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Учреждение образования  
«Гомельский государственный медицинский университет»

Кафедра патологической физиологии  
Обсуждено на заседании кафедры  
Протокол №7 от 30.08.2017

**МЕТОДИЧЕСКАЯ РАЗРАБОТКА**  
Для проведения занятия со студентами  
3 курса ФПСЗС, обучающихся на английском языке  
по патологической физиологии

**Тема: Патофизиология системы кровообращения. Нарушения функции сердца**

**Theme: Pathophysiology of blood circulatory system. Cardiac malfunction**

Время 3 ак. часа

**1.Actuality of the theme.** Strife with a heart insufficiency - major problem of national public health services. Its national significance is determined by a high morbidity and death rate, large labor losses, considerable traumatism. The heart insufficiency often arises on ground of necrotic damages of cardiac muscle. Quantity both coronarygenic and epinephrine and norepinephrine genesis damages of the myocardium recently increases, which one result from a stress, mental overstress, excessive physical loads. The warning of necrotic, inflammatory, metabolic, neuroendocrine and other damages of the myocardium is the constituent of preventive maintenance of heart insufficiency. The new scientific direction - preventive cardiology was now formed, problems by which one include warning and early detection of cardiovascular system function disorders.

**Learning goals of the lesson:** to study etiology, pathogenesis main manifestations and mechanisms of compensations of heart failure and IHD.

**Educational goals of the lesson:** formation of scientific outlook and theoretical basis of future specialists on the basis of fundamental knowledge and the latest achievements of pathological physiology.

**Objectives of the lesson:**

1. To know causes, mechanisms of development, main manifestations and hemodynamic signs and mechanisms of compensation of various forms of heart failure.
2. To study clinical forms of coronary insufficiency, forms, causes, mechanisms of development of ischemic heart disease (IHD).

**To repeat the following questions from related disciplines to ensure absolute mastery of the material:**

1. Structure of myocardium (histology, cytology, embryology disciplines).
2. Main physiological features of heart function (normal physiology discipline).

**Control questions of the lesson:**

1. Circulatory insufficiency, forms, causes, hemodynamic indices and manifestations.
2. Heart failure: definition, types.
3. Overloading form of heart failure: types, etiology, pathogenesis.
4. Myocardial form of heart failure, its causes and mechanisms.
5. Extreme and long-term mechanisms of compensation of heart failure. Mechanisms of decompensation.
6. Principles of therapy and prevention of heart failure.
7. Coronary insufficiency: types, clinical forms.
8. Ischemic heart disease: forms, causes, mechanisms of development, complications and outcomes.

**Calculation of study time**

Total study time 3 ac.hours

№ п/п	Contents	Calculation of study time
1.	Introduction. Motivational characteristic of the theme	3 minutes
2.	Written control of students on the topic of the lesson	15 minutes
3.	Interviews with students about the topic of the lesson	60 minutes
4.	Self-managed student work	15 minutes
5.	Summing up the results of the lesson	5 minutes
6.	Decision of situational tasks	20 minutes
7.	Task for the next lesson	2 minutes

### **Additional material:**

According to WHO, CVD (cardiovascular disease) have the first rank among the causes of disability and death of working-age population in the developed countries. Death from CVD is 45–52% of overall mortality. Causes of the increased mortality from CVD are: the disappearance of serious infectious diseases (plague, smallpox), the increased life expectancy, the high pace of life, urbanization, rejuvenation of pathology (an increase in incidence of CVD in young people up to 35 years).

#### **Causes of cardiovascular system dysfunction :**

1. factors primarily affecting **the heart**:
  - leading to inflammatory and degenerative processes
  - genetic factors and disorders in embryonic development
2. factors primarily affecting **the vascular wall**:
  - changing the structure of the vascular wall
  - inducing violation of vascular tone

#### **Risk factors for cardiovascular disease**

1. Unmanaged:
  - Heredity (if heart disease have blood relatives)
  - Gender (higher risk in men than in women, but the differences decrease with age)
  - Age aged 30 to 70 years risk in men 3 times > women; men over 55, women over 65 years are subject CVD; at age 75 fatal outcome from CVD is identical in men and women
2. **Managed**:
  - hypertension
  - dislipoproteinemia
  - endocrinopathies
  - smoking, alcohol abuse
  - physical inactivity
  - overweight
  - stress

### **Circulatory failure**

**Circulatory failure** – inability of the cardiovascular system to supply the cells of the body with enough oxygenated blood to meet their metabolic demands.

The main reasons for circulatory failure

1. cardiac disorders
2. disturbances of blood vessel tone
3. changes total blood volume and / or blood rheology

#### **Classification:**

1. According to mechanism of development:
  - heart failure;
  - vascular insufficiency;
  - mixed (cardiovascular) deficiency.
2. According to compensation:
  - compensated (signs detected on load);
  - subcompensated;
  - decompensated.
3. By acuity of development:
  - Acute (hours-days). Causes: MI, AHF, arrhythmias, shock, acute blood loss;
  - Chronic (months, years). Causes: pericarditis, long-term myocarditis, myocardial dystrophy, cardiosclerosis, hyper-and hypotensive state, anemia, hypovolemia.
4. According to expression of characteristics (3 stage)
  - Stage I (initial): signs - ↓ rate of myocardial contraction and ↓ ejection fraction (55-75%), shortness of breath, palpitations, fatigue - detected during physical exertion;
  - Stage II - detected signs in rest;

- Stage III (final) - significantly disturbed cardiac function and hemodynamics at rest, significant degenerative and structural changes in organs and tissues.

### **Functional classification of patients with heart disease**

**Class I** Patients with cardiac disease but without the resulting limitations in physical activity. Ordinary activity does not cause undue fatigue, palpitation, dyspnea, or angina pain.

**Class II** Patients with heart disease resulting in slight limitations of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

**Class III** Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.

**Class IV** Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. The symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

### **Heart failure**

The definition of the ACC / AHA 2001: *heart failure* – is a complex syndrome that can be caused by any structural or functional heart disease, which impair ventricular blood fill or banish it.

