UDC 004.9:612.822 **https://doi.org/10.15407/biotech18.04.041**

HYPOXIC EFFECTS IN EXTREME STRESSFUL CONDITIONS: SOME RESEARCH TECHNOLOGIES FOR IMPROVING HEALTH AND LONGEVITY

O.M. KLYUCHKO[1], *Yu.M. ONOPCHUK*[2], *G.V. LIZUNOV*[3], *K. S. LYMAN*[4], *A. G. LIZUNOVA*[5]

[1] State University «Kyiv Aviation Institute", Ukraine
[2] Institute of Cybernetics of V. M. Glushkov National Academy of Sciences, Kyiv, Ukraine
[3] Space Research Institute of the National Academy of Sciences of Ukraine, Kyiv
[4] Washington State University, USA
[5] Luxoft Global Operations GmbH: Zug, CH, USA

E-mails: kelenaXX@ kai.edu.ua

Received 2025/04/30
Revised 2025/05/29
Accepted 2025/12/15

Aim. Description of some technologies of many years of research and their results in the age aspect in extreme situations (such as hypoxia), application of these technologies to improve the survival of organisms in stressful situations, their treatment and rehabilitation, as well as longevity.

Methods. Numerous observations on changes in biometric indicators in the comparative-age aspect of individuals in extreme highland conditions using standard methods of laboratory analysis of bioindicators in mountain conditions were analyzed. The digital indicators input to databases; mathematical, program modeling were used.

Results. The data on observations and measurements of various physiological characteristics of people, presented in a comparative age aspect, are presented. The influence of high-altitude factors on the longevity of bioorganisms, as well as some problems in aging physiology and hypoxic states, is described. The results of examinations of veteran climbers regarding adaptation to hypoxic barium, active gradual (stepwise) adaptation, the hypoxic therapy method, and combinations of these methods are discussed. A mathematical model of ischemic heart disease is presented, and technologies for the survival of people of different ages under extreme, stressful conditions are developed.

Conclusion. During the study of age-related aspects of adaptation to hypoxybaria, it was found that it increases the organism's performance, its resistance, protects against premature aging, and promotes longevity. With age, the organism's ability to adapt to hypoxia decreases but is not entirely lost — older people can adapt up to 5000 m a.s.l. The results of a survey of veteran mountain climbers regarding adaptation to hypoxic media using a number of developed technologies are presented. The results of mathematical modeling are demonstrated. Obtained results are essential for the further development of technologies for the survival of human of different ages in extreme, stressful conditions, their treatment, and rehabilitation.

Keywords: hypoxia, adaptation, extreme stressful conditions, numerical indices of physiological functions, long-livers, mathematical modeling.

The problems linked with aging and longevity were in the focus of attention of scientists for many years, different sides of these problems were studied [1–9], and some mechanisms of these phenomena were disclosed [1–4]. In parallel, nowadays, significant attention in the world is paid to studying the stress influences on human organisms under extreme conditions, and numerous publications have been devoted to this topic [3, 7, 10–39].

Citation: Klyuchko, O. M., Onopchuk, Yu. M., Lizunov, G. V., Lyman, K. S., Lizunova, A. G. (2025). Hypoxic effects in extreme stressful conditions: some research technologies for improving health and longevity. *Biotechnologia Acta*, 18(6), 41–57. https://doi.org/10.15407/biotech18.06.041

During long years in the National Academy of Sciences of Ukraine (NASU), numerical researchers studied the problems linked with a person's stay in mountains and the influence of extreme stress mountain conditions on human organisms [40–47]. Since human organisms react to all external influences, a person's stay in the mountains consequently leads to significant physiological changes.

Such influences of hypoxia could be characterized by constructive as well as destructive manifestations [40, 44]. A hypoxic environment, as well as high levels of radiation at altitudes and other extreme factors [41–49], can cause destructive influences. It was characterized phenomena of hypoxia influences in mountain conditions [40, 42], as well as organism adaptation to it [44–46]. In the present article, we would like to "add the third dimension" to this study — aging, i.e., to study the development of the first two processes over time. The more interesting since the phenomenon of longevity is often recorded specifically for mountainous highlands. The positive effect of staying in the mountains can help in the medical treatment of some diseases, rehabilitate lost functions of disabled people who were injured as a result of war, as a result of the Chernobyl accident, or other disasters, etc. [40]. Due to the positive effects of mountain climate conditions, it is possible to increase an organism's resistance to extreme influences; these effects were used for the training of rescuers, pilots, and special forces and improved sports results during the training of athletes [40]. In contemporary Ukraine, such programs can be realized in the Carpathian Mountains, for example, at low highlands in traditionally known Ukrainian resorts like Truskavetz, and Skhidnytsia, or in resorts, sportive bases at higher altitudes of Transcarpathia (Yasinya, Kvasy, etc.), Ivano-Frankivsk region, and others. Investigations in the highlands of effects mentioned above were supported by the development of novel methods of mathematical simulation [48–50]. A set of other novel information technologies for these and linked tasks was developed in the highlands in the process of the works [51–54].

The phenomenon of long-living mountain aborigines attracted the most excellent attention of NASU scientists ever, but their reasons have not yet been thoroughly studied. The researchers of the Ukrainian scientific school headed by Prof. M.M. Syrotinin worked for many years in the highlands of the Caucasus, first in expeditionary conditions, and since 1973, in stationary conditions at the Elbrus Medical and Biological Station (EMBS) NASU. This Ukrainian scientific school was the first who comprehensively study the mechanisms of adaptation to oxygen deficiency in evolutionary, comparative-physiological, and age-related aspects — thereby it laid the foundation for the development of such branches of science as comparative and age-related physiology of hypoxic conditions.

Representatives of this school studied the mechanisms of the reliability of organism functioning [40, 49] in extreme conditions at the submolecular, molecular, cellular, organ, and systemic levels, tried to understand the patterns of interdependencies at all levels because the organism is complex, unified, integral, integrated, multilevel, balanced, coordinated, ordered, multifunctional, organized system with interdependent relationships.

The objective of the article is to outline briefly some of the results of research by Ukrainian scientists on health and longevity in high altitude conditions.

Peculiarities of the influence of highland factors on biological organisms

The meaning of the term "mountain climate". Conditions in the mountains are characterized not only by low barometric pressure and associated hypoxybaria. According to numerous investigations, the following indicators are changed with the height [40–44, 48, 55]:

– temperature;
– air humidity;
– physical and chemical characteristics of air;
– wind speed and intensity;
– Earth's electric and magnetic field strengths;
– intensity of the flow of cosmic particles;
– solar radiation in the range from infrared to ultraviolet;
– radiation exposure in the range from X-ray to UV radiation.

These factors cause changes in the environment in which a person is located. They change the properties of water molecules, cause dissociation and ionization of oxygen molecules, and increase their level of excitation. Features of the mountain climate have a significant physiological effect on organisms. It was supposed that the transport of oxygen was changed in mountain's conditions, and its utilization in tissues occurs in ways that differ from processes involving oxygen in normal conditions. As a result, there may be changes in the methods of oxygen diffusion, its solubility in water, binding to hemoglobin, skin permeability, etc.

In addition, it excludes the direct influence of changed electric and magnetic fields of the Earth on the hemoglobin molecule itself, on the system of erythrocytes transfer (because they are electrodynamically active charged particles), which causes the appearance of convection currents and changes in the rheological properties of blood. The effect of highland conditions on organisms also contains an information component [40–44]. Thus, the altitude has its specifics in the processes of heredity, adaptation, evolution, and changes in structures in ontogenesis and phylogenesis.

The analysis of the conducted research allowed us to formulate the concept of "information" diseases and related methods of "information" treatment and rehabilitation. These methods include climatotherapy methods, the effectiveness of which increases in the mountains [40, 44].

Problems of the physiology of aging and hypoxic states

A significant contribution has been made at EMBS in the field of age-related physiology. The research was based on the observation that organisms of different ages demonstrate different capacities for adaptation to hypoxic environments, in particular, in mountain conditions.

Newborn mammal cubs demonstrated high resistance in a hypoxic environment; they maintained a high level of activity. Newborn rats, cats, dogs, and rabbits could survive at very low levels of p02 in the atmosphere. In the pressure chamber, this corresponded to values of altitudes of 14,000–16,000 m above sea level (m a.s.l.), at which the life of adult organisms is no longer possible without special defense.

During such experiments, no degenerative changes in the neurons of the higher brain regions, cerebellum, and cerebral cortex were recorded in newborn mammals. In addition, they studied the peculiarities of adaptive reactions of newborn mammals to oxygen deficiency. For example, the heart of a newborn dog without perfusion of the coronary vessels can contract in physiological solution for 4–5 hours. The survival period of the heart after clinical death is much shorter. Reflex mechanisms for regulating the breathing of newborn human babies are not formed in the same way as in adults. Still, their respiratory center can function in conditions of oxygen deficiency for up to 20 minutes. Clinical and experimental studies have shown that higher values of compensatory and adaptive parameters of newborns under hypoxia, compared to adult organisms, were registered due to the activation of anaerobic glycogenesis in them and higher tissue oxygen utilization capacity. If, based on such studies, medications with appropriate directions and mechanisms of action to introduced into therapeutic complexes, this will contribute to a significant reduction in newborn mortality and their normal postnatal adaptation (for example, it is possible to recommend ethymisole, sodium oxybutyrate, etc.).

