol comes in macrophage only due to concentration gradient**
- 3. They can accumulate a lot of Cholesterol inside the cell (process is controlled by HDL).**

## STAGE 3 – “FOAM CELLS”

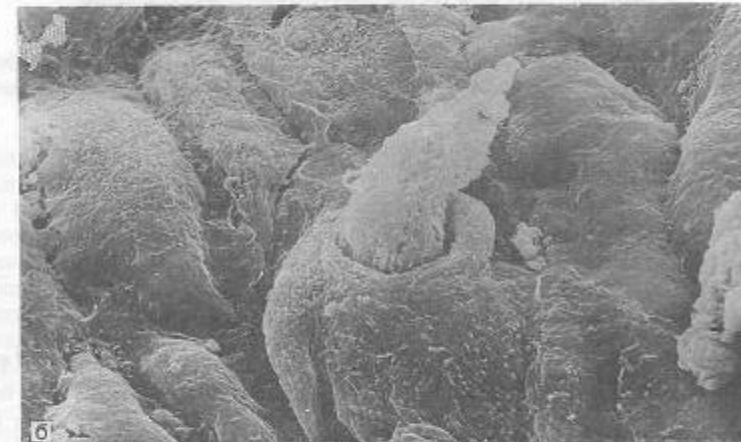
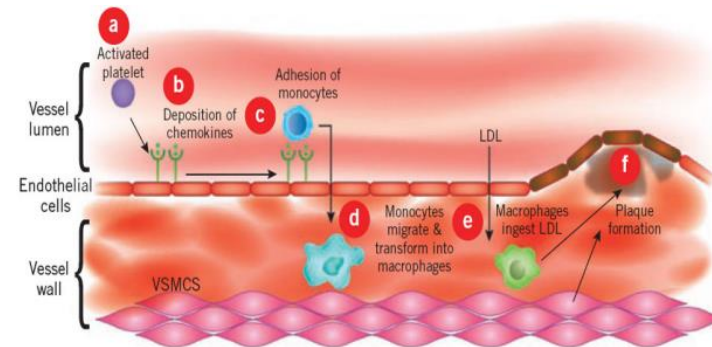
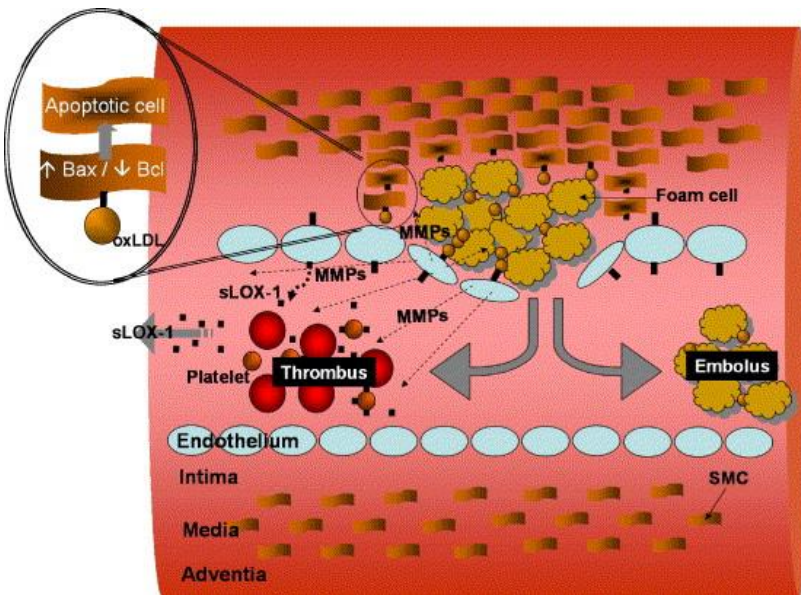
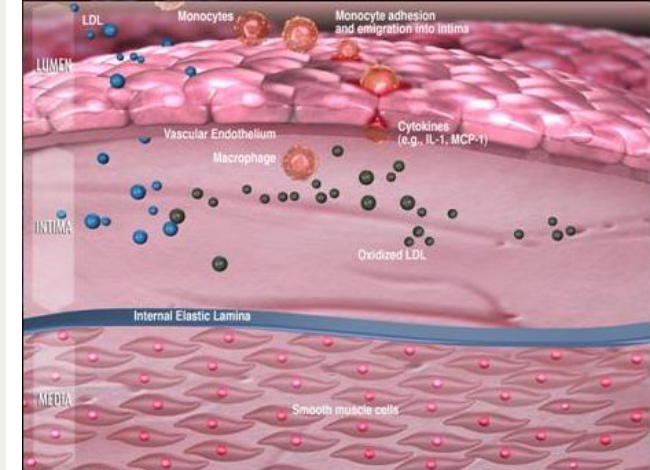
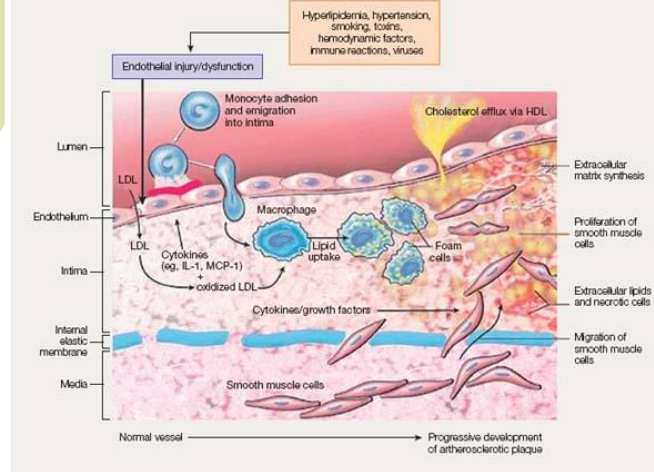