#### ***The main causes of heart failure***

Direct damaging effect on the myocardium

*physical factors*: compression of the heart (exudate, blood, emphysematous lungs, a tumor); effects of electric current (electric shock, cardiac defibrillation); mechanical injury of the heart.

*chemical factors*: chemical compounds (uncouplers OX-F salt Ca, lipid hydroperoxides), drugs in inadequate doses (antagonists of  $\text{Ca}^{2+}$ , glycosides, blockers), lack of oxygen and the compounds needed for metabolism (salt of Me)

*biological factors*: high levels or lack of BAS, long-term ischemia or infarction, cardiomyopathy, myocarditis, myocardiodystrophy.

#### **Classification of heart failure:**

##### **1. According to origin:**

- myocardial
- overload
  - ✓ by volume
  - ✓ by pressure
- mixed

##### **2. According to the rate of development:**

- acute (minutes up to hours) — in acute MI, acute cardiac tamponade, infectious diseases, pulmonary embolism,
- chronic (weeks, months up to years) — in hypertension, chronic anemia, heart pathologies, progressive atherosclerosis.

##### **3. According to the primary mechanism of development:**

- primary (cardiogenic) — mainly a decrease in contractility of the heart at close to normal value of venous blood flow;

By involvement of coronary blood circulation:

- ✓ *coronarogenic*
- ✓ *non-coronarogenic*

- secondary (non-cardiogenic) — mainly a decrease in venous flow to the heart at close to normal value of myocardial contractile function

##### **4. According to the primary lesion of the heart**

- left ventricular. Cause: over left ventricle — in aortic stenosis, hypertension; a decrease in contractive function, papillary muscle isolation. It results in: a decrease in ejection of blood in the systemic blood circle, overdistension of left atrium, and standstill in the pulmonary blood circle. Clinically: cardiac asthma and pulmonary edema.

- right ventricular. Cause: right ventricular overload - when the pulmonary artery valve is reduced in size, it results in high pressure into the pulmonary artery. It results in: a decrease in ejection of blood in the pulmonary circle, overdistension of right atrium and standstill in systemic circle.

- total

### 5. According to the predominant lack of cardiac cycle phases

- Diastolic (a decrease in ventricular filling). Cause: hypertrophic cardiomyopathy, isolated mitral stenosis, and constrictive pericardial effusion, cardiosclerosis, amyloidosis, sarcoidosis, etc. It results in: an increase in the final diastolic pressure and the occurrence of heart failure.
- Systolic (chronic) – associated with a number of diseases. It results in: violation of the pumping heart function, a decrease in cardiac output.

There are changes in intracardiac hemodynamics in patients with heart failure. Heart failure is accompanied by characteristic changes in intracardiac hemodynamics:

- an increase in final systolic volume as a result of incomplete systole due to myocardial damage, an increase in resistance in the aorta, excessive blood flow due to valvular insufficiency.
- an increase in final diastolic pressure as a result of myocardial sub-contraction associated with an excess of calcium in the cytosol and myofibrils of cardiomyocytes
- an increase in arterio-venous oxygen ratio
- dilatation of the heart
- an increase in pressure in the heart cavities results in supply of blood to the primarily affected part of the heart.
- a decrease in systolic contractions and diastolic relaxation as a result of decreased energy supply, damage of myofibrile membrane, sarcoplasmic network and sarcoplasm, a decrease in activity of calcium-dependent ATP-ases.

#### Stages:

- compensation the minute volume of heart (HMF) and a speed of blood flow are supported normal:

- ✓ emergency
- ✓ stable

- decompensation ↓ HMF, congestion in circulatory system develops

**Basic cellular and molecular mechanisms of pathogenesis of heart failure:** lack of energy in cardiomyocytes, damage of membranes and enzymes in cardiomyocytes, imbalance of ions and fluid in cardiomyocytes, violation of the genetic program of cardiomyocyte, the disorders of neurohumoral regulation of heart activity

Insufficiency of energy supply results from damage of energy production, transport and disposal. Higher fatty acids (65–70%), glucose (15–20%), lactic acid (10–15%) and oxidation of a molecule of palmitic acid are the main substrates for ATP synthesis in aerobic conditions.

#### Changes in intracardiac hemodynamics

- ↑ final systolic volume
- ✓ incomplete systole due to myocardial damage
- ✓ ↑ resistance in the aorta
- ✓ ↑ back blood flow due to valvular insufficiency
- ↑ final diastolic pressure
- ↑ arterio-venous oxygen ratio
- ↑ BP in heart cavities
- heart dilatation
- ↓ systolic contractions
- ↓ diastolic relaxation

### Mechanisms for emergency hemodynamic compensation in heart failure

#### I. Intracardial hemodynamic mechanisms:

1. Heterometric mechanism Frank-Starling (volume overload) — the linear relationship between the degree of stretching the muscle fiber and forced contractions, which provides an increase in myocardial tension => increase in vivo.

2. Homeometric mechanism (pressure overload) – an acute increase in tension of muscle fibers in their length = it strengthens each subsequent contraction of the previous one.

#### II. Extracardiac unloading reflexes:

1. Bainbridge reflex — an increase in heart rate in response to an increase in circulating blood volume during the stimulation of mechanoreceptors in vv. cavae and pulmonary veins => an increase in minute cardiac volume.
2. Bezold-Jarisch reflex — increased dilation of systemic circle arteries in response to stimulation of mechano- and chemoreceptors of ventricles and atria => a decrease in blood pressure and cardiac rate => unloading of left ventricle.
3. Increased activity of sympathetic nervous system => beta-adrenergic stimulation of myocardium (increase in arterial blood pressure) and cells of juxtaglomerular apparatus (an increase renin secretion) => an increase in cardiac output and minute cardiac volume
4. Parin's reflex (overload of right ventricle resulting in pulmonary embolism) — strengthening tonic effect on n.Vagus => a decrease in arterial blood pressure, minute cardiac volume, and circulating blood volume.

