

Министерство здравоохранения республики Беларусь
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: **Гипоксия**

Theme: **Нурохіа**

Время 3 ак. часа

1.Actuality of the theme. The problem of an oxygen deficiency causes practical interest in clinic of internal illnesses (prophylaxis and treatment of myocardium infarction, diseases of the system of breathing, anemias), in neurologic clinic (prophylaxis and treatment of ischemic damages of the brain), in surgical clinic (treatment obliteric endarteriitis, operations on vital important organs), in obstetric practice (struggle with hypoxia of fetus and neonatal). Professional selection of high-resistant to hypoxia people, and also adaptation to an oxygen insufficiency become relevant problem of medicine.

Learning goals of the lesson: to study etiology and pathogenesis of hypoxic conditions, their types, main manifestations, extreme and long-term mechanisms of compensatory-adaptive reactions.

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 general laws of origin, development, outcome of hypoxic conditions.
2. To know pathophysiological processes that develop in acute and chronic hypoxia at cellular and organ level.
3. To know mechanisms of emergency and long-term adaptation of organism to hypoxia.

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

1. Biochemical bases of biological oxidation. Conjugation of oxidation and phosphorylation. (biochemistry discipline).

Control questions of the lesson:

1. Hypoxia: definition. Resistance of organs and tissues to oxygen starvation.
2. Principles of classification of hypoxic conditions. Types of hypoxia.
3. Etiology and pathogenesis of main types of hypoxia. Effect of hyper- and hypocapnia on the development of hypoxia.
4. Laboratory indicators of gas composition of arterial and venous blood for certain types of hypoxia.
5. Mechanisms of emergency and long-term adaptive-compensatory reactions in hypoxia.
6. Disorders of metabolism, structure and function of cells, physiological functions in acute and chronic hypoxia. Reversibility of hypoxic conditions.
7. Pathophysiological basis of prevention and therapy of hypoxic conditions.

Calculation of study time

Total study time 3 ac.hours

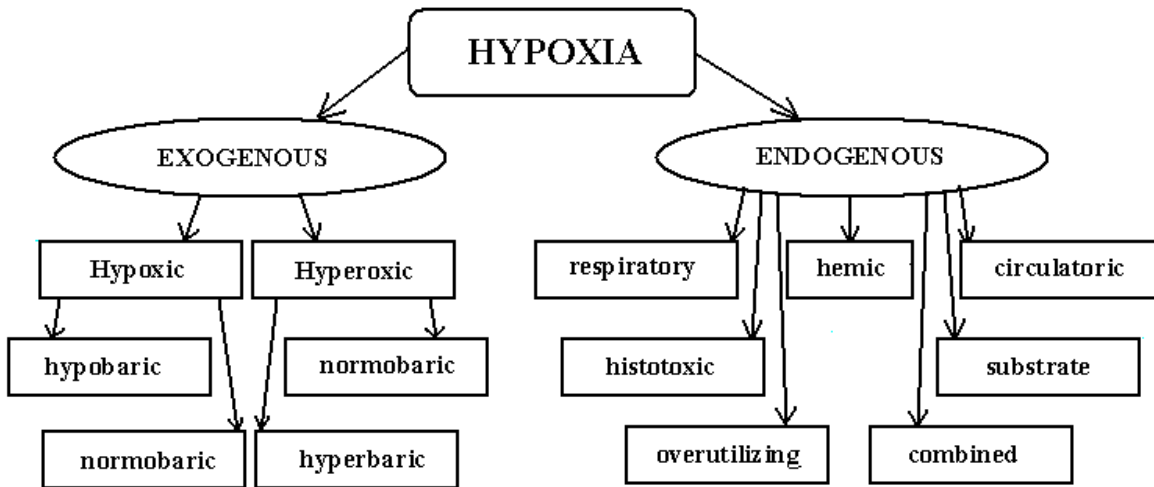
№ п/п	Contents	Calculation of study time
1.	Introduction. Motivational characteristic of the theme	3 minutes
2.	Written control of students on the topic of the lesson	15 minutes
3.	Interviews with students about the topic of the lesson	60 minutes
4.	Self-managed student work	15 minutes
5.	Summing up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

Additional materials:

Hypoxia is a typical pathological process resulting from the insufficient biologic oxidation. It is characterized by the impairment of energy supply and plastic processes in organism.