Рис. 34. Миграция моноцитов/макрофагов через неповрежденный эндотелий аорты кролика, получавшего с пищей холестерин в течение 6 нед.  
а – миграция в интиму; б – миграция из интимы. СЭМ.  $\times 4500$ .



# STAGE 3 – “FOAM CELLS”



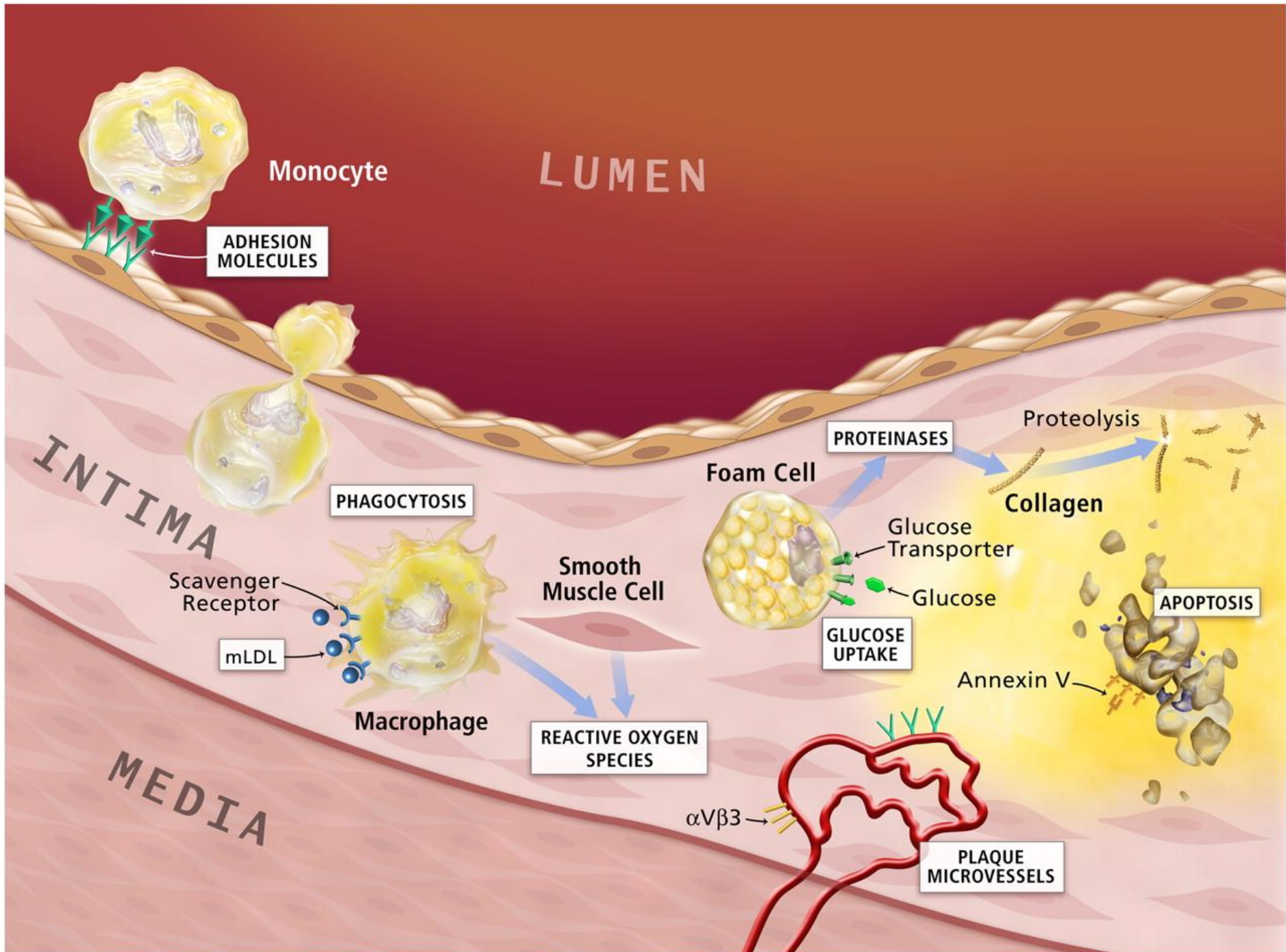
Migration of  
macrophage  
in intima

Capture of LDL

Decrease of LDL  
concentration in intima

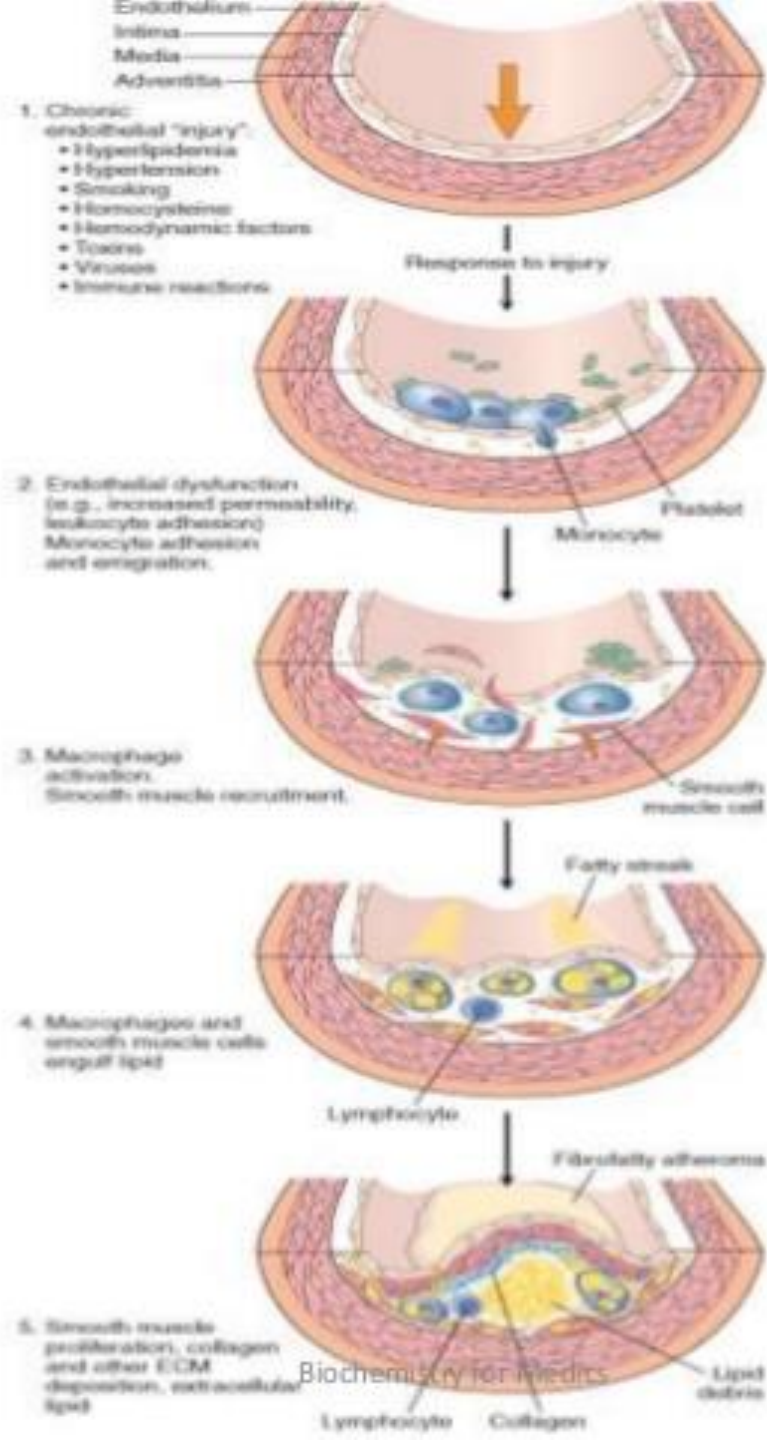
Many macrophages change  
into “foam cells”