Investigation of the role of hypoxia in the pathogenesis of diseases and pathological states in the perinatal period has revealed a correlation between the specificity of gas exchange, oxygen mass transfer in pregnant women with late-stage gestosis, inherited heart disease, and rheumatic diseases, and the states of embryos and newborns. A comprehensive study of oxybiotic parameters in comparison with indicators of central and regional (local) hemodynamics and microcirculation allowed us to register chronic hypoxia of mixed type in this group of pregnant women. It demonstrated the existence of correlational dependencies between detected hypoxic conditions in the mothers' organisms, the frequency of complications during pregnancy and childbirth, and perinatal pathologies in embryos and newborns. All obtained data are essential for obstetrics and gynecology.

Complex studies of people of five age groups were conducted at EMBS:

– children of preschool age;
– schoolchildren of young age (7–11 years old);
– schoolchildren in the pubertal period;
– middle-aged people;
– older adults.

The obtained results revealed that at mountainous altitudes (3–4 km above sea level), the activity of the higher nervous system is most vulnerable in older adults and puberty.

In the latter group, childhood characteristics are already disappearing, but the levels of development of adult compensatory mechanisms have not yet been reached. For example, when the level of p02 in the air was reduced to 115 mm Hg, it was registered that the oxygen saturation of arterial blood in young men was 84–86%, and in middle-aged men, 87–90%. However, despite their high sensitivity to hypoxybaria, young men can adapt to it quickly and very well. Consequently, children at a young age need special attention from pediatricians, teachers, and coaches.

Older people can often be diagnosed with arterial hypoxemia. In addition, their oxygen transport systems are less efficient.

In the mountains, respiratory volume per minute (RVM) for elderly persons increases dramatically, while alveolar ventilation (AV) almost does not improve, and the ratio AV/RVM decreases. Older adults have relatively low levels of RVM and AV, lower respiratory efficiency, and the lowest level of blood oxygen saturation not only under normal conditions (at sea level) but also under conditions of reduced p02. However, older people are able to adapt themselves to the conditions of highlands up to 5000 m a.s.l.

Some results obtained in the framework of these projects are given in Tables 1–3. They reflect the data registered at various stages of adaptation in highland conditions at an altitude of 2100m a.s.l. At the scientific base of EMBS NASU, Caucasus, Terscol [44]. In Table 1, the results of an examination of middle-aged people from the t. Chernobyl is represented (men and women who obtained low doses of radiation after the Chernobyl accident on April 26, 1986. In Tables 2 and 3, the results of medical observations of schoolchildren in the pubertal period are given (boys and girls from c. Kyiv, Ukraine).

Results of examinations of veteran climbers in adaptation to hypoxybaria

The problems of older people, in particular, sports veterans, attract special attention. The studies of limits of their capabilities, levels of physical and mental capacity, adaptation, adaptability, etc., were conducted at the EMBS in order to develop optimal ways to extend the duration of active, creative life, in particular, using the numerical method of hypoxytherapy and combinations of techniques. The proposal of researchers to organize sports competitions at the EMBS, taking into account different age categories, was supported by the International Union of Mountaineering Associations.

Ukraine became the first country to officially start mountaineer competitions in the high-altitude and age class. This enabled scientists to identify factors that ensure the high stability and work capacity of older people. Japanese rock climbers proved that a person aged 70 can climb even to the top of Mount Everest and at 102 — to the top of Mount Fuji [40].

In Ukraine, we have registered the same achievements, too. Ukrainian veteran climber Volodymyr D. Monogarov was regularly trained and examined at EMBS. At the age of 75 years, he was able to climb the top of Mount Elbrus in the Caucasus (5641 m a.s.l.) four times in one season, and being 80 years old, he celebrated his birthday on this peak again in 2007. Another Ukrainian mountain climber, Rafail D. Vilenkin, celebrated his 90th birthday by climbing to the top of Mount Hoverla in 2008 (Ukrainian Carpathians, 2060 m a.s.l.). These achievements may qualify for inclusion in the Guinness Book of Records.

A group of veteran climbers aged 50 to 78 years was examined at the EMBS.

Among the symptoms of diseases in veterans, the first place was taken by:

– changes in the cardiovascular system — vegetative-vascular dystonia, mainly of the hypertensive type;

– extrasystoles;

– partial blockade of the pedicle of the bundle of His (mainly the right one);

– disorders of the gastrointestinal tract (dyskinesias, chronic inflammatory processes).

Veterans were diagnosed with:

– arterial hypoxemia;

– less efficient and economical oxygen transport systems;

– relatively low hemoglobin content (114±4 g/l);

– slight hypochromia of erythrocytes;

– high variability in platelet count and increased tendency to aggregation.

Gradual adaptation to mountain conditions most often led to the improvement of physiological parameters and reduced the degree of these listed deviations. It was found that mountaineering veterans who train themselves annually in the mountains have a greater reserve of safety during exposure to hypoxic environments and cold. They have less pronounced stress reactions, a wider range of gas transport and hemodynamic reactions, and more economical and faster recovery after physical loads of the gas exchange and

Table 1

Changes in central hemodynamic parameters in the process of adaptation of middle-aged people "chernobyltsy" to mountain altitude conditions on the 2nd (A) and 20th (B) days (2100 m a.s.l.) [44]

Patient		Ds, mm	Dd, mm	PWD, mm	LVET, msec	SV, ml	Q, $l.min^{-1}$	HR, b/min	EF,%
1. P1	A	35.0	48.0	9.0	270	56.8	4.4	76	52
	B	35.5	48.5	9.1	360	54.0	3.6	64	56
2. P2	A	34.0	45.0	8.9	290	62.4	4.6	75	53
	B	33.0	46.0	8.7	296	56.0	3.7	76	58
3. P3	A	34.0	48.0	10.5	286	60.3	4.4	73	56
	B	34.5	44.0	15.0	302	40.2	3.4	60	59
4. P4	A	35.0	45.0	10.0	260	55.0	4.9	72	54
	B	32.0	45.0	12.5	312	51.0	4.5	70	56
5. P5	A	30.0	45.0	10.0	255	58.0	4.0	70	51
	B	35.0	47.0	14.5	307	51.5	3.3	66	54
6. P6	A	36.0	49.0	11.5	285	61.0	4.28	71	48
	B	34.0	48.0	14.5	323	60.3	3.7	63	56
7. P7	A	34.0	47.0	11.0	276	63.9	4.9	72	54
	B	32.0	48.0	12.0	280	60.0	4.1	68	58
P8	A		–	–	–	–	–	–	–
	B	35.0	47.5	13.0	296	51.5	3.2	63	50
M	A	34.0	46.7	10.1	274	59.6	4.5	73	52
	B	33.8	46.8	12.4	310	53.0	3.6	66	67
G	A	1.9	1.7	0.96	13	3.2	0.3	2.1	2.6
	B	1.4	1.6	2.41	24	6.3	0.4	5.0	1.7
m	A	0.7	0.6	0.36	5.1	1.2	0.12	0.8	0.9
	B	0.4	0.5	0.85	8.4	2.2	0.15	1.7	0.6
CV	A	0.05	0.04	0.09	0.05	0.05	0.07	0.03	0.05
	B	0.04	0.03	0.19	0.07	0.12	0.11	0.07	0.03
t		0.25	0.13	2.49	3.66	2.63	4.69	3.73	4.62
P		>0.03	>0.03	<0.05	<0.05	<0.03	<0.05	<0.05	<0.03

Note. Ds — anteroposterior dimension of the left ventricle in systole, Dd — anteroposterior dimension of the left ventricle in diastole, PwD — myocardial thickness in diastole, LVET — contraction time of the posterior wall of the left ventricle, SV — stroke volume, Q — minute blood volume, HR — heart rate, EF — ejection fraction

circulatory systems.

Methods of medical treatment based on adaptation to a hypoxic environment

The attention of M. M. Syrotinin and his followers was focused on the development of methods in which adaptation to hypoxybaria was used to treat diseases in which hypoxia plays a significant role in the pathogenesis.

A set of highly effective methods was developed at EMBS: active stepwise adaptation to high-altitude concentrations, training in pressure chambers, inhalation of gas mixtures with low concentration of oxygen, and the method of intermittent hypoxic training have been successfully implemented in numerous clinical institutions, hospitals, and sports centers in Ukraine and neighboring countries. Initially, the process of gradual (stepwise adaptation) to a low level of p02 in inhaled air in a pressure chamber (barochamber) was developed to treat patients with bronchial asthma. When this method proved to be effective, it was also used for the treatment of children with whooping cough.