### **Mechanisms of long-term compensation of cardiac function:**

#### ***I. Intracardial hemodynamic mechanisms:***

1. Compensatory hyperfunction of the heart - in contrast to physiological heart hyperfunction it is a prolonged and continuous.
  - ***Isometric hyperfunction*** - increase in external heart work is associated with the rise of pressure in the aorta → leads to a marked ↑ myocardial O<sub>2</sub> requirements. Development hyperfunction associated with increased myocardial tension with an insignificant change in the amplitude of contractions. Hypertrophy is progressing fast enough.
  - ***Isotonic hyperfunction*** - overload of the myocardium is caused by an increase in BCV.
2. Compensatory hypertrophy of the myocardium.

#### ***II. Extracardiac unloading reflexes:***

1. Bainbridge reflex
2. Reflex Kitaev – "triggered" with mitral stenosis - a reflex spasm of the pulmonary arterioles in response to increased pressure in the left atrium, thereby expressed ↑ pressure in LA (acute pulmonary hypertension) and development of right ventricular failure.

### **Heart hypertrophy**

#### **Stages of compensatory heart hypertrophy:**

1. Emergency (emergency hyperfunction)
2. Stable (completed hypertrophy and relatively stable hyperfunction)
3. Decompensation

#### ***1. Emergency hyperfunction***

- develops immediately after the beginning of overload
- short-term and energetically uneconomical
- ↑ force of the heart contractions
- ↑ load to muscular mass and intensity of structure functioning

#### ***Pathologic changes in the myocardium:***

- mobilization of glycolysis
- disappearance of glycogen
- accumulation of lactate
- ↓ creatinphosphate level
- intracellular :↓ K<sup>+</sup> and ↑ Na<sup>+</sup>

#### ***2. Completed hypertrophy and relatively stable hyperfunction***

- hypertrophy of myofibrils, capillaries and nerve ends
- hyperfunction of myocardium = plastic requirements
- uptake of O<sub>2</sub>, energy formation and content of macroergic compounds are within the norm
- hemodynamic indices are normal

### 3. *Decompensation*

- $\uparrow\uparrow\uparrow$  mass of myofibrils  $>$   $\uparrow$  capillaries,  $\uparrow$  nuclear material and  $\uparrow$  nerve endings  $\rightarrow$  hypoxia + disturbance of myocardial trophism  $\rightarrow$  cardiosclerosis, pathological accumulation of  $\text{Ca}^{2+}$ -ions in cardiomyocytes  $\rightarrow$   $\downarrow$  mass of working cardiomyocytes.

Main mechanism of decompensation of hypertrophic myocardium:

- delayed growth of capillaries and nerve fibers of muscles
- cell volume increases more than the specific surface area  $\Rightarrow$  worsen conditions for the
- transport of metabolic products
- a decrease in plastic cell supply
- change in in-cell structure ratio.
- activation of cardiomyocyte apoptosis  $\Rightarrow$  cardiosclerosis.

It results in myogenic dilation of the heart: a decrease in heart contractions.

## Coronarogenic damage of myocardium

### Coronary insufficiency

**Coronary insufficiency** is a typical form of heart disease, which is characterized by the excess of myocardial oxygen demands and metabolic substrates over their influx by the coronary arteries, as well as a violation of the outflow from the myocardium of exchange products, active substances, ions and other agents.

The leading pathogenic factor — myocardial ischemia (a mismatch between the needs of oxygen and the level of cardiomyocyte oxygenation). Clinical manifestations – IHD. The term «coronary heart disease» was proposed by WHO in 1962.

Coronary insufficiency according to the mechanism of occurrence is classified into:

- absolute — the basis for the limitation of blood flow in aa.coronaris.
- relative — increase in oxygen supply in absence of coronary blood flow limitation

Differences between **reversible** and **irreversible** coronary insufficiency.

Reversible is manifested by the following clinical forms: stable and unstable angina, variable, the state after myocardial revascularization. Irreversible infarction is manifested by MI (myocardial infarction).

All possible causes of coronary insufficiency are classified into: coronarogenic and non-coronarogenic.

**Coronarogenic factor** causing the absolute decrease in coronary blood flow: atherosclerosis of aa.coronaris, blood particle conglomerates and blood clots in aa.coronaris, spasm of a.coronaris, a decrease in blood flow to the heart and perfusion pressure in aa.coronaris. The concept of dynamic stenosis of aa.coronaris is based on the mechanism of the complex interaction of the triad of factors: contraction of smooth muscles, a decrease in diameter of aa.coronaris, obstruction of the blood vessel lumen by blood particles.

**Noncoronarogenic factors:** a significant increase in level of catecholamines in the heart, a prolonged hypertrophy the heart, resulting from:

- excessive physical exertion
- acute hypertension
- marked haemoconcentration
- prolonged tachycardia
- activation of sympathetic nervous system
- hypervolemia

The phenomenon of hormone neuromediator dissociation of catecholamines occurs in coronary insufficiency. It is characterized by a significant increase in adrenaline (and at the same moment a decrease in noradrenaline) in ischemic myocardium. In this state myocardium injury results from:

- a decrease in utilization of oxygen and substrate exchange by chronotropic (positive) and inotropic effects
- a decrease in effectiveness of the mechanisms of ATP resynthesis

- a decrease in of coronary blood flow
- an excess of reactive oxygen and lipid peroxides.

### **Pathogenesis of coronary insufficiency**

1. Associated with *atherosclerotic* disease that produces fixed obstruction of the coronary arteries. It occurs when the metabolic needs of the myocardium exceed the ability of the occluded coronary arteries to deliver adequate blood flow during physical exertion, emotional stress, or exposure to cold. The adrenalin blood concentration in such conditions increases, so rate and force of the heart contractions and O<sub>2</sub> need increase too. Adequate dilation of the heart vessels is impossible in the condition when coronary arteries are inelastic. Adrenalin excess violates cardiomyocytes metabolism and electrolyte balance.
2. The syndrome of variant angina or Prinzmetal's angina was first described Prinzmetal. It is caused by *spasm* of the coronary arteries; this condition is also called vasospastic angina. Unlike the classic form of angina, which occurs with exertion or stress, variant angina usually occurs during rest, smoking or with minimal exercises, and frequently occurs nocturnally. The mechanism of coronary vasospasm is uncertain. It may be the result of hyperactive sympathetic nervous system responses, the result of calcium metabolism defect in vascular smooth muscle, or the result of reduced synthesis of prostaglandin I<sub>2</sub> or NO, which promotes vasodilation. Arrhythmias often occur when the pain is severe; ECG changes include ST segment elevation or depression, T- wave peaking, rhythm disturbances.
3. **Coronary artery thrombosis.**

Pain syndrome in heart ischemic disease (HID) — *angina*. Angina pectoris (in latin «ango» — squeeze, angina pectoris — «chest compression»).