Classification of hypoxia

According to reason:



According to severity:

- mild
- moderate
- severe
- critical (lethal)

According to clinical manifestations:

- latent
- compensate
- sub-compensate
- decompensate
- terminal

According to localization:

- local
- general

According to the rate of occurrence:

- **flash-like** (several seconds, e.g., depressurization of the aircraft on a large (more than 9000-11000m altitude) or as a result of the rapid loss of large amounts of blood (eg, injuries or rupture the walls of major arterial aneurysm)
- **acute** (several minutes — 1 hour, e.g., from acute hemorrhage or acute respiratory failure)
- **sub-acute** (several hours — 1 day, e.g., by enters to the body methemoglobin formers (nitrates, nitrogen oxides, benzene), venous blood loss, slow increasing of respiratory or cardiac failure)
- **chronic** (several days (weeks, months, years), e.g., chronic anemia, cardiac or respiratory failure)

Acute hypoxia

- several minutes - several hours
- $P_{aO_2} = 25 - 40$ mm Hg
- symptoms are similar to alcohol intoxication: ataxia, slowed reflexes, slurred speech, overconfidence, and eventually unconsciousness
- if the compensatory mechanisms of the body are not adequate → coma and death

Chronic hypoxia

- $P_{aO_2} = 40 - 60$ mm Hg

- Symptoms of chronic hypoxia are similar to severe fatigue, dyspnea and breathlessness (Cheyne-Stokes breathing)

Resistance to hypoxia

The most resistant to hypoxia are bones, cartilages, ligaments, tendons. There are no significant morphologic changes in these tissues even in conditions of severe hypoxia.

Changes in **skeletal musculature** are revealed in **100–120 minutes**.

Morphologic changes and function impairments are revealed in **liver and kidneys** in **20–30 minutes**.

Consequences of hypoxia are determined by the degree of injury and time of their development.

Nervous system processes are the least resistant to hypoxia. Its' different parts resistance to hypoxia varies. Resistance of nervous cells decreases in the following line: peripheral nerve ganglions, spinal chord, medulla oblongata, cerebellum, cerebral cortex.

Cessation of **cerebral cortex** oxygenation causes profound structural and functional changes in **2–3 minutes**, in **medulla oblongata** in **8–12 minutes**, in ganglions of the **vegetative nervous system** in **50–60 minutes**.

In newborns, the automatism of the respiratory center in hypoxia can be supported by the primitive form of carbohydrate metabolism (anaerobic). The blood of newborns contains more fetal hemoglobin, which can realize the res-piratory function in a condition of a lower partial pressure of oxygen in the blood. But the most important fact is a poor development in the newborns central nervous system.

There are some individual differences in sensitivity to hypoxia. Markers of increased sensitivity to hypoxia are – hyperglycemia, hyperlipidemia, acidemia, lower content of insulin in the blood, increased content of thyroxin, prevalence of nonsaturated fatty acids (arachidonic) in membranes, more intensive metabolism, hyperparathyreosis, sympathotonia, high level of peroxide metabolism, decreased level of such antioxidizing erythrocytic enzyme as superoxidedismutase. Markers of higher resistance to hypoxia are - hypoglycemia, hypolipidemia, increased level of insulin, decreased level of thyroxin and somatotropin, prevalence of saturated fatty acids in membranes, vagotonia.

Some conditions, characterized by deep inhibition of a central nervous system and metabolism (sleep, narcosis, hypothermia), provide reduction of organism sensitivity to hypoxia.

Pathways of glucose utilization in cells:

1. anaerobic glycolysis in cytoplasm
2. aerobic glycolysis in mitochondria
3. hexose mono-phosphate shunt

Types of hypoxia, etiology and pathogenesis

I. EXOGENOUS

1. Hypoxic hypobaric hypoxia is a generalized hypoxia, an inadequate supply of oxygen to the body as a whole.

Etiology: low atmospheric barometric pressure + low level of oxygen in air: e.g., mountain sickness, altitude sickness.

Pathogenesis:

Results from the decrease in atmosphere barometric pressure (e.g. mountain disease, altitude sickness) → ↓ PaO₂ in blood (arterial hypoxemia) → hypoxia → compensatory hyperventilation → hypocapnia → Bohr effect (hemoglobin's oxygen binding affinity is inversely related both to acidity and to the concentration of carbon dioxide) → ↑ hemoglobin's oxygen binding affinity → tissues hypoxia

2. Hypoxic normobaric hypoxia

Etiology: normal atmospheric barometric pressure + low level of oxygen in air: e.g., stay in confined spaces (mines, wells), faulty anesthetic equipment.