In mountain conditions, the method of gradual (stepwise) adaptation was used to treat patients with some mental disorders (catatonic

Table 2

Indicators of hemodynamics and hypoxic state obtained during examination under the conditions of basic metabolism on the third (1) and twentieth (2) days of adaptation in children aged 10–13 years, (*M* ± *m*) [44]

Groups of children	Number of children	Examination	MBV, minute blood volume, l/min	HE, hemodynamic equivalent	OECC, oxygen effect of cardiac contraction, ml/bt.	BOC, blood oxygen capacity, vol.%	CaO_2, arterial blood oxygen content, vol.%	CvO_2, oxygen content in mixed venous blood, vol.%
Boys	14	1	3.8 ±0.2	37.0±9.1	1.6 ±0.1	18±1.1	15.5±1.4	11.2±2.0
		2	3.3 ±0.3	29.1 ±7.2	1.5 ±0.1	20 ±1.2	15.8±1.8	12.0 ±1.8
Girls	12	1	3.3 ±0.2	28.1 ±5.3	2.3±0.3	17.6±0.4	15.28 ±0.53	9.62±0.83
		2	3.3 ±0.3	26.3 ±3.7	1.9 ±0.2	18.7 ±0.4	12.18 ±0.37	12.18 ±0.28

Table 3

Hemodynamic and blood parameters obtained during examination under conditions of basic metabolism on the third (1) and twentieth (2) days of adaptation in children aged 10–13 years,(*M* ± *n*) [44]

Groups of children	Number of children	Examination	MBV, minute blood volume, l/min	CO, systolic volume, ml	FHC, heart rate (frequency of heart contractions), b/min	SP, systolic pressure, mm Hg	DP, diastolic pressure, mm Hg	SaO_2, saturation of arterial blood with oxygen, %	Hb, hemoglobin content, g/l	pH
Boys	14	1	4.13±0.17	51.9±1.6	78.4±3.4	98.5 ±2.2	62.5 ±1.8	88.5±0.8	129 ±4.2	7.32 ±0.01
		2	3.35±0.14	50.6±1.9	67.2 ±2.7	104.0±2.6	68.0±2.8	89.7 ±0.7	141 ±2.3	7.35 ±0.01
Girls	12	1	4.50 ±0.14	48 ±2.8	68 ±2.5	106 ±4.2	67.9±2.4	88.2±1.1	125 ±3.3	7.35±0.01
		2	3.70 ±0.30	48 ±3.3	69±3.7	109 ±3.4	71.4±2.6	87.0 ±0.7	138 ±2.9	7.36±0.14

schizophrenia), bronchial asthma, and chronic nonspecific lung diseases.

In the last quarter of the 20th century, the EMBS organized a clinical unit to provide health improvement, rehabilitation, and medical treatment of patients from environmentally disadvantaged areas. There were patients from t. Chornobyl (Ukraine) and t. Shevchenko (Kazakh Republic). Developed methods of medical treatment were based on the phenomena of adaptation to the hypoxic environment in the Elbrus mountain region. These methods were later successfully used for the treatment of many patients with respiratory allergies, anemia, hypertension, diabetes, coronary heart disease, arrhythmia, neurodystonia, "post-Chernobyl syndrome", juvenile dysfunctional bleeding, etc. During the treatment process, for its successful implementation, doctors first had to research thoroughly the peculiarities of the genesis of hypoxic states, and mechanisms of sanogenesis.

A lot of work was done to develop methods of treatment and rehabilitation of the population from the Chernobyl zone, as well as liquidators of the consequences of the accident at the Chernobyl nuclear power plant. Works in this direction were started immediately after the Chernobyl accident in May 1986. As a result, the symptoms of diseases in liquidators were identified, and the mechanisms of diseases caused by radiation in children from the "fourth zone of radiation contamination" were investigated. It was revealed and registered that multifunctional disorders in the systems of oxygen transportation and utilization play a crucial role in the genesis of the "Chernobyl syndrome", resulting in the development of hypoxic states with such clinical manifestations as vegetative-vascular dystonia, anemia, respiratory allergies, discirculatory encephalopathy, etc. It has been reported that as a result of the adaptation of Chernobyl victims ("chernobyltsy") to the mountain climate, they demonstrated (see also Table 1):

– improved psycho-emotional state, levels of functional mobility, and dynamics of nervous processes;

– states of oxygen utilization and transport systems were improved;

– regulation of vegetative functions was changed: the parameters of breathing, hemodynamics, and immune status of the blood were normalized, as well as for heart — modes of contraction and electrical activity were normalized too;

– degenerative changes in blood cells were reduced, and the process of their regeneration was activated;

– following indices were increased: oxygen content in arterial blood, the activity of succinate dehydrogenase and creatine phosphate, the lysosomal activity of white blood cells;

– DNA synthesis was increased;

– aerobic and anaerobic tissue enzymes were activated.

Models for the estimation of the development of hypoxia in case of ischemic heart disease

Ischemic heart disease (IHD) is one of the most common and dangerous diseases for human health, which occurs for various reasons. It causes oxygen deficiency in body tissues and organs. This prompted Profs. Onopchuk Yu., Aralova N., with colleagues, to develop a mathematical model of IHD development in connection with the study of the problems of hypoxia, in particular in the age aspect, within the framework of studies at EMBS. Ischemic heart disease is a well-studied pathology, and therapeutic and radical methods of its treatment are relatively well-developed. However, its impact on the behavior of the entire organism and its functional systems is still to be studied [45, 48, 49, 51].

A mathematical model of the functional respiratory system (FRS) that describes the transport and mass exchange of respiratory gases and nitrogen in the respiratory tract, alveolar space, and blood of the pulmonary capillaries. The FRS model can become a tool for researching the process of oxygen delivery to metabolizing tissues and organs functioning with IHD. Arterial blood, tissue capillary blood, and mixed venous blood during the respiratory cycle.

The FRS model is essentially a multi-criteria problem of optimal control of a nonlinear dynamic system for variable structure, with the right-hand sides in the equations changing during the phases of inhalation, exhalation, and pause. Therefore, its solution is objectively complex.

The results of computational experiments provide evidence of the adequacy of the description of the breathing process for various conditions of the human body's vital activity. The clinical symptomatology of IHD is mainly determined by the presence and degree of expressiveness of fibro-atheromatous plaques in epicardial coronary arteries.

According to foreign and domestic literature [40, 44], from 10 to 30% of patients with clinical and instrumental signs of IHD after selective coronary angiography have unchanged or little changed coronary arteries.

There are several hypotheses of pathogenesis to identify the causes and mechanisms of IHD with intact coronary arteries. The following mechanisms of IHD syndrome development are discussed: generalized microvascular endothelial dysfunction, hypoestrogenism, hemorheological disorders, hyperactivity of the sympathoadrenal system, potassium pump dysfunction in cardiomyocytes, increased pain receptor sensitivity, left ventricular hypertrophy, etc. The lack of a unified and clear understanding of the etiology and pathogenesis of IHD complicates the development of reliable criteria for the diagnosis and treatment of this disease.

The purpose of the conducted research was not to identify the causes of IHD development, but to study the hypoxic states of the entire organism, its organs and tissues, in particular the heart muscle, during IHD. The mathematical model of FRS describes in the dynamics of the respiratory cycle the transport of respiratory gases in organisms, their mass exchange, tissue respiration, the work of self-regulation mechanisms of the primary function of breathing — adequate and timely delivery of oxygen to metabolizing tissues, and removal of carbon dioxide formed in tissues as a result of metabolic processes [44]. Myocardial muscles are one of the executive organs of self-regulation.

The FRS model is quite structured. Depending on the goals of modeling, it is possible to present any organ or system in the form of its interdependent components under the condition that it is possible to decompose the function of the organ. In particular, the pumping function of the heart is determined by the work of the right, and left atrium right and left ventricle.

The heart muscle, as the executive organ of regulation of the primary respiratory function, is the most vulnerable link in the system of self-regulation mechanisms. Its regulatory resources are minimal. In untrained (non-adapted) individuals, the heart muscle is able to increase its activity by five to six times. In extreme situations, the respiratory muscles (intercostal and diaphragmatic) can involve the muscles of the forearms, chest, and back to strengthen their regulatory functions.

In some tissue reservoirs, in particular, skeletal muscles, the vascular system is able to develop in conditions of constantly occurring hypoxic conditions, increasing the density of the capillary network.

The heart muscle can increase the intensity of its activity only at a high level of adaptation of the whole organism to hypoxia or in some conditions of life by increasing its mass, which has both positive and negative significance for human health and work capacity.

Whatever the cause of the IHD development, a diseased heart cannot generate the volume rate of systemic blood flow necessary for these conditions of vital activity. Coronary vessel lesions and "necrosis" of the myocardial areas adjacent to them reduce the contractility of the heart and, as a result, cannot provide the necessary blood output. Thus, IHD is the cause of circulatory hypoxia in the body. Of course, the reason for the development of circulatory hypoxia in the body can be the loss of elasticity of the smooth muscles of tissue vessels, the loss of the ability to undergo massive vasodilation, and vasoconstriction.

The FRS model is easily modified to the conditions when IHD is present, or it develops in the body. When simulating organism hypoxic states in conditions with IHD, the following can be assumed:

– oxygen tension in arterial blood has normal values for the state of rest or exercise, that is, the external respiration system and its regulatory mechanisms operate normally;

– there are no deviations of the basic metabolism in tissues;

– the degree of decrease in the volumetric velocity of blood circulation is directly proportional to the degree of development of IHD and the decrease in the contractility of the heart.