#### **Clinical classification of HID according to Medical Disease Classification 10:**

1. Sudden coronary death (primary cardiac arrest).
2. Angina
  - 2.1. Angina:
    - 2.1.1. For the first time emerged (de novo)
    - 2.1.2. Stable, indicating FC (from I to IV)
    - 2.1.3 Progressing
  - 2.2. Spontaneous (vasospastic) angina
3. Myocardial infarction:
  - 3.1. Q wave MI (macrofocal, transmural)
  - 3.2. MI without Q wave (small focal, intramural, subendocardial)
4. Myocardial infarction (MI)
5. Cardiac arrhythmias.
6. Circulatory failure (ischemic cardiomyopathy)
7. Painless (silent) ischemia
8. Microvascular (distal), coronary artery disease — small vessel disease
9. New Ischemic Syndromes («hibernate», «stating», «intermittent ischaemia»)

Angina occurring during exercise, called exertional angina.

However painful attacks may occur at rest. This is called angina at rest. It shows a pronounced stenotic coronary artery atherosclerosis, in which the capillary myocardial reserve completely exhausted.

Silent myocardial ischemia occurs in the absence of anginal pain. The factors that cause silent myocardial ischemia appear the same – impaired blood flow in the result of coronary atherosclerosis or vasospasm. The reason for the painless episodes of ischemia is unclear. The episodes may be shorter and involve less myocardial tissue than those producing pain. Another explanation is that persons with silent angina have defects in pain threshold, pain transmission, or automatic neuropathy with sensory denervation. There is evidence of an increased incidence of silent myocardial ischemia in person with diabetes mellitus, probably the result of autonomic neuropathy, which is a common complication of diabetes.



Unstable angina is the result of atherosclerotic plaque disruption. Because of its propensity to lead to infarction, it is some times referred to as preinfarction angina. Plaque disruption may occur with or without thrombosis, it increases the degree of coronary artery obstruction. When the plaque injury is mild, intermittent thrombotic occlusion may occur and cause episodes of anginal pain at rest. Vasoconstricting factors (thromboxane, serotonin, and platelet-derived growth factor) are released from platelets that aggregate at the site of injury. These platelet factors contribute, even at rest, to episodes of reduced coronary blood flow and silent or symptomatic myocardial ischemia. Thrombus formation can progress until the coronary artery becomes occluded, leading to myocardial infarction.

## ACUTE MYOCARDIAL INFARCTION

Myocardial infarction (MI) is the irreversible necrosis of heart muscle secondary to prolonged ischemia. It is a result from an imbalance of oxygen supply and demand.

### The pathogenesis can include:

- Occlusive intracoronary thrombus - a thrombus overlying an plaque causes 75% of myocardial infarctions, with superficial plaque erosion present in the remaining 25%. Secondary to vasculitis.
- Vasospasm - with or without coronary atherosclerosis and possible association with platelet aggregation.
- Coronary emboli - from left sided mural thrombosis, vegetative endocarditis, or paradoxical emboli from the right side of heart through a patent foramen ovale.
- Cocaine use
- Coronary artery dissection (during pregnancy)
- Thrombosis syndromes (e.g., antithrombin III deficiency, polycythemia)