Pathogenesis: decrease in oxygen level in air → arterial hypoxemia → hypoxia

3. Hyperoxic normobaric hypoxia

Etiology: normal atmospheric barometric pressure + high level of oxygen in air: e.g., prolonged hyperoxic artificial lung ventilation of newborn, infant, elderly people.

Pathogenesis:

Excess of O₂ at norm can be neutralized by antioxidant system. Infant and elderly people have poor antioxidant protection.

Excess of O₂ is:

- 1) inhibits processes of biological oxidation → inhibits cell respiration → hypoxia
- 2) source of free radicals → lipid peroxidation → accumulation of toxic products → damage of lung epithelium, alveolar deflation → hypoxia → convulsions, coma

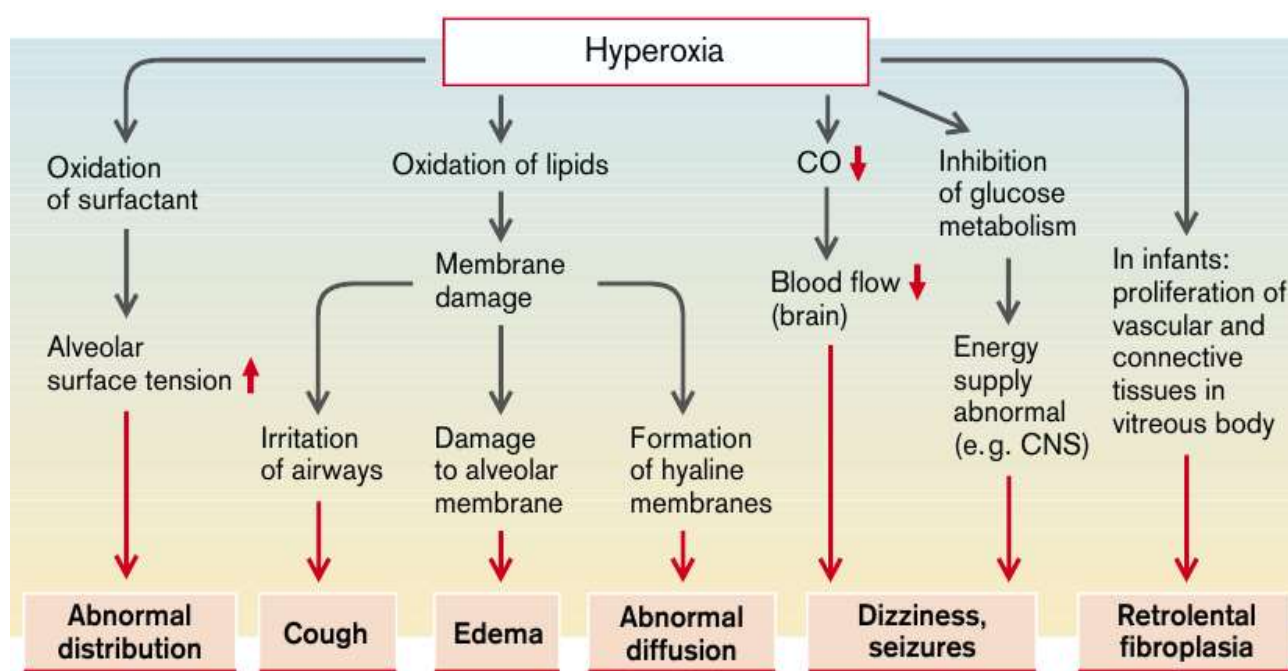
4. Hyperoxic hyperbaric hypoxia

Etiology: high atmospheric barometric pressure + high level of oxygen in air: e.g., inadequate artificial lung ventilation

Pathogenesis:

Excess of O₂ is:

- 1) inhibits processes of biological oxidation → inhibits cell respiration → hypoxia
- 2) source of free radicals → lipid peroxidation → accumulation of toxic products → damage of lung epithelium, alveolar deflation → hypoxia → convulsions, coma



II. ENDOGENOUS

1. **Respiratory hypoxia.** It results from insufficiency of oxygen transport from atmosphere into the blood plasma as a consequence of **external respiration impairments**.