Of course, in the case of IHD, the problem of individualizing the FRS model arises. The FRS model was developed for a healthy average person, and its individualization for a specific subject consists of determining the main parameters of the external respiration and blood circulation system at rest and exercise. On the FRS model, the experiment was simulated, and the coefficients of sensitivity to hypoxia and hypercapnia were selected so that the experimental data and those obtained by mathematical modeling coincided. There is no sense in conducting experiments with patients in order to individualize the model. Experimental data will correspond to the state of a sick person. If the examinee's data are stored when he was still healthy, the problem of individualization of the FRS model is solved. Otherwise, the FRS model is individualized only by determining body weight, growth, and the structure of muscle tissue. It is possible to take into account the age data. Usually, the modeling process takes into account the mechanisms of compensation for hypoxic conditions and develops recommendations for correction. In the case of patients with IHD, suggestions and corrections of compensatory mechanisms can be made by comparing the data of mathematical analysis of the results of patients and healthy ndividuals.

The procedure for investigating hypoxic conditions in patients with IHD using the FRS model is quite simple

The ventilation rate and the volume rate of systemic blood flow ***Q*** are determined on the basis of the FRS model with anthropometric data of the patient, which is distributed to organs and tissues according to a simplified method. At oxygen and carbon dioxide tensions in all structural parts of the respiratory system are determined. Experimentally determined minute blood circulation in IHD patients is distributed by the organs and body tissues. The data ***Q*** and are input into the model as given (stated), and the oxygen and carbon dioxide regimes in a patient with IHD are calculated.

By comparing the data of these calculations, it is possible to recognize the degree of development of hypoxia in each organ and tissue area.

For an average healthy person in a normoxic, undisturbed environment at rest, the oxygen profile is determined by oxygen tension:

– alveolar air — 105 mm Hg;
– arterial blood — 90.5 mm Hg;
– brain tissues — 38.1 mm Hg;
– heart — 28.7 mm Hg;

– liver — 42.4 mm Hg;
– kidneys — 66.7 mm Hg;
– skeletal muscles — 31.8 mm Hg;
– skin — 37 mm Hg;
– other organs — 37 mm Hg;
– mixed venous blood — 39.9 mm Hg.

These data were obtained using a mathematical model for = 8.0 l/min:

Q = 5.1 l/min;

q_t = 0.258 l/min.

If we assume that the level of minute blood volume in the IHD patient decreases to 4.1 l/min (by 20%), then according to the ratio established using regression methods, $q_{1cm} = 0.0022Q + 0.121$

The rate of oxygen consumption in the heart muscle should be 0.27 ml/s instead of 0.33 ml/s in an average person. Since the state of rest is simulated and the rate of oxygen consumption in each region does not change (except one for the heart muscle), cardiac output and minute blood volume that are inadequate for this state will lead to a significant change in the oxygen and carbon dioxide tensions in them.

Oxygen tension will decrease in almost all organs (except for the kidneys) by 5–6 mm Hg, and the tension of carbon dioxide will increase by 4–5 mm Hg. Such a decrease in oxygen tension and an increase in carbon dioxide tension should cause damage to the functions of organs and tissues. In the case of physical activity, even of moderate intensity, the stress gradient is slightly higher, and this does not lead to tissue dysfunction. However, in contrast to the temporary effects on the body of disturbances such as physical activity, in the case of IHD, the inadequacy associated with a decrease in minute blood volume is long-term. Undoubtedly, when the body is exposed to severe hypoxia for a long time, this can cause changes in functions and the development of pathologies in tissues and organs.

It seems that under IHD, the heart muscle feels quite comfortable in regard to oxygen supply. Thus, in a healthy person, the hemodynamic equivalent (HE), which characterizes the efficiency of the circulatory system, for the heart muscle is 14.4, while in a patient with IHD (at a volume blood flow rate of 4.1 ml/s) it is 15.3. In reality, this is not true.

Heart failure leads not only to secondary tissue hypoxia but also to excessive accumulation of carbon dioxide in the blood and tissues. This causes acidification of the blood (pH in the blood and tissues decreases) and, as a result, a shift of the hemoglobin oxygenation curve to the right.

The leading transporter of oxygen in the body is hemoglobin, which moves with the circulating blood. A decrease in the degree of its oxygenation reduces the oxygen capacity of the blood, and as a result, one volume unit of blood contains less oxygen. Although it moves in the capillary channel of the heart muscles, it would seem to move quite efficiently. Therefore, hypoxia in the heart muscle will be well visible at IHD. The mathematical model of FRS in IHD demonstrates that there are two ways to overcome such a mismatch of the factor due to passive regulation mechanisms:

– due to an increase in oxygen capacity of the blood with an increase in the number of erythrocytes in the blood (initiation of erythropoiesis);

– as a result of an increase in the concentration of buffer bases in the blood (increase of blood pH).

Both of these processes are associated with the risk of thrombocytosis because they cause an increase in blood density. And of course, both of these mechanisms are involved in work at IHD, but they cannot effectively prevent the oxygen starvation of tissues, including the heart muscle.

To a greater extent, the mitigation of oxygen deficiency in the body is possible due to increased activity of the external respiratory system.

The selection of optimal modes of the external breathing system for a given situation can increase the oxygen content in arterial blood and thereby slightly increase the oxygen capacity of the blood and improve the delivery of oxygen to the tissues. The selection of optimal modes of the external breathing system for given situation can increase the oxygen content in arterial blood and thereby slightly increase the oxygen capacity of the blood and improve the delivery of oxygen to the tissues. In this case, the respiratory muscles fulfill the work that the heart muscle cannot do. It is due to a significant increase in the rate of oxygen consumption in them. Let's take into account that with heart failure, the volumetric rate of blood flow in them is inadequate to the rate of consumption. The acute hypoxia that develops in them cannot compensate for the heart failure for an extended period.

Therefore, there is a new task of choosing the optimal modes of the external breathing system in case of IHD, which maximally helps to reduce the level of tissue hypoxia.

In the case of IHD, it is challenging to give a holistic and unified view of the oxygen tension in the heart structures (right atrium and right ventricle, left atrium and left ventricle). Much will depend on those disorders that caused an IHD development, in particular, damage to the coronary arteries and hypertrophy of the left ventricle. The degree of coronary artery damage can be partially simulated on the model of partial occlusion of the arterial vessels of the heart muscle or their branches.

The case of partial occlusion of the artery supplying blood to the heart, which is divided into arterial vessels of the right and left parts of the heart. With partial occlusion of a coronary artery, the equations describing changes in oxygen tension will be as follows.

This is due to a significant increase in the rate of oxygen consumption in them. Let's take into account that with heart failure, the volumetric rate of blood flow in them is inadequate to the rate of consumption. The acute hypoxia that develops in them cannot compensate the heart failure for an extended period.

Therefore, there is a new task of choosing the optimal modes of the external breathing system in case of IHD, which maximally helps to reduce the level of tissue hypoxia.

In the case of IHD, it is challenging to give a holistic and unified view of the oxygen tension in the heart structures (right atrium and right ventricle, left atrium and left ventricle). Much will depend on those disorders that caused an IHD, in particular, damage to the coronary arteries and hypertrophy of the left ventricle. The degree of coronary artery damage can be partially simulated on the model of partial occlusion of the arterial vessels of the heart muscle or their branches.

The case of partial occlusion of the artery supplying blood to the heart, which is divided into arterial vessels of the right and left parts of the heart is of interest. With partial occlusion of a coronary artery, the equations describing changes in oxygen tension will be as follows [40, 44]:

$$\frac{dP_{1cti}}{d\tau} = \frac{1}{\left(V_{cti} - \int_{\tau_0}^{T}(Q_{ti} - \tilde{Q}_{ti})d\tau\right)\left(\alpha + \gamma_{Hb}Hb\frac{\partial\eta_{cti}}{\partial P_{1cti}}\right)} \times$$

$$\times \left(\alpha_1\tilde{Q}_{ti}P_a + \gamma_{Hb}Hb\tilde{Q}_{ti}\eta_a - G_{1ti} - \alpha_1\tilde{Q}_{ti}P_{cti} + \gamma_{Hb}Hb\tilde{Q}_{cti}\right)$$

$$\frac{dP_{1cti}}{d\tau} = \frac{1}{V_{ti}\left(\alpha + \gamma_{Mb}Mb\frac{\partial\eta_{ti}}{\partial P_{1ti}}\right)}(G_{1ti} - q_{1ti})$$

where $i = r, l$ — right and left parts of the heart;

Q_{ti} — is the volume velocity of coronary blood flow determined by the FRS model;

$\tilde{Q}_{ti}$ — is the actual blood flow velocity in the case of heart damage.

Obviously, it makes sense to examine the case when $\tilde{Q}_{ti} < Q_{ti}$.

One of the possible assumptions is that the coronary vessels of the right and left parts of the heart are not affected. With partial occlusion of the blood-supplying artery, the gradients of oxygen tension will be greater in absolute value than the corresponding gradients of the unaffected vessel. And, depending on the degree of occlusion, hypoxia in the heart muscle will be more or less pronounced.

According to another assumption, the arterial vessel of the right or left part of the heart is affected, or the degree of their damage is different.