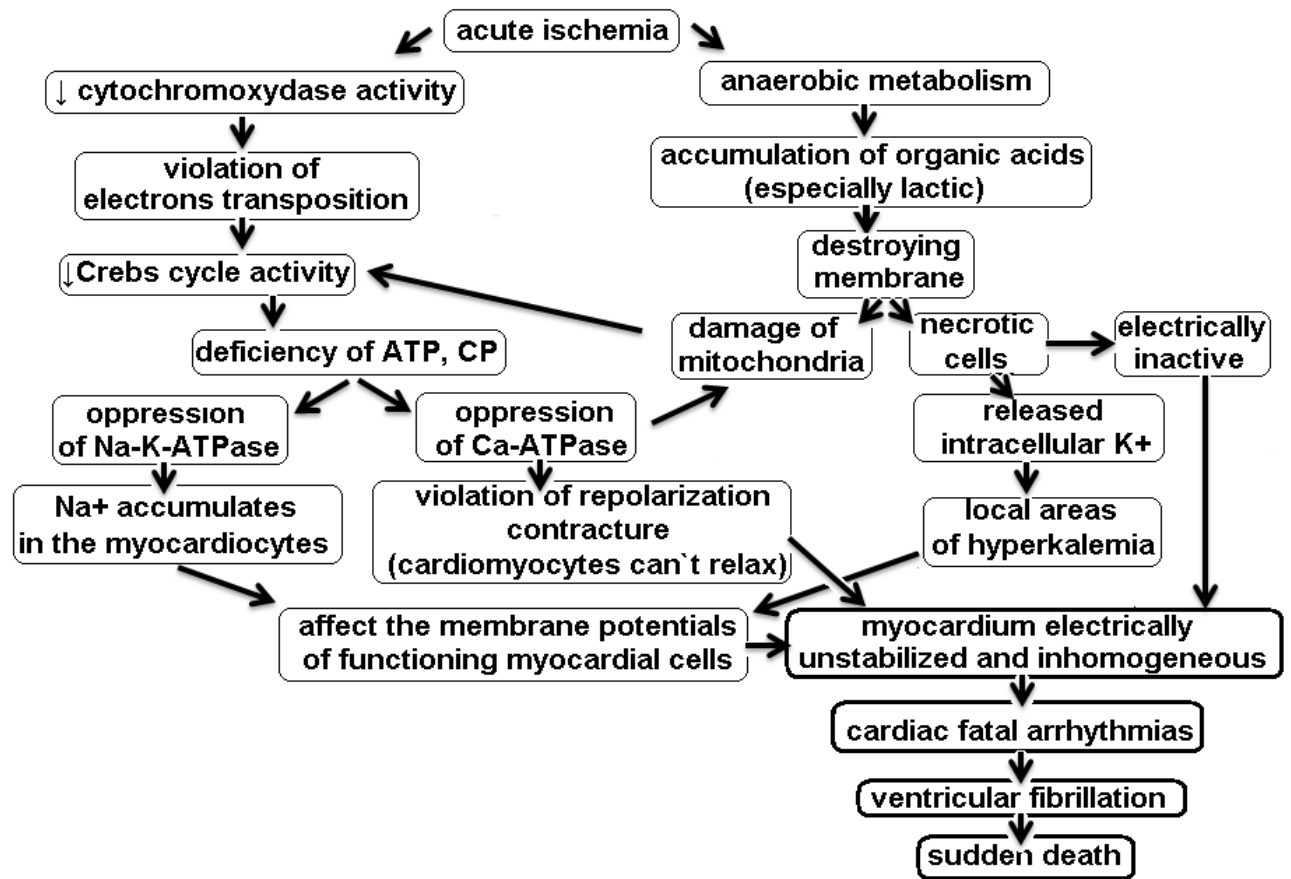
### Types of myocardial infarction

- Transmural infarction (Q-wave infarction)
  - ✓ Involves the full thickness of the myocardium
  - ✓ New Q waves develop in an electrocardiogram (ECG).
- Subendocardial infarction (non-Q wave infarction)
  - Involves the inner third of the myocardium
  - Q waves are absent.

### Clinical picture

- Sudden onset of severe retrosternal **pain** (lasts more than 20 minutes, not relieved by nitroglycerin, radiates down the left arm into the shoulders or into the jaw or epigastrium, associated with sweating (diaphoresis), anxiety, and hypotension)
- **"Silent"** acute MIs (may occur in the elderly and in individuals with diabetes mellitus, due to high pain threshold or problems with nervous system)
- **Painless myocardial infarction**, in which pain is absent. It is believed that this form of myocardial infarction develops in people with high levels of endogenous opioid peptide, a potent analgesic compound. On the front of the clinical picture there are symptoms of heart failure and arrhythmias.
- **Abdominal** (gastralgie) form - the pain is felt mainly in the epigastric, umbilical and subcostal areas.
- Cardiac arrhythmias are almost always accompanied by the development of myocardial infarction, and in its silent form may be the leading symptom (**arrhythmic** myocardial infarction).
- Symptoms of heart failure (shortness of breath, tachycardia, edema and hypotension) are typical manifestations of myocardial infarction. The appearance of these symptoms associated with impaired cardiac pump function, which decreases in direct proportion to the size of necrosis.

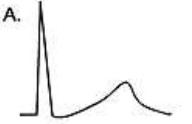

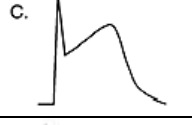



## Mechanisms of changes in myocard during MI



Associated symptoms: may be associated with nausea, vomiting, diaphoresis, dyspnea, fatigue, or palpitations. Atypical chest pain is common in diabetics and in elderly patients. Shortness of breath or symptoms of pulmonary venous congestion may be the patient's anginal equivalent.

### Physical Examination

#### I. Electrocardiograph (ECG)

A. Normal ECG prior to MI	
B. Hyperacute T wave changes - increased T wave amplitude and width; may also see ST elevation	
C. Marked ST elevation with hyperacute T wave changes (transmural injury)	
D. Pathologic Q waves, less ST elevation, terminal T wave inversion (necrosis) (Pathologic Q waves are usually defined as duration >0.04 s or >25% of R-wave amplitude)	
E. Pathologic Q waves, T wave inversion (necrosis and fibrosis)	
F. Pathologic Q waves, upright T waves (fibrosis)	

**II.** The following **biomarkers** have been described in association with acute myocardial infarction:

**Creatine Kinase - Total:** The total CK is a simple and inexpensive test that is readily available using many laboratory instruments. However, an elevation in total CK is not specific for myocardial injury, because most CK is located in skeletal muscle, and elevations are possible from a variety of non-cardiac conditions.

**Creatine Kinase - MB Fraction:** Creatine kinase can be further subdivided into three isoenzymes: MM, MB, and BB. The MM fraction is present in both cardiac and skeletal muscle, but the MB fraction is much more specific for cardiac muscle: about 15 to 40% of CK in cardiac muscle is MB, while less than 2% in skeletal muscle is MB. The BB fraction (found in brain, bowel, and bladder) is not routinely measured.

The creatine kinase-MB fraction (CK-MB) is part of total CK and more specific for cardiac muscle than other striated muscle. It tends to increase within 3 to 4 hours of myocardial necrosis, then peak in a day and return to normal within 36 hours. It is less sensitive than troponins. The CK-MB is also useful for diagnosis of reinfarction or extension of an MI because it begins to fall after a day, so subsequent elevations are indicative of another event.

**Troponins:** Troponin I and T are structural components of cardiac muscle. They are released into the bloodstream with myocardial injury. They are highly specific for myocardial injury--more so than CK-MB--and help to exclude elevations of CK with skeletal muscle trauma. Troponins will begin to increase following MI within 3 to 12 hours, about the same time frame as CK-MB. However, the rate of rise for early infarction may not be as dramatic as for CK-MB.

Troponins will remain elevated longer than CK--up to 5 to 10 days for troponin I and up to 2 weeks for troponin T. This makes troponins a superior marker for diagnosing myocardial infarction in the recent past--better than lactate dehydrogenase (LDH). However, this continued elevation has the disadvantage of making it more difficult to diagnose reinfarction or extension of infarction in a patient who has already suffered an initial MI. Troponin T lacks some specificity because elevations can appear with skeletal myopathies and with renal failure.