Mechanisms of gas exchange insufficiency

1. alveolar hypoventilation
2. impairments of ventilation perfusion ratio
3. impairments of pulmonary perfusion
4. impairment of alveolar capillary diffusion
5. pathological venous shunts in lungs

2. Circulatory hypoxia

1. heart failure and decrease in vascular tone
2. hypovolemia results from the acute massive blood loss
3. loss of plasma results from burns, cholera (secretory diarrhea)

4. a decrease in blood volume (a decrease in blood depot, myocardial contractibility and pump function)

3. Hemic hypoxia. It results from the:

a) a decrease in the concentration of hemoglobin (a decrease in the oxygen capacity of the blood).

Due to anemia, or inactivation of hemoglobin;

b) a decrease in saturation of hemoglobin with oxygen (in hereditary hemoglobinopathy (thalassemia, sickle cell anemia), elevated blood levels of methemoglobin-forming agents, carbon monoxide, carbilaminohemoglobin, nitroxyhemoglobin);

c) shift of dissociation curve of HbO_2 .

Methemoglobin-forming agents are a group of substances responsible for the transition of iron ion from ferrous form (Fe^{2+}) to an oxide (Fe^{3+}). The formation of methemoglobin (MetHb) is a reversible process. MetHb is not able to carry oxygen. In this regard, the oxygen capacity of the blood decreases.

Carbon monoxide has a high affinity for Hb. In the interaction of carbon monoxide with Hb, carboxyhemoglobin (HbCO) forms, losing the ability to transport oxygen to tissues.

Hb compounds (eg, carbylamine hemoglobin, nitroxyhemoglobin) formed under the influence of strong oxidants also reduce the transport capacity of Hb and cause the development of hemic hypoxia.

The formation and dissociation of HbO_2 largely depend on the physico-chemical properties of the blood plasma. Changes in pH, osmotic pressure, 2,3-diphosphoglycerate content, rheological properties reduce the transport properties of Hb and the ability of HbO_2 to give oxygen to tissues.

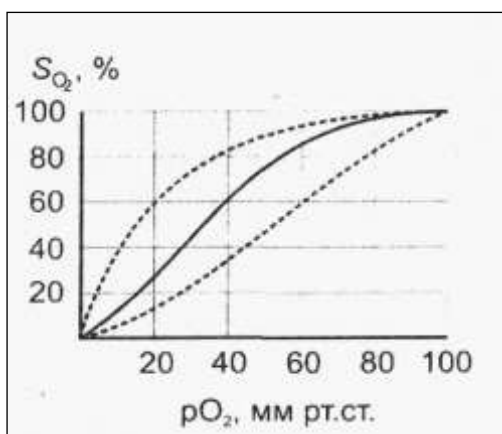


Figure 1. - Dissociation curve of oxyhemoglobin

Oxygen-Hemoglobin Dissociation Curve. Progressive increase in the percentage of hemoglobin bound with oxygen as blood $p\text{O}_2$ increases, which is called the *percent saturation of hemoglobin*. Because the blood leaving the lungs and entering the systemic arteries usually has a $p\text{O}_2$ of about 95 mm Hg, one can see from the dissociation curve that the *usual oxygen saturation of systemic arterial blood averages 97 percent*. Conversely, in normal venous blood returning from the peripheral, the $p\text{O}_2$ is about 40 mm Hg, and *the saturation of hemoglobin averages 75 percent*.

A shift of the curve to the left occurs when: temperature decreases; alkalose; hypocapnia; reduction in erythrocytes of 2,3-diphosphoglycerate; poisoning with carbon oxide; appearance of hereditarily conditioned pathological forms of hemoglobin, which do not give oxygen to tissues.

When the curve is shifted to the left, hemoglobin binds oxygen more easily in the capillaries of the lungs, but gives it worse to tissues.

The reason for the shift in the dissociation curve of oxyhemoglobin to the right can be: an increase in temperature; acidosis; hypercapnia; an increase in the content of 2,3-diphosphoglycerate in erythrocytes. The effect of acidosis and hypercapnia on the dissociation of oxyhemoglobin is known as the Bohr effect. When the curve is shifted to the right, hemoglobin poorly attaches oxygen in the capillaries of the lungs, but it gives it better to the tissues. This is associated with the protective-compensatory value of the Bohr effect in oxygen starvation.