In the first case, hypoxia occurs due to partial occlusion in one of the parts of the heart muscle. In the other, the volume blood flow rate will be higher than necessary and will lead to an increase in oxygen tension. This will create an asymmetry in the distribution of oxygen tension in the intact heart muscle.

In the second case, when the degree of damages to the arterial vessels supplying blood to the right and left parts is different, hypoxia develops in the muscles of both parts/ This hypoxia is caused by the partial occlusion of vessels of varying severity, and the distribution of oxygen tension will be asymmetric.

The model can be a tool for analyzing situations when a complete occlusion of the capillary flow bed occurs in an elementary tissue region of the heart muscle.

In the initial period, there is a sharp depletion of oxygen from the blood, a mismatch between the oxygen delivery and the needs of the tissue surrounding the capillary. As a result, in this tissue region, $p0_2$ enters the zone of critical values, and the tissue region cannot participate in the work of the whole heart in case of ensuring the pumping function.

So, if the coronary vessels are affected, the oxygen portrait of the heart muscle is built depending on the degree of damage and on where, and in which part of the capillary bed of the heart muscle, the damage occurred.

The authors of the model believe that the conclusion that hypertrophy of the left ventricle can be the reason for IHD development is quite controversial. Let's suppose that the muscle mass of the left ventricle of the heart has increased by the value of AV. Then the equation for the change in oxygen tension can be given in the form:

$$\frac{dP_{1l}}{d\tau} = \frac{1}{(V+\Delta V)\left(\alpha_{1l} + \gamma_{Mb} Mb \frac{\partial \eta_l}{\partial P_{1l}}\right)}(G_{1l} - q_{1l})$$

Since is determined mainly by the intensity of the work of the left ventricle rather than by its mass, the average oxygen tension in the hypertrophied ventricle at $G_{1l} - q_{1l} < 0$ will change less than in other parts of the heart muscle. Similarly, the gradient of changes in P_{1l} at $G_{1l} - q_{1l} < 0$ will be less than in the nonhypertrophied heart ventricle. The model shows that left ventricular hypertrophy is a factor in stabilizing oxygen tensions in the event of various perturbations. At the same time, there is a pronounced asymmetry in the distribution of $p0_2$ in the structures of the heart. At IHD, there is a decrease in the minute blood volume in a person compared to the expected value in an average person under certain types of perturbations. However, if such a decrease is recorded, this in itself does not indicate that this person has IHD.

In many cases, a reduced level of minute blood volume indicates sufficient adaptation of organism to disturbing factors. There are three periods (phases) of the organism adaptation to hypoxia — short-term (instant), medium-term and long-term.

With a change in external and internal conditions of vital activity, associated with oxygen deficiency in the breathing mixture or intense muscle activity, the FRS self-regulation system will develop the following modes of functioning of the external respiratory system, cardiovascular system (parameters $\dot{V}$, Q, $Q_{ti}, i = \overline{1,m}$), which can provide compensation for hypoxic states. According to our assumptions, there is a "decision-making center" in the organism to regulate the parameters of its vital activity in case of deviations from the norm in the environment.

Usually, hypoxia develops in organs and tissues because the regulatory decision-making center is forced to resolve the compromise conflict situations that arise in the organism between the tissues of executive regulatory organs and all other organs and tissues that consume oxygen.

In conditions of decreasing partial pressure of oxygen in the breathing mixture, a conflict situation is added to ensure the balance of oxygen delivery and carbon dioxide removal systems. However, the resulting tissue hypoxia is not as severe as it would be if there were no short-term adaptation mechanisms. The reaction of these mechanisms is almost instantaneous and leaves no structural traces of adaptation. These mechanisms of self-regulation have evolved evolutionarily way and are characteristic of healthy or sick human organisms of any age. Repetitive perturbations of the system and continuous disturbance for a long time require a more efficient organization of the self-regulation process. In other words, the executive mechanisms of self-regulation, especially of the heart muscle, whose resources are minimal, will be constantly stressed, which can lead to disruption of the regulatory system, significant deterioration in the quality of its functioning, and, as a result, to the decrease of productivity of all functional organs and tissues of organism. Suppose the sensitivity coefficients decrease with prolonged exposure of the system to disturbing factors. In that case, the results of solving the self-organization model of the problem of choosing optimal $\dot{V}$, Q, $Q_{ti}, i = \overline{1,m}$, parameters will have smaller values. Thus, the dynamic system control resource increases. Naturally, the oxygen tension in the tissue blood and tissues decreases, and the carbon dioxide tension increases. It is imperative that, in the case of getting used to oxygen deficiency, the oxygen sensitivity coefficient does not decrease to the value at which $p0_2$ in the tissues will fall to a critical level, when the tissues will not be able to perform their assigned functions. At such a threshold value, it can (and actually it happens), FRS deregulation. Under the conditions when the system is periodically and constantly affected by perturbations of a specific nature, simultaneously with the change in the organism's sensitivity to hypoxia, there is an economization of the process of functioning of organs and tissues.

Oxygen utilization releases not only the energy required for the functions of individual organs and tissues, but also other types of energy, primarily thermal ones. Therefore, it can be assumed that

$$q_{1ti} = q_{1ti}^{av} + q_{1ti}^{h}, i = \overline{1,m}$$

where q_{1ti}^{av} is the part of the oxygen consumption rate that provides the function; q_{1ti}^{h} is the thermal component of the oxygen consumption rate.

Experimental and research data allow us to confirm that for each type of activity of a certain intensity

$$q_{1ti}^{av} = C_i = const, i = \overline{1,m}$$

whereas, after experience is gained, better organization of functions can lead to a significant reduction of $q_{1ti}^{m}, i = \overline{1,m}$. This stage of adaptation will be referred to the medium-term adaptation period.

Reducing the coefficients of sensitivity and oxygen demand of tissues and organs *qlti* contributes to the decrease of tensions in the work of executive elements of self-regulation and increasing their resources.

Let's suppose that under such assumptions:

$$q_{1ti}^{m} = q_{1ti}^{m_0} + q_{1ti}^{m_{вих}} e^{-\sigma_{ti}}$$

$$\rho = \rho^{пор} + \rho^{вих} e^{-R_{ti}\tau}$$

where $q_{1ti}^{m_0}$ is the rate of oxygen utilization required to ensure the thermal balance of the organism;

σ_{ti}, R_{ti} is the rate of the organization (economy) of metabolic processes in tissues;

$\rho^{пор}$ is the limit value of the sensitivity coefficients ρ.

If these assumptions are correct, then the stage of medium-term adaptation in coronary artery disease cannot eliminate (compensate) tissue hypoxia, but only mitigates its degree of severity by changing the organism's sensitivity to hypoxia and more efficiently organizing metabolic processes in tissues.

In the process of long-term adaptation to hypoxia, this stage is observed in IHD patients. At the same time, structural changes in the body must necessarily occur because the function of oxygen delivery and carbon dioxide excretion has changed due to damage to one of the executive organs of self-regulation (the heart). Such structural changes, according to the analysis of the FRS model, can occur primarily due to changes in the volumes of tissues and organs.

An increase in $\dot{V}_{ti}$ leads to a decrease in the ratio of V_{cti}/V_{ti} and, the sensitivity coefficient, which further reduces the sensitivity of this organ to hypoxia. This significantly affects the solution of the optimal choice problem *V*, ***Q*** and Q_{ti} for a given level of perturbation. Since compensation for hypoxic conditions is carried out mainly by the intensive activity of respiratory muscles and vascular smooth muscle, at this stage, first of all, their volumes should increase.

However, in necessary cases for lung ventilation, the respiratory muscles can involve the efforts of the muscles of the forearms, chest, and back muscles . Hence, an increase in their volume is not necessary.

The volume of vascular smooth muscle usually does not change, and during the formation of new capillary ducts, if it does change, then the value of these changes is relatively small.

Only hypertrophy of the heart muscles, in particular, the left ventricular muscles, can help reduce the organism's sensitivity to hypoxia and thereby improve oxygen supply. Hypertrophy of the heart muscle is an adaptive mechanism to hypoxia that develops in an organism in case of long-term effects of disturbances on the system. Of course, hypertrophy of the heart muscle does not occur in everyone and not always.

Thus, in the process of age-related aspects of adaptation to hypoxybaria studying (taking into account age-related changes in the organism's reactivity), it was found that it increases the organism's performance, its resistance, protects against premature aging, and promotes longevity. With age, the organism's ability to adapt to hypoxia decreases, but is not entirely lost — older people can adapt to mountain altitudes up to 5000 meters.

It is well-known the fact, that there was a large number of long-lived people among the native population in some regions of Ukraine with healthy ecological conditions and good conditions for life. It was possible in locations with a favorable climate and ecology the use natural products; also, due to the traditions in culture and religion, a satisfactory level of public medicine. The number of geronts was high enough in our country in the past peaceful years. In the 20th century, it was so in peaceful decades between the Second World War and the contemporary war, with enemy troops' invasion of the territory of Ukraine since March 2014, and more since February 23, 2022. The last caused the mass extinction of the peaceful population of all ages, from newborns to older adults, who were helpless in contact with armed contingents. Trying to help in this situation, we turned to the experience of Ukrainian scientists from NASU [40–46, 50].