**Myoglobin:** Myoglobin is a protein found in skeletal and cardiac muscle which binds oxygen. It is a very sensitive indicator of muscle injury. However, it is not specific for cardiac muscle, and can be elevated with any form of injury to skeletal muscle. The rise in myoglobin can help to determine the size of an infarction. A negative myoglobin can help to rule out myocardial infarction. It is elevated even before CK-MB.

**BNP:** B-type natriuretic peptide (BNP) is released from ventricular myocardium. BNP release can be stimulated by systolic and diastolic left ventricular dysfunction, acute coronary syndromes, stable coronary heart disease, valvular heart disease, acute and chronic right ventricular failure, and left and right ventricular hypertrophy secondary to arterial or pulmonary hypertension. BNP is a marker for heart failure.

**CRP:** C-reactive protein (CRP) is an acute phase protein elevated when inflammation is present. Since inflammation is part of atheroma formation, then CRP may reflect the extent of atheromatous plaque formation and predict risk for acute coronary events. However, CRP lacks specificity for vascular events.

### **Restoration of coronary blood flow**

Restoration of coronary blood flow even after short ischemia can cause reperfusion heart damage, which is characterized by the following symptoms:

1. contractile heart dysfunction;
2. cardiac arrhythmias;
3. phenomenon of unrestored coronary blood flow

#### **1. Contractile heart dysfunction**

It is reduce of force contractions + incomplete myocardial diastolic relaxation → decreased cardiac output

***Mechanisms:***

*Calcium paradox*

- it is overload of cardiomyocytes by calcium ions
- in reperfusion abruptly activated  $\text{Na}^+/\text{Ca}^{2+}$  transport (intracellular  $\text{Na}^+$  exchange to extracellular  $\text{Ca}^{2+}$ ), which is carried by carrier-protein located at the sarcolemma
- $\text{Ca}^{2+}$  accumulate in the sarcoplasmic reticulum and mitochondria
- Calcium overload of cardiomyocytes leads to a slowdown in the process of the heart relaxation (reperfusion contracture)  $\rightarrow$   $\downarrow$  diastolic volume of the heart and  $\downarrow$  cardiac output
- energy deficit (large part of the energy is spent on accumulation of  $\text{Ca}^{2+}$  in the intracellular organelles)

#### *Oxygen paradox*

- It's a toxic effect of oxygen which undergoes myocardium at the moment of reoxygenation after ischemia:
- Lack of oxygen leads to the restoration of electron carriers (NADH dehydrogenase, ubiquinone, cytochromes) in the mitochondrial respiratory chain. At the moment of reoxygenation these carriers are electron donors for oxygen molecules  $\rightarrow$   $\text{ROS}^* \rightarrow$  damage molecules of enzyme carrying energy-dependent ion transport in cardiomyocytes  $\rightarrow$  overload of cardiomyocytes  $\text{Ca}^{2+}$

## 2. Cardiac reperfusion arrhythmias

Pathogenesis is due:

- calcium and oxygen paradox
- changes in neurohormonal effects on the heart: increase in tonic activity of sympathoadrenal system and stimulation  $\alpha$ -adrenoreceptors of the myocardium by endogenous norepinephrine  $\rightarrow$  increase in intracellular calcium

## 3. Phenomenon of unrestored coronary blood flow (no reflow phenomenon)

- It is preservation of coronary perfusion deficit after the resumption of magistral blood flow in branches of the coronary arteries feeding the ischemic areas of the myocardium:
- endothelial cell swelling
- aggregation of formed elements and increase blood viscosity
- formation of blood clots
- "marginal standing" of leukocytes in the walls of microvessels and infiltration of the vascular wall

***Syndrome of hibernating myocardium.*** Hibernating myocardium is ischemic myocardium supplied by a narrowed coronary artery in which ischemic cells remain viable but contraction is chronically depressed.

***«Stunned» myocardium.*** Stunned myocardium is viable myocardium salvaged by coronary reperfusion that exhibits prolonged postischemic dysfunction after reperfusion.

Stunned myocardium can be differentiated from hibernating myocardium by three clinical parameters:

1. LV wall motion
2. myocardial perfusion
3. myocardial metabolism.

Stunned myocardium has abnormal wall motion that tends to normalize in response to inotropes and postextrasystolic potentiation. Perfusion is adequate and metabolism is also adequate.

Hibernating myocardium also has abnormal wall motion, which normalizes after nitrates, inotropes. Myocardial perfusion is reduced but can be reversed with percutaneous transluminal coronary angiography or coronary artery bypass graft and metabolism is adequate.

Reperfusion injury is characterized by the phenomenon of "NO reflow» (renewed blood flow). It means maintenance of blood supply deficiency after the resumption of coronary perfusion, feeding the ischemic myocardial areas.

Factors affecting the coronary RED microcirculation after reperfusion:

- swelling of endothelial cells;
- aggregation of the blood particles and increased blood viscosity;

- the formation of blood clots;
- margination of leukocytes

### NON-CORONAROGENIC DAMAGE OF MYOCARDIUM

**Myocardiodystrophy** – non-coronarogenic myocardium disease, that developed in action of extracardiogenic factors. It manifested by disturbances of metabolism and contractile function of the heart.