4. Histotoxic hypoxia. It results from the decrease in ability of the tissue to use oxygen even though the supply is normal or greater than normal. Reasons: inactivation of respiratory enzymes, disruption of synthesis of respiratory enzymes, uncouples of oxidation and phosphorylation, damage to mitochondria.

5. Over-utilizing hypoxia is due to increase in the demand of tissues for oxygen. It results in deficiency of macroergic compounds and cell hyperfunction.

6. **Substrate hypoxia** is due to substrate deficiency (glucose), which is necessary for biologic oxidation. It results in a decrease in ATP level, impairments of plastic processes and metabolism.

7. **Combined hypoxia**. It results from factor action impairing two and more mechanisms of oxygen supply or oxygen utilizing. It is observed in severe hypoxia in case of oxygen transport impairments.

Acute blood loss results in haemic or hemodynamic hypoxia.

Table 1. Types of hypoxia

Parameters of oxygen regimen in organism	norm	exogenous	respiratory	circulatoric	haemic	histotoxic
P_{AO_2}	100–110 mm Hg	↓*	N, ↑	N	N	N
P_{aO_2}	85–95 mm Hg	↓	↓*	N	N	N
S_{aO_2}	96–98%	↓	↓	N	N, ↓	N
P_{vO_2}	35–40 mm Hg	↓	↓	↓	N	↑
a/v O_2	~6 (vol%)	N	N	↑*	N	↓*
Oxygen blood capacity	~16–25 (vol%)	N, ↓	N	N	↓*	N

P_{AO_2} — oxygen partial pressure in alveolar air

P_{aO_2} — oxygen partial pressure in arterial blood

S_{aO_2} — arterial blood oxygen saturation

P_{vO_2} — oxygen partial pressure in venous blood

a/v O_2 — oxygen arterial venous ratio

* — change with the diagnostic role in this type of hypoxia

↓ — a decrease

↑ — an increase

N — normal

Disturbances of organs and tissues functions in hypoxia

The severity of violations of organs and tissues functions is determined by:

- resistance of organs to hypoxia;
- rate of its development;
- degree and duration of hypoxia effects on a body.

Violations of the **higher nervous activity** are revealed after a few seconds and are manifested:

- a decrease in ability to adequately assess current events and the environment;
- sensations of **discomfort, heaviness** in the head, **headache**;
- **discoordination** of movements;
- **slowing down of logical thinking and decision-making** (including simple ones).
- a **disorder of consciousness** and its loss in severe cases.
- violation of bulbar functions, which leads to disorders of the heart and respiratory functions,

until their termination.

Circulatory disorders are manifested:

- **decrease in contractile function of myocardium**, decrease in stroke and cardiac emissions;
- disorder of blood flow in heart vessels and development of **coronary insufficiency**, which causes episodes of angina and even myocardial infarction;
- development of **cardiac arrhythmias**, including atrial and ventricular fibrillation;
- **hypertensive** reactions, alternating arterial hypotension, including acute (i.e. collapse);
- change in volume and rheological properties of blood.

Disorders of **external respiration** are manifested:

- **first**, an **increase in volume of alveolar ventilation, and then** (with increase in degree of hypoxia and damage to nervous system) its **progressive decrease**;

- **reduction of general and regional lung perfusion**. This is due to a drop in cardiac output, as well as regional vasoconstriction in hypoxic conditions;
- violation of ventilation perfusion ratio (due to local perfusion and ventilation disorders in different parts of the lungs).
- **reduction of diffusion of gases through the air-blood barrier** (in connection with a development of **edema** and swelling of the interalveolar septal cells).

As a result, respiratory failure develops, aggravating the degree of hypoxia.

Severe **kidney** damage in **severe forms of hypoxia** can lead to the development of renal failure, **uremia** and **coma**.

Violation of **liver functions** under hypoxic conditions develops, as a rule, with its **chronic** course. In this case, there are signs of both partial and total liver dysfunction. The most frequent are:

- **metabolic disorders** (carbohydrate, lipid, protein, vitamins);
- **violations of antitoxic liver function**;
- **inhibition of formation of various substances** in it (f.e. factors of hemostatic system, coenzymes, urea, bile pigments, etc.).