In the conditions of the highlands, it was possible to obtain the following characteristics of the reactions of organisms in natural conditions and to track such regularities that cannot be obtained at sea level. And put them in the base for the development of new, highly effective methods of medical treatment, which were widely used later in many resorts, hospitals, and other medical and health facilities. We would like to hope that these findings will contribute to further development of the knowledge about the influences of different extreme conditions on living objects and will be added to other ideas in this sphere [41–50]. The obtained results and conclusions correlate well with the domestic as well as foreign findings in this sphere [54–70].

Within the framework of above above-described research, a model of IHD was created, which became a theoretical generalization of previously obtained results, enriching the understanding of the mechanisms of this disease, in particular in the age aspect. Further development of algorithmic and software analysis of the results of computer research will allow clarifying some of the provisions included in the construction of the model, confirming or refuting formulated assumptions and hypotheses.

Conclusions

The process of building up the heart muscle develops mainly in people who are constantly engaged in intensive physical work, in highly qualified athletes, in people who are often exposed to stressful situations in their professional activities, and perhaps in the inhabitants of the highlands. The process of hypertrophy of the heart muscle is not so positive for human health. Still, it is a necessary adaptation process to severe hypoxia, regardless of the reasons for its occurrence.

The negative consequences of heart hypertrophy are usually found in conditions where the organism is not affected by such intense functional loads over a long period of life that previously caused an increase in heart weight. The high activity of the heart muscle is no longer required; the muscles are overtrained, they lose their elasticity and contractility, which causes heart failure under the influence of loads that occur from time to time.

Given that some medical scientists call left ventricular hypertrophy one of the causes, we can formulate a hypothesis. During the period of active human activity, hypertrophy of the left ventricle of the heart is a necessary adaptive process to hypoxia. In the post-active period of life, it can cause the development of IHD.

Author Contributions.
O.M. Klyuchko — data supply and analysis, carrying out some observations and investigations, manuscript article writing, editing, translation, and paper preparation, provided the new literature data for review. Yu.M. Onopchuk — formal analysis and modeling, supervision of works in mathematical and computer modeling. G.V. Lizunov — theoretical analysis, mathematical modeling. K.S. Lyman — mathematical modeling, algorithm construction. A.G. Lizunova — computer simulation, algorithm construction. All authors contributed to the manuscript's revision and read and approved the submitted version.

Funding
The study was funded under the themes according the State registration 0107U002666 and No.177-X04.

Conflict of Interest
The authors declare no conflict of interests.

Acknowledgments. The authors express their gratitude for the help to the research group of cybernetics Prof. Dr. Aralova N. I., and Drs. Mashkin V.I., Mashkina I.V., Semchik T.A. who was related with the development of some mathematical models in framework of the projects observed in this article.

REFERENCES

1. Ollé-Vila, A., Seoane, L. F., Solé, R. (2020). Ageing, computation and the evolution of neural regeneration processes. *J.of the Royal Society Interface.,* 17(168), 1-10. https://doi.org/10.1098/rsif.2020.0181
2. Sofiat Makanjuola-Akinola. (2021). What is the biggest benefit technology will have on ageing and longevity? *Health and healthcare systems*. Publ.: 2021. Updated: 2024. E-publication. https://www.weforum.org/stories/2021/03/what-is-the-biggest-benefit-technology-ageing-longevity-global-future-council-tech-for-good/
3. Peng, X. Chen, Leyuan, Zhang,, Di Chen, Ye Tian. (2023). Mitochondrial stress and aging: Lessons from C. elegans. 10849521. https://doi.org/10.1016/j.semcdb.2023.02.010
4. Quinlan, R. A., Clark, J. I. (2022). Insights into the biochemical and biophysical mechanisms mediating the longevity of the transparent optics of the eye lens. *JBC Rewievs.* 1-22. E-publication, 1–22. https://doi.org/10.1016/j.jbc.2022.102537
5. Xu, S., Wang, J., Guo, Z., He, Z., Shi, S. (2020). Genomic convergence in the adaptation to extreme environments. *Plant Commun.*,

1(6), 872–879 . https://doi. org/10.1016/j. xplc.2020.100117

6. Manni, M., Berkeley, M. R., Seppey, M., Simão, F. A., Zdobnov, E. M. (2021). BUSCO update: novel and streamlined workflows along with broader and deeper phylogenetic coverage for scoring of eukaryotic, prokaryotic, and viral genomes. *Mol. Biol. Evol.*, 38, 4647–4654. https://doi. org/10.1093/molbev/msab199
7. Carter, C. S., Kingsbury, M. A. (2022). Oxytocin and oxygen: the evolution of a solution to the 'stress of life. *Philos. Trans. R. Soc. Lond. B Biol. Sci.*, 377(1858), 20210054. https://doi.org/10.1098/rstb.2021.0054.
8. González-Buenfil, R., Vieyra-Sánchez, S., Quinto-Cortés, C. D., Oppenheimer, S. J., Pomat, W., Laman, M., Cervantes-Hernández, M.C., ..., Moreno-Estrada, (2024). Genetic Signatures of Positive Selection in Human Populations Adapted to High Altitude in Papua New Guinea. *Genome Biology and Evolution*, 16(8), evae161. https://doi. org/10.1093/gbe/evae161
9. Badran, B. W., Caulfield, K. A., Cox, C., Lopez, J. W., Borckardt, J. J., DeVries, W. H., Summers, P., ..., Roberts, D. R. (2020). Brain stimulation in zero gravity: transcranial magnetic stimulation (TMS) motor threshold decreases during zero gravity induced by parabolic flight. *NPJ Microgravity*, 6, 26. https://doi.org/10.1038/s41526-020- 00116-6
10. Angeloni, D., Demontis, G.C. (2020). Endocrine adaptations across physical and psychological stressors in long-term space flights. *Curr. Opin. Endocr. Metab. Res*. https://doi.org/10.1016/j. coemr.2019.12.005
11. Vianna, J. A., Fernandes, F. A. N., Frugone, M. J., Figueiró, H. V., Pertierra, L. R., Noll, D., Bi, K., Wang-Claypool, C. Y., ..., Bowie, R. C. K. (2020). Genome- wide analyses reveal drivers of penguin diversification. *Proc. Natl. Acad. Sci. USA*, 117(36), 22303–22310. https://doi.org/10.1073/pnas.2006659117.
12. Pham, K., Parikh, K., Heinrich, E. C. (2021). Hypoxia and inflammation: insights from high-altitude physiology. *Front Physiol.*, 12, 676782. https://doi.org/10.3389/ fphys.2021.676782.
13. Cunha, C. E. X., Oliveira, A. F., Dantas, G. F. G., Castro, L. R., Vitor de Omena Jucá, J., Vieira, G. C. F., Ribeiro, M. V. M. R. (2021). Neuropsychiatric aspects of the space missions: scientific overview of the last 15 years. *Int. Physiol. Med. Rehabil. J.*, 6 (1), 4-9. https://doi.org/10.15406/ ipmrj.2021.06.00270
14. León, F., Pizarro, E. J., Noll, D., Pertierra, L. R., Gonzalez, B. A., Johnson, W. E., Marín, J. C., Vianna, J. A. (2024). History of Diversification and Adaptation from North to South Revealed by Genomic Data: Guanacos from the Desert to Sub-Antarctica. *Genome Biology and Evolution*, 16(5), evae085, https://doi.org/10.1093/gbe/evae085
15. Davis, J., Stepanak, J., Fogarty, J., Blue, R. (2021). Fundamentals of Aerospace Medicine (fourth ed.*), Lippincott Williams & Wilkins*.
16. Ding, W., Zhang, X., Zhao, X., Jing, W., Cao, Z., Li, J., Huang, Y., ..., Bing, X. (2021). A chromosome-level genome assembly of the mandarin fish (*Siniperca chuatsi*). *Front Genet.*, 12, 1–15. https://doi. org/10.3389/fgene.2021.671650
17. Clément, G. R., Boyle, R. D., George, K. A., Nelson, G. A., Reschke, M. F., Williams, T. J., Paloski, W. H. (2020). Challenges to the central nervous system during human spaceflight missions to Mars. *J. Neurophysiol.*, 123, 2037–2063. https://doi. org/10.1152/jn.00476.2019
18. Chaumeil, P. A., Mussig, A. J., Hugenholtz, P., Parks, D. H. (2020). GTDB-Tk: a toolkit to classify genomes with the genome taxonomy database. *Bioinformatics*, 36, 1925–1927. https://doi.org/10.1093/bioinformatics/ btz848
19. Kang, D. D., Li, F., Kirton, E., Thomas, A., Egan, R., An, H., Wang, Z. (2019). MetaBAT 2:an adaptive binning algorithm for robust and efficient genome reconstruction from metagenome assemblies. *PeerJ.*, 7, e7359. https://doi.org/10.7287/peerj. preprints.27522v1
20. Koonin, E. V., Makarova, K. S., Wolf, Y. I., Krupovic, M. (2020). Evolutionary entanglement of mobile genetic elements and host defence systems: guns for hire. *Nat. Rev. Genet.*, 21, 119–131. https://doi. org/10.1038/s41576-019-0172-9
21. Meziti, A., Rodriguez-R.L.M., Hatt, J. K., Peña-Gonzalez, A., Levy, K., Konstantinidis, K. T. (2021). The reliability of metagenome-assembled genomes (MAGs) in representing natural populations: Insights from comparing MAGs against isolate genomes derived from the same fecal sample. *Appl. Environ. Microbiol.*, 87, 02593–20. https://doi.org/10.1128/AEM.02593-20
22. Milewska, K., Krause, K., Szalewska-Pałasz, A. (2020). The stringent response of marine bacteria–assessment of (p) ppGpp accumulation upon stress conditions. *J. Appl. Genet.*, 6, 123–130. https://doi. org/10.1007/s13353-019-00531-w
23. Tozzi, A., Ahmad, M. Z., Peters, J. F. (2020). Neural computing in four spatial dimensions. *Neurodyn.*
24. Ozerov, M. Y., Flajshans, M., Noreikiene, K., Vasemägi, A., Gross, R., Flajšhans, M., Noreikiene, K., ..., Gross, R. (2020). Draft genome assembly of the freshwater apex predator wels catfish (*Silurus glanis*)