#### ***Etiology:***

- anemia
- starvations
- avitaminosis
- liver and renal disorders
- endocrine disease
- systemic disease, intoxications

#### ***Stages:***

- adaptive myocardial hyperfunction
- metabolic and structural changes that lead to heart function impairments with clinical signs of heart failure.
- hard disorders of metabolism, function and structure of myocard manifested as circulatory failure

### **Myocarditis**

- Inflammatory myocardial damage develop in direct or indirect by allergic reactions damage action

#### ***Etiology:***

- Rheumatic
- Non rheumatic:
  - ✓ Infectious factors: microbial pathogens (Trypanosoma cruzi, Leishmania), viruses (Coxsackie virus), fungi
  - ✓ Non infectious factor: diphtheria toxin, drugs (doxorubicin), vaccine

#### ***Manifestations:***

- ✓ chest pain
- ✓ symptoms of HF
- ✓ conductive disorders
- ✓ arrhythmias
- ✓ leucocytosis, eosinophilia, ↑ ESR

### **Pericarditis**

#### ***Types:***

- fibrinous
- exudative
- infectious (tbc, bacterial, viruses)
- aseptic (post infarct pericarditis, uremic )

#### ***Manifestations:***

- Precardial **chest pain** (relieved when leaning forward, increases with inspiration)
- Pericardial **friction rub** (scratchy, three-component rub (systole, early, and late diastole))
- Pericardial **effusion**
- muffled heart sounds (fluid surrounds the heart)
- hypotension associated with pulsus paradoxus (drop in systolic blood pressure greater than 10 mm Hg during inspiration)
- neck vein distention on inspiration (blood cannot enter the right atrium and refluxes into the jugular vein (Kussmaul's sign)).
- chest radiograph shows a "water bottle" configuration.

### **Cardiomyopathy**

Group of diseases that primarily involve the myocardium and produce myocardial dysfunction

**Types:**

- Dilated (congestive)
- Hypertrophic
- Restrictive

**Infective endocarditis (IE)****Etiology:**

- *Streptococcus viridans* (overall cause)
- *Staphylococcus aureus* (intravenous drug abuse)
- *Staphylococcus epidermidis* (prosthetic devices)
- *Streptococcus bovis* (ulcerative colitis or colorectal cancer)

**Pathogenesis:**

Valves involved in IE: **mitral** valve, more rare **tricuspid** valve and **aortic** valve

- *Streptococcus viridans* infects previously damaged valves, *Staphylococcus aureus* infects normal or previously damaged valves → inflammation of endocardium and vegetations on valve → vegetations embolize → abscesses and infarctions in distant organ sites
- Valve destruction leads to regurgitation murmurs.

**Myocardial damage in systemic diseases: vitamin deficiency diseases, diabetes, obesity, collagen, endocrine disorders.**

A wide variety of systemic diseases may affect the heart by a number of different mechanisms, including increasing demands on the heart, causing arrhythmias, affecting the structure of the heart or promoting cardiovascular disease and therefore coronary heart disease. Common cardiac associations with systemic disease include:

Group of pathology	Disease	Cardiac associations
Endocrine disease	Diabetes mellitus	coronary artery disease, cardiomyopathy, congestive HF
	Hyperthyroidism	supraventricular tachycardia, atrial fibrillation, hypertension
	Hypothyroidism	bradycardia, dilated cardiomyopathy, HF, pericardial effusion
	Phaeochromocytoma	hypertension, tachycardia, congestive HF.
	Acromegaly	HF
Nutrition pathology	Malnutrition	dilated cardiomyopathy, HF
	Thiamine deficiency	high-output HF, dilated cardiomyopathy
	Hyperhomocysteinaemia	premature atherosclerosis
	Obesity	cardiomyopathy, HF
Multisystem diseases	Rheumatoid arthritis	pericarditis, pericardial effusion, coronary arteritis, myocarditis, valvulitis
	Systemic lupus erythematosus (SLE)	pericarditis, Libman-Sacks endocarditis, myocarditis, thrombosis (arterial and venous)
	Amyloidosis	HF, restrictive cardiomyopathy, valvular regurgitation, pericardial effusion
	Marfan's syndrome	aortic aneurysm and dissection, aortic insufficiency, mitral valve prolapse
	HIV infection	myocarditis, dilated cardiomyopathy, pericardial effusion

**Hypertension**

Any cause of secondary hypertension, such as renal disease (eg, glomerulonephritis, polyarteritis nodosa, systemic sclerosis, chronic pyelonephritis, or polycystic kidneys), or endocrine disease (eg, Cushing's syndrome, Conn's syndrome, phaeochromocytoma, acromegaly, hyperparathyroidism), may cause hypertensive heart disease, which may lead to left ventricular hypertrophy.

**Diabetes**

Diabetes is a prime risk factor for cardiovascular disease. Vascular disorders include retinopathy and nephropathy, peripheral vascular disease, stroke, and coronary artery disease. Diabetes also affects the heart muscle, causing both systolic and diastolic heart failure. The etiology of this excess

cardiovascular morbidity and mortality is not completely clear. Heart failure in a patient with diabetes may arise from myocardial damage resulting from an ischemic, thrombotic event. In this case, endothelial dysfunction, oxidation and glycation of atherogenic lipids, and the hypercoagulability of the blood are major contributors to the patient's resulting heart failure.