Disturbances in **digestive system**:

- **eating disorders** (as a rule, its **decrease**);
- violation of the motility of the stomach and intestines (usually - reduced peristalsis, tone and slowing the evacuation of gastric and / or intestinal contents);
- **development of erosion and ulcers** (especially with prolonged severe hypoxia).

In chronic and severe hypoxic conditions, the effectiveness of the **immunobiological surveillance system** decreases, which is manifested by:

- **low activity of immunocompetent cells**;
- **inadequate effectiveness of factors of nonspecific defense**: complement, If, muraminidase, acute phase proteins, natural killers, etc.

Metabolic disorders in cell during hypoxia

- Energy formation deficiency
- Accumulation of the intermediate metabolic products
- Negative nitrous balance
- Metabolic acidosis
- POL activation
- Accumulation of the toxic products
- Metabolic energy-dependent processes get inhibited
 - ✓ protein synthesis
 - ✓ compounds lipids synthesis
 - ✓ synthesis of nervous mediators
 - ✓ hormones synthesis
 - ✓ electrolyte transport

Hypoxia → anaerobic glycolysis → accumulates lactic acid and pyruvic acid → acidosis → glycolysis inhibition → disruption of K^+ / Na^+ - pump → entry into the cell Na^+ → intracellular edema → necrosis

Hypoxia → acidosis + Ca^{2+} → activation of lysosomal enzymes → enhance lipolysis and proteolysis → enhance lipid peroxidation → membrane damage

Mechanisms of extreme adaptation

- an increase in alveolar ventilation
- tachycardia, an increase in cardiac output

- an increase in circulating blood volume
- redistribution of blood flow with the increase in cerebral and coronary blood flow
- an increase in blood oxygen capacity because of the change in Hb properties and release of

Er from the depot

- an increase in association of oxidation and phosphorylation
- glycolysis activation
- a decrease in organ and tissue functioning

Mechanisms of long-term adaptation

- a decrease in metabolic processes and the demands of oxygen
- an increase in gas exchange function (an increase in alveoli and capillary number, an increase in activity of respiratory musculature)
- myocardial hypertrophy
- an increase Hb and Er blood level
- inhibition of control system reactions on different stimuli

Stages of adaptation

- extreme adaptation
- transient stage
- stable long-term adaptation
- decompensation

Levels of adaptation to hypoxia

- 1) an increase in oxygen consumption results from:
 - hyperventilation and an increase in cardiac output
 - an increase in Er number in blood
 - an increase in blood oxygen capacity
- 2) an increase in oxygen transport in cells
 - opening of arteriole and post-capillary sphincters
 - an increase in ATP in-cell level
 - mobilization of reserve capillaries
 - a decrease in oxygen diffusion
 - an increase in oxygen tension gradient
- 3) an increase in oxygen utilizing cell abilities:
 - an increase in cytochromoxidase sensitivity to oxygen
 - an increase in mitochondrion number
 - an increase in energy consumption in anaerobic glycolysis

Types of hypoxic training

(according to A.E. Kolchiskaya)

1) *hypobaric*

- continuous (in mountains)
- discontinuous (in pressure chamber)

2) *normobaric*

- discontinuous
- interval hypoxic training

Treatment and prevention of hypoxia

Etiotropic principle: 1) exogenous hypoxia — normalization of pO_2 in inhaled air, 2) add of carbon dioxide in inhaled air, 3) endogenous hypoxia — elimination of pathologic process or disease.

Pathogenic principle: decrease in acidosis, ion or electrolyte imbalance; decrease in membrane destruction, membrane injury by enzymes; an increase in activity of biologic oxidation.

Symptomatic principle: getting rid of discomfort sense inhibiting the health state.

Sanogenic principle: prevention of hypoxia.

Questions for self-control of knowledge:

1. Define term "hypoxia"?
2. Name and describe types of hypoxia
3. What are main compensatory-adaptive reactions developing during hypoxia?
4. Describe phenomenon of "hypoxic vicious circle."
5. What are most sensitive to hypoxia tissue, and why?
6. What are basic principles of reversal and prevention of hypoxia?
7. What is resistant of single organs and tissues to oxygen starvation?

Tasks for self-managed student work:

1. Optimization of functional state of human body in mountains.
2. Therapeutic effect of hyperoxia: use of hyperbaric oxygenation in medicine.
3. Experimental models of various types of hypoxia.

Literature**Basis literature:**

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_____ K.A. Kidun