using linked-read sequencing. *G3- Genes Genom Genet*., 10, 3897–3906. https://doi.org/10.1534/g3.120.401711
25. Di Concilio, A., Guadagni, C., Peters, J. F., Ramanna, S. (2018). Descriptive proximities, properties and interplay between classical proximities and overlap. *Comp. Sci.*, 12, 91–106. https://doi.org/10.1007/s11786-017-0328-y
26. Peters, J. F. (2020). Computational Geometry, Topology and Physics of Digital Images with Applications. Shape Complexes, Optical Vortex Nerves and Proximities. *Springer Nature: Cham, Switzerland,* xxv+440.
27. Barkaszi, I., Takács, E., Czigler, I., Balázs, L. (2016). Extreme environment effects on cognitive functions: a longitudinal study in high altitude in Antarctica. *Hum. Neurosci*., 10, 331. https://doi.org/10.3389/fnhum.2016.00331
28. de Arcangelis, L., Herrmann, H. J. (2010). Learning as a phenomenon occurring in a critical state. *Natl. Acad. Sci. USA*, 107, 3977–3981.
29. Setubal, J. C.(2021). Metagenome-assembled genomes: concepts, analogies, and challenges. *Biophys. Rev*., 13(6), 905–909. https://doi.org/10.1007/s12551-021-00865-y
30. Muhammad Faisal Shahzad, Awudu Abdulai. (2020). Adaptation to extreme weather conditions and farm performance in rural Pakistan. *Agricultural Systems*, 180, 102772. https://doi.org/10.1016/j.agsy.2019.102772.
31. Cunha, C. E. X., Oliveira, A. F., Dantas, G. F. G., Castro, L.R., de Omena, V., Jucá, J., Vieira, G. C. F., Ribeiro, M. V. M. R. (2021). Neuropsychiatric aspects of the space missions: scientific overview of the last 15 years. *Physiol. Med. Rehabil. J.,* 6 (1), 4-9. https://doi.org/10.15406/ipmrj.2021.06.00270
32. Badran, B. W., Caulfield, K. A., Cox, C., Lopez, J. W., Borckardt, J. J., DeVries, W. H., Summers, P., Kerns, S., Hanlon, C. A., McTeague, L. M., George, M. S., Roberts, D. R. (2020). Brain stimulation in zero gravity: transcranial magnetic stimulation (TMS) motor threshold decreases during zero gravity induced by parabolic flight. *NPJ Microgravity.,* 6, 26. https://doi.org/1038/s41526-020-00116-6
33. Bloomberg, J., Reschke, M., Clément, G., Mulavara, A., Taylor, L. C. (2015). Evidence Report: Risk of Impaired Control of Spacecraft/Associated Systems and Decreased Mobility Due to Vestibular/Sensorimotor Alterations Associated with Space flight. *NASA Johnson Space Center.*
34. Bloomberg, J. J., Peters, B.T., Cohen, H.S., Mulavara, A.P. (2015). Enhancing astronaut performance using sensorimotor adaptability training. *Syst. Neurosci.,* 9, 129. https://doi.org/10.3389/fnsys.2015.00129.
35. Brainard, G. C., Barger, L. K., Soler, R. R., Hanifin, J. P. (2016). The development of lighting countermeasures for sleep disruption and circadian misalignment during spaceflight. *Opin. Pulm. Med*., 22(6), 535–544. https://doi.org/10.1097/MCP.0000000000000329.
36. Clément G. R., Boyle R .D., George K. A., Nelson G. A., Reschke M. F., Williams T. J., Paloski W. H. (2020). Challenges to the central nervous system during human spaceflight missions to Mars. *Neurophysiol.*, 123, 2037-2063, https://doi.org/10.1152/jn.00476.2019
37. Zubieta-Calleja, G. (2024). Redefining chronic mountain sickness: insights from high-altitude research and clinical experience. *Medical Review,* 5(1), 44–65. https://doi.org/10.1515/mr-2024-0036
38. Zubieta-Calleja, G., Zubieta-DeUrioste, N. (2022). High Altitude Pulmonary Edema, High Altitude Cerebral Edema, and Acute Mountain Sickness: an enhanced opinion from the High Andes — La Paz, Bolivia 3,500 m. *Reviews on Environmental Health,* 38(2), 327–338. https://doi.org/10.1515/reveh-2021-0172
39. Zubieta-Calleja, G., Zubieta-DeUrioste, N. (2021). The oxygen transport triad in high-altitude pulmonary edema: a perspective from the high Andes. *Int. J. Environ. Res. Publ. Health,* 18, 7619. https://doi.org/10.3390/ijerph18147619
40. Beloshitsky P. V. Chronicle of biomedical research in Elbrus region (1929 — 2006). (2014). *Ukrainian Academy of Sciences*, 550 p. (In Ukrainian). URL: https://www.dovidnyk.in.ua/directories/business_kyiv/id/69790
41. Ulloa, N. A., Cook, J. (2025). *Altitude-Induced Pulmonary Hypertension.* StatPearls Publishing: Treasure Island, FL, USA. https://www.ncbi.nlm.nih.gov/books/NBK555925/
42. Szymczak, R. K., Marosz, M., Grzywacz, T., Sawicka, M., Naczyk, M. (2021). Death Zone Weather Extremes Mountaineers Have Experienced in Successful Ascents. *Front. Physiol.*, 12, 998. https://doi.org/10.3389/fphys.2021.696335
43. Richalet, J. P. (2021). *Adaption to chronic hypoxaemia by populations living at high altitude. I*n Revue des Maladies Respiratoires; Elsevier Masson s.r.l. Issy-les-Moulineaux: Paris, France, pp. 395–403 https://doi.org/10.1016/j.rmr.2020.11.007
44. Beloshitsky, P. V., Baraboy, V. A., Krasyuk, A. N., Korkach, V. I., Torbin, V. F. (1996). *Postradiation rehabilitation in mountain conditions*. Kyiv. 230 p. (In Ukrainian).
45. Serebrovskaya, T. V., Karaban, I. N., Kolesnikova,E.E.,Mishunina,T.M.,Swanson,R.J., Beloshitsky, P. V., Ilyin, V. N., ..., Kuzmins-

kaya, L. A. (2000). Geriatric Men at Altitude: Hypoxic Ventilatory Sensitivity and Blood Dopamine Changes. *Respiration*, 67 (3), 253–260. https://doi.org/10.1159/000029507