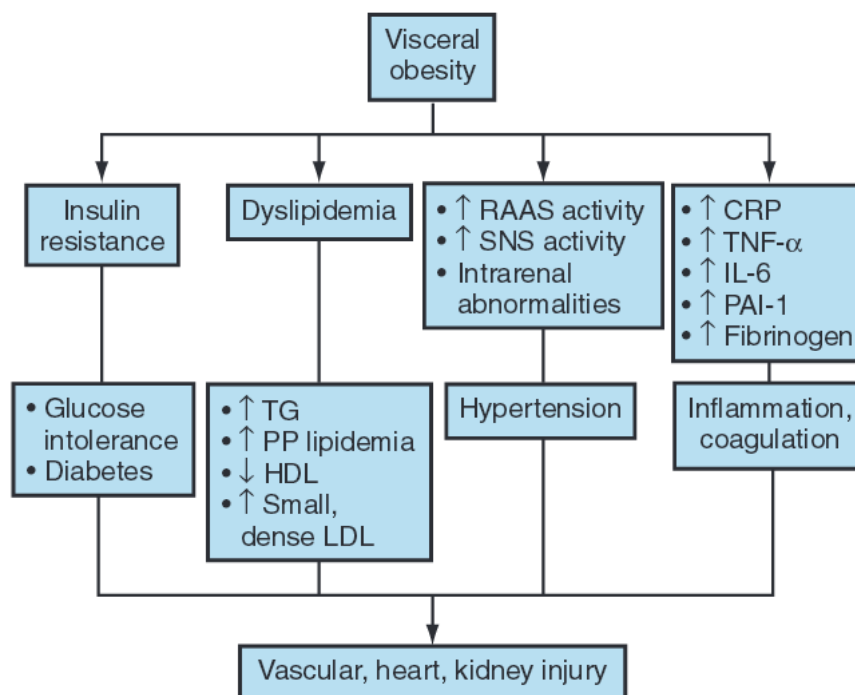
### Obesity

Obesity is a major risk factor for vascular, cardiac, and renal disease through diabetes and hypertension and perhaps other mechanisms such as “lipotoxicity” (ectopic lipid accumulation within organs). Cardiovascular disease, occurring through multiple mechanisms (including hypertension, diabetes, dyslipidemia, and atherosclerosis) is another major consequence of excess weight gain. Many risk factors for cardiovascular disease are interdependent and are often grouped as the “metabolic syndrome.”

Excess weight gain, especially when associated with increased visceral adiposity, is a major cause of human primary (essential) hypertension.

Abnormal kidney function and hypertension in obesity are mediated by increased sympathetic nervous system (SNS) activity, activation of the renin-angiotensin-aldosterone system (RAAS), and physical compression of the kidneys by extrarenal fat and by increased intrarenal extracellular matrix.

Increased renal tubular sodium reabsorption and impaired pressure natriuresis play a major role in initiating obesity hypertension.



**Figure** Cardiovascular, metabolic, and renal disease associated with visceral obesity. (Abbreviations: TG, triglycerides; PP, postprandial; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; CRP, C-reactive protein; PAI, platelet activator inhibitor; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; and IL-6, interleukin-6.)

### Hyperthyroidism

On the basis of the understanding of the cellular mechanisms of thyroid hormone action on the heart and cardiovascular system, it is possible to explain the changes in cardiac output, cardiac contractility, blood pressure, vascular resistance, and rhythm disturbances that result from thyroid dysfunction.

Uncoupling of oxidation and phosphorylation leads to energy deficit, activation of glycolysis, reduction of glycogen and protein synthesis, enhance protein degradation, decreased ATP and creatinine → relative coronary insufficiency. Cardiac contractility is enhanced, and resting heart rate and cardiac output are increased. Cardiac output may be increased by 50% to 300% over that of normal subjects as a result of the combined effect of increases in resting heart rate, contractility, ejection fraction, and blood volume with a decrease in SVR

### Hypothyroidism

The most common cardiovascular signs and symptoms of hypothyroidism are diametrically opposed to those described for hyperthyroidism and may include bradycardia, mild hypertension (diastolic), narrowed pulse pressure, cold intolerance, and fatigue. Hypothyroidism is associated with reduced blood flow to the myocardium, protein synthesis, the sodium content, increased SVR, decreased cardiac contractility, decreased cardiac output, and accelerated atherosclerosis and coronary artery disease.

### Cushing's disease

Cardiovascular complications are a major cause of morbidity and mortality in patients with Cushing's syndrome. Increased blood pressure, glucose intolerance or diabetes, central obesity, and metabolic syndrome together with chronic hypokalemia and a direct toxic effect of cortisol can all affect cardiac structure and function. Overproduction of ACTH and glucocorticoid and mineralocorticoid → cardiomyopathy with hyalinosis.

**Questions for self-control of knowledge:**

1. What is principles classification of heart failure?
2. How does change heart performance in its failure?
3. Give a characteristic of main links in pathogenesis of heart failure at cellular and molecular level.
4. Describe mechanisms of heart adaptation. Which of these mechanisms is evolutionarily more recent?
5. Which of compensation mechanisms (homeometric or heterometric) saving and why?
6. Give a definition of "coronary insufficiency", call types and causes of coronary insufficiency.
7. Describe mechanisms of myocardial damage during coronary insufficiency.
8. What are clinical manifestations of myocardial infarction?
9. What is genesis of specific electrocardiographic changes in myocardial infarction?
10. What is the genesis of the characteristic electrocardiographic changes during stenocardia?
11. Give a definition of postischemic myocardial reperfusion.
12. What are principles of diagnosis of myocardial infarction.
13. In which systemic diseases appear myocardial damage?

**Tasks for self-managed student work:**

1. Biochemical markers of ischemic myocardial damage.
2. Molecular-cellular aspects of development of physiological and pathological myocardium hypertrophy.
3. Mechanisms of damage to cardiomyocytes in postischemic myocardial reperfusion.
4. Myocardial damage in systemic diseases: avitaminosis, diabetes, obesity, collagen diseases, endocrine disorders.

**Literature**

**Basis literature:**

1. Литвицкий, П. Ф. Патофизиология = Pathophysiology: лекции, тесты, задачи : учеб. Пособие / П. Ф. Литвицкий, С. В. Пирожков, Е. Б. Тезиков. – М. : ГЭОТАР-Медиа, 2016.– 432 с.

**Additional literature:**

2. Kumar, V. Robbins and Cotran Pathologic basis of disease, 7th Edition / V.Kumar, A.K. Abbas, N. Fausto. — Philadelphia: Elsevier Inc., 2005. — 1629 p. Режим доступа: <http://www.rkmyat.in/up1/34/1629.pdf>. – Дата доступа: 30.08.2016.
3. Кидун, К. А. Тестовые задания по патологической физиологии = Test tasks on pathological physiology : в 3-х ч. Ч. 3, Частная патофизиология : учеб.-метод. пособие для студ. 3 курса фак. по подг. спец. для зарубеж. стран, обуч. на англ. яз. по спец. «Лечебное дело», мед. вузов / А. К. Кидун. – Гомель : ГомГМУ, 2015. – 113 с.
4. Научная электронная библиотека eLIBRARY.RU [Электронный ресурс] / Научная электронная библиотека. – М., 2005. – Режим доступа: <http://www.elibrary.ru>. – Дата доступа: 26.08.2017.

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