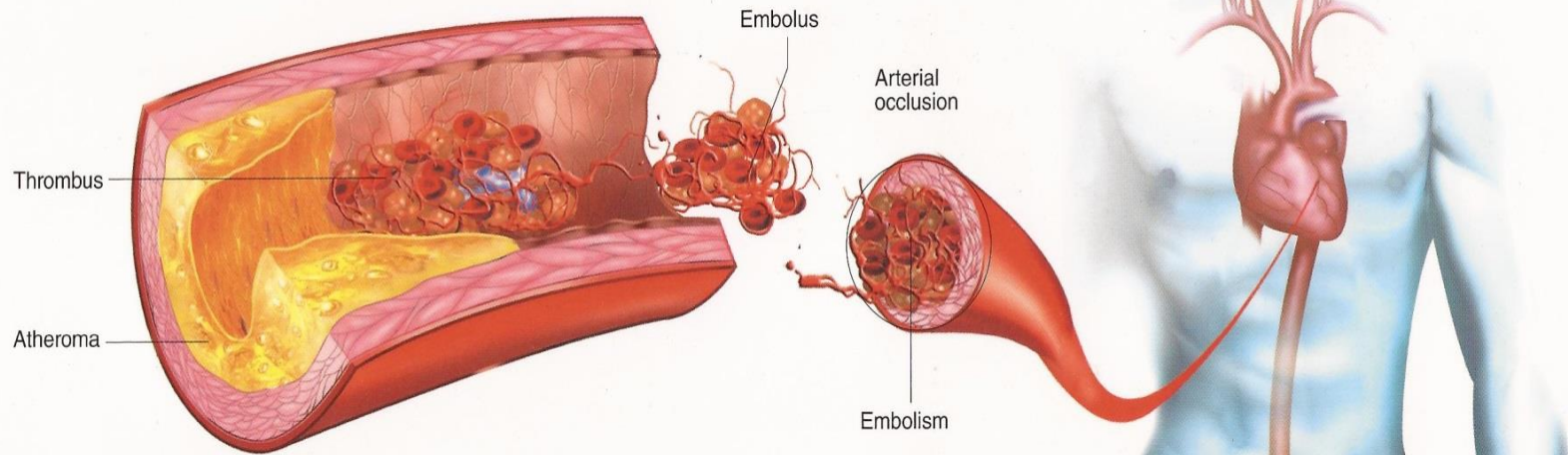
### Pathogenesis of Atherosclerosis (reaction to injury hypothesis)





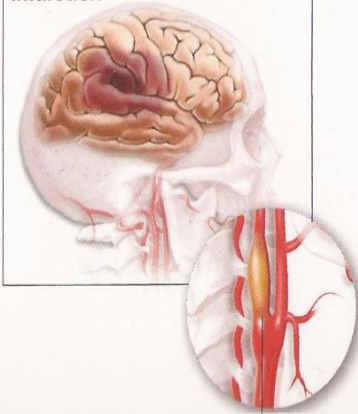


# Atherosclerosis and cardiovascular disease

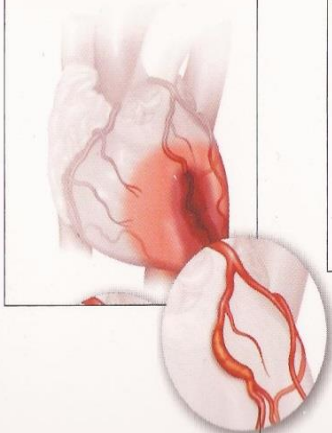


## Atherosclerosis complications

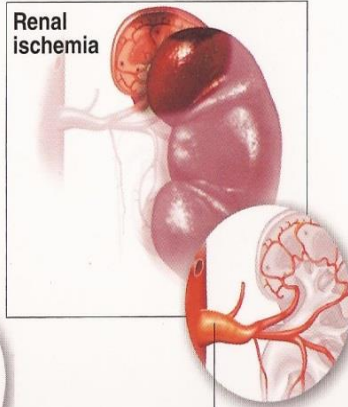
Ischemia and cerebral infarction



Myocardial infarction



Renal ischemia



Intermittent claudication