46. Arias-Reyes, C., Zubieta-DeUrioste, N., Poma-Machicao, L., Aliaga-Raduan, F., Carvajal-Rodriguez, F., Dutschmann, M., …, Soliz, J. (2020). Does the pathogenesis of SARS-CoV-2 virus decrease at high-altitude? *Respiratory Physiology & Neurobiology*, 277, 103443. https://doi.org/10.1016/j.resp.2020.103443
47. Zubieta-Calleja, G., Zubieta-DeUrioste, N. (2021). Acute Mountain Sickness, High Altitude Pulmonary Edema, and High Altitude Cerebral Edema: A view from the High Andes. *Respir Physiol. Neurobiol.,* 287, 103628. https://doi.org/10.1016/j.resp.2021.103628
48. Onopchuk, Yu. M., Misyura A. G. (2008) Methods of the mathematical modeling and control in theoretical studies and solution of applied problems of medicine and physiology. *Sport. Meditsyna*, 1, 181–188.
49. Beloshitsky, P. V., Onopchuk, Yu. M., Aralova, N.I., Semchik, T. A. (2004). Mathematic modeling of hypoxic states at heart ischemia. *Physiol. J*., 50(3), 139–143.
50. Beloshitsky, P. V., Onopchuk, Yu. M., Aralova, N. I. (2003). Mathematical methods for the investigation of the problem of organism functioning reliability at extreme high mountains conditions. *Physiol. J*., 49(3), 47–54.
51. Archer, S. L., Sharp, W. W., Weir, E. K. (2020). Differentiating COVID-19 Pneumonia from Acute Respiratory Distress Syndrome and High Altitude Pulmonary Edema: Therapeutic Implications. *Circulation*. 142(2). https://doi.org/10.1161/CIRCULATIONAHA.120.047915
52. Luks, A. M., Swenson, E. R. (2020). COVID-19 Lung Injury and High Altitude Pulmonary Edema: A False Equation with Dangerous Implications. *Ann. Am. Thorac. Soc*. https://doi.org/10.1513/AnnalsATS.202004-327CME.
53. Strapazzon, G., Hilty, M. P., Bouzat, P., Pratali, L., Brugger, H., Rauch, S. (2020). To compare the incomparable: COVID-19 pneumonia and high-altitude disease. *Eur. Respir. J*. https://doi.org/10.1183/13993003.01362-2020
54. Herrmann, J., Mori, V., Bates, J. H. T., Suki, B. (2020). Modeling lung perfusion abnormalities to explain early COVID-19 hypoxemia. *Nat. Commun.,* 11, 1–9. https://www.nature.com/articles/s41467-020-18672-6
55. Ren, L. L., Wang, Y. M., Wu, Z. Q., Xiang, Z. C., Guo, L., Xu, T., Jiang, Y. Z., …, Wang, J.W. (2020). Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. *Chin. Med. J*. https://doi.org/10.1097/CM9.0000000000000722.
56. Van de Ville, D., Britz, J., Michel, C. M. (2020). EEG microstate sequences in healthy humans at rest reveal scale-free dynamics. *Natl. Acad. Sci. USA*, 107, 18179–18184.
57. Barger, L. K., Sullivan, J. P., Lockley, S. W., Czeisler, C. A. (2021). Exposure to short wavelength-enriched white light and exercise improves alertness and performance in operational NASA flight controllers working overnight shifts. *Occup. Environ. Med.* 2021, 63(2), 111–118, https://doi.org/10.1097/JOM.0000000000002054.
58. Brasher, K. S., Sparshott, K. F., Weir, A. B., Day, A. J., Bridger, R. S. (2021). Two-year follow-up study of stressors and occupational stress in submariners. *Med.,* 62 (7), 563-565. https://doi.org/10.1093/occmed/kqs104.
59. Chariker, L., Shapley, R., Young, L.-S. (2018). Rhythm and Synchrony in a Cortical Network Model. *J. Neurosci*., 38, 8621–8634. https://doi.org/10.1523/JNEUROSCI.0675-18.2018
60. Bartone, P. T., Krueger, G. P., Bartone, G. V. (2018). Individual differences in adaptability to isolated, confined, and extreme environments. *Med. Hum. Perform*., 89 (6), 536–546. https://doi.org/10.3357/AMHP.4951.2018
61. Angélil, O., Stone, D., Wehner, M., Paciorek, C. J., Krishnan, H., Collins, W. (2017). An independent assessment of anthropogenic attribution statements for recent extreme temperature and rainfall events. *J. Clim*., 30, 5–16. https://doi.org/10.1175/JCLI-D-16-0077.1.
62. Balza, U., Baldi, R., Rodríguez-Planes, L., Ojeda, R, Schiavini, A. (2023). Scientific evidence does not support the translocation of guanacos in Argentina. *Conserv. Sci. Pract*., 5(11), e13031. https://doi.org/10.1111/csp2.13031.
63. Diaz-Maroto, P., Rey-Iglesia, A., Cartajena, I., Núñez, L., Westbury, M.V., Varas, V., Moraga, M., …, Hansen, J. (2021). Ancient DNA reveals the lost domestication history of South American camelids in Northern Chile and across the Andes. *eLife*, 10, e63390. https://doi.org/10.7554/eLife.63390.
64. Flores, C., Lichtenstein, G., Schiavini, A. (2023). Human–wildlife conflicts in Patagonia: ranchers' perceptions of guanaco Lama guanicoe abundance. *Oryx*, 57(5), 615–625. https://doi.org/10.1017/S0030605322001508.
65. Iranzo, E. C., Smith, C., Moraga, C. A., Radic-Schilling, S., Corti, P. (2022). Patterns of guanaco distribution and microhabitat use in Tierra del Fuego: from protected to sheep ranching areas. *Acta Oecol*., 116, 103853. https://doi.org/10.1016/j.actao.2022.103853.
66. Mesas, A., Cuéllar-Soto, E., Romero, K., Zegers, T., Varas, V., González, B. A., Johnson, W. E., Marín, J. C. (2021). Assessing patterns of genetic diversity and connectivity among guanacos (Lama guanicoe) in the Bolivian Chaco: implications for designing management strategies. *Stud. Neotrop. Fau-*

na Environ., 58(1), 94–103 https://doi.org/10.1080/01650521.2021.1914294.
67. Mesas, A., Baldi, R., González, B. A., Burgi, V., Chávez, A., Johnson, W. E., Marín, J. C. (2021). Past and recent effects of livestock activity on the genetic diversity and population structure of native guanaco populations of arid patagonia. *Animals (Basel)*, 11(5), 1218 . https://doi.org/10.3390/ani11051218.
68. Merchant, N. N., Ivanova, A., Hart, D. W., García, C., Bennett, N.C., Portugal, S. J., Faulkes, C. G. (2024). Patterns of Genetic Diversity and Gene Flow Associated With an Aridity Gradient in Populations of Common Mole-rats, Cryptomys hottentotus. *Genome Biology and Evolution*, 16(7), evae144. https://doi.org/10.1093/gbe/evae144
69. Herrera-Álvarez, S., Karlsson, E., Ryder, O. A., Lindblad-Toh, K., Crawford, A. J. (2021). How to make a rodent giant: genomic basis and tradeoffs of gigantism in the capybara, the world's largest rodent. *Mol. Biol. Evol.*, 38(5), 1715–1730. https://doi. org/10.1093/molbev/msaa285.
70. Bosi, E., Taviani, E., Avesani, A., Doni, L., Auguste, M., Oliveri, C., Leonessi, M., ..., Vezzulli, L. (2024). Pan-Genome Provides Insights into Vibrio Evolution and Adaptation to Hydrothermal Vents. *Genome Biology and Evolution*, 16(7), evae131. https://doi.org/10.1093/gbe/evae131

ЕФЕКТ ГІПОКСІЇ ЗА ЕКСТРЕМАЛЬНИХ СТРЕСОВИХ УМОВ: ДЕЯКІ ТЕХНОЛОГІЇ ДОСЛІДЖЕНЬ ДЛЯ ПОКРАЩЕННЯ ЗДОРОВ'Я ТА ДОВГОЛІТТЯ

Ключко О.М. [1], *Онопчук Ю.М.*[2], *Лізунов Г.В.*[3], *Lyman K.S.*[4], *Lizunova A.G.*[5]

[1] Державний університет «Київський авіаційний інститут», Україна
[2] Інститут кібернетики ім. В. М. Глушкова НАН, Київ, Україна
[3] Інститут космічних досліджень НАН України, Київ
[4] Washington State University, USA
[5] Luxoft Global Operations GmbH: Zug, CH, USA

E-mail: 2kelenaXX@kai.edu.ua

Вивчення механізмів адаптації до екстремальних факторів середовища (гіпоксії, тощо) є важливою задачею, яку також необхідно аналізувати й за віковим аспктом.

Мета. Опис деяких технологій багаторічних досліджень та їхні результати щодо вікового аспекту за екстремальних умов (гіпоксія тощо), застосування цих технологій для покращення виживання організмів за стресових умов, лікування, реабілітації та довголіття.

Методи. Проаналізовано дані численних спостережень щодо змін біометричних показників у порівняльно-віковому аспекті осіб за екстремальних високогірних умов з використанням стандартних методів лабораторного аналізу біоіндикаторів та введенням цифрових показників до баз даних, застосовано математичне, програмне моделювання.

Результати. Розглянуто результати численних багаторічних досліджень дії на організми людей високогірних факторів, які впливають на здоров 'я та довголіття (гіпоксія, радіаційний вплив тощо). Наведено дані спостережень та вимірювань різних фізіологічних характеристик людей у порівняльно-віковому аспекті. Описано особливості впливу високогірних факторів на біологічні організми, їх довголіття, деякі проблеми фізіології старіння та гіпоксичних станів, результати обстеження ветеранів-скелелазів щодо адаптації до гіпоксибарії (активна поступова (ступінчаста) адаптація, чисельний метод гіпокситерапії та комбінації методів та ін.). Продемонстровано результати математичного моделювання розвитку ішемічної хвороби серця у зв'язку з вивченням проблем гіпоксії та інформацію щодо розробленої технології та лікувальні методики.

Висновок. Під час вивчення вікових аспектів адаптації до гіпоксибарії встановлено, що адаптація підвищує працездатність організму, його стійкість, захищає від передчасного старіння та сприяє довголіттю. З віком здатність організму адаптуватися до гіпоксії знижується, але не втрачається повністю — літні люди можуть адаптуватися до 5000 м р.м. Наведено результати обстеження ветеранів гірських сходжень щодо адаптації до гіпоксибарії із застосуванням ряду розроблених технологій. Продемонстровано результати математичного моделювання. Отримані результати є важливими для подальшого розроблення технологій виживання людей різного віку за екстремальних стресових умов, їх лікування й реабілітації.

Ключові слова: довголіття, гіпоксія, адаптація, екстремальні стресові умови, числові показники фізіологічних функцій, математичне моделювання.