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HEMATOLOGICAL PROFILE OF ALPHA-TOCOPHEROL PRE-TREATED RABBITS AT REPEATED HYPOXIC EXPOSURE

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The article discusses the importance and necessity of studying blood system one of the most significant functional systems of the body during hypoxia. Under conditions of repetitive (within 3 days) acute hypobaric hypoxia, shifts in the hematological parameters of rabbits were revealed. The study of physiological mechanisms and, especially, the use of preventive measures such as antioxidants can ensure the safe functioning of a body in unfavorable hypoxic conditions. The article considers the use of alpha-tocopherol as a strong immunomodulator to mitigate negative changes in the hematological system caused by hypoxia.

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Keywords: hematological indices, hypobaric hypoxia, reoxygenation.

Introduction. Clinical and experimental study of the effect of hypoxia as a life-threatening factor has now become one of the urgent tasks of medical and biological significance. Lack of oxygen in the atmospheric air and various diseases cause several disorders in the body. The study of their physiological mechanisms is one of the important modern theoretical and practical areas of biology.

The pathological condition caused by hypoxia is determined by impaired oxygenation and tissue assimilation, resulting in irreversible changes in the organism. A growing body of evidence implicates that severe hypoxia plays a critical role in the pathogenesis of major causes of mortality including cancer, myocardial ischemia, metabolic diseases, chronic heart and kidney, and reproductive diseases. Exposure to acute hypoxia leads to deviations in hematological and biochemical parameters, which indicates acute failure and often irreversible disruption of the functioning of vital organs such as kidneys, liver, heart, respiration, etc. Central nervous and blood systems, heart muscle, kidney, and liver tissue are most sensitive to lack of oxygen [1–8]. These changes are often due to violations of the permeability of the cell membranes of these systems [6, 9].

To reduce the negative effect of hypoxia, pharmacological methods and means are used, which enhance the supply of oxygen to the body and improve oxygen assimilation, decreasing the oxygen demand in organs and tissues. Antioxidants and antihypoxants aimed at suppressing free radical oxidation of membrane lipids have

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recently become widespread and have a direct benefit [7, 10 –13]. Recently, antioxidant agents have been widely used to provide a broad spectrum of action while maintaining long-term effects. The latter is aimed at free radical oxidation of membrane lipids and, as a result, hypoxic tissue damage [7, 11, 13, 14]. Antioxidants and antihypoxants contribute to more economical consumption and absorption of oxygen in tissues and increase the body's resistance to oxygen deficiency affecting the processes of biological oxidation [7, 11].

The latter increases the body's resistance to oxygen deficiency and contributes to the most "economical" consumption and absorption of oxygen in the tissues.

The anti-hypoxic effect is associated with the presence of biologically active substances in them, such as flavonoids, carotenoids, and components of the citric acid cycle, which, together with vitamins and trace elements (selenium, zinc, iron, copper, magnesium, etc.), interfere with bioenergetic processes: increasing the body's resistance to oxygen deficiency [2, 8].

Based on the literature data, alpha-tocopherol, as a strong immunomodulator, is considered a universal protector of cell membranes from oxidative damage. It is embedded in the membrane in such a way that it prevents oxygen from contacting the unsaturated lipids of the membranes, which protects biomembranes from peroxidative damage. The membrane-stabilizing action of tocopherol is manifested by its ability to protect protein groups of the membrane from oxidation [9, 11, 12, 14, 15].

Materials and Methods. This study focuses on the reveal of changes in some blood hematological indices after 3-day repeated acute hypoxia, as well as the effectiveness of the use of alpha-tocopherol to mitigate the observed deviations.

Experiments were carried out on 10 rabbits of 2.2–2.5 *kg* in weight and stored and fed in equal conditions. Research has been done in two groups of animals: the control group (5 rabbits), which includes tocopherol untreated rabbits, and the experimental group with tocopherol pre-treated animals (5 rabbits). In the first stage, recordings of hematological parameters in both groups of animals were carried out before hypoxia under normal conditions of atmospheric pressure (P_{O_2} = 160 *mm* Hg, 21%), then in the dynamics of oxygen deficiency – 30 *min* after the exposure, 3 *h*, and 10 days later. In the second phase, the effectiveness of alpha-tocopherol treatment on hypoxia-related changes in the same diagram has been studied.

The hypobaric hypoxia model was used for experiments. During the experiment, the velocity of compression and decompression in the hypobaric chamber was 15–20 *m*/*s*. The animal is "raised" at an "altitude" of 5000 *m* (P_{O_2} = 98–85 *mm* Hg, 12.7–11.0%) and stored for 3 days per 30 *min*. Before the experiment, an animal was fixed at the experimental desk and kept for 30 *min* to adjust to the fixed state. Blood samples were taken from rabbits in the way of cardio-punction.

Hematological indices have been recorded using the semiautomatic analyzer Hemalyzer 3, which recorded the following parameters: white blood cells (WBC), lymphocyte count (LIM), monocyte count (MID), granulocyte count (GRA), red blood cells (RBC), hematocrit, hemoglobin (HGB), mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), red cell distribution width (RDW), platelet count (PLT). Alpha-tocopherol was purchased from the "Sigma Pharmaceuticals" company. It was given to animals per os

(400 μL/day) for 12 days until the start of the study [12]. The reliability of the recorded deviations in the research was determined by the Steward statistical method, at least at $p < 0.05$.

Experiments were performed following the Helsinki Declaration on the Humane Treatment of Animals.

Experimental Part.

Results. The study of the qualitative and quantitative contents of blood cells after reoxygenation showed significant changes. Thus, immediately after exposure to hypoxia, WBC content was 14.1±1.8 ($\times 10^9/L$), which is 15% higher than in the norm 12.3 ± 1.08 ($\times 10^9/L$) ($p < 0.004$). Moreover, a certain increase in the level of lymphocytes and monocytes was observed, making 5.2 ± 0.9 and 2.1 ± 1.8 ($\times 10^9/L$) ($p < 0.005$ and 0.000), while in the norm it was 3.88 ± 1.52 and 1.2 ± 0.54 ($\times 10^9/L$), i.e. exceeding baseline data by 34% and 75%, correspondingly. Changes in the number of granular leukocytes were not reliable, consisting of 6.84 ± 2.6 ($\times 10^9/L$) (the norm was 7.2 ± 1.4 ($\times 10^9/L$)) (Tab. 1).

Table 1

Effect of alpha-tocopherol on changes in rabbit's peripheral blood parameters under conditions of 3-day repeated acute hypoxia

Test	WBC, $\times 10^9/L$	LYM, $\times 10^9/L$	MID, $\times 10^9/L$	GRA, $\times 10^9/L$	RBC, $\times 10^{12}/L$	HGB, g/dL
I, norm	12.3 ± 1.1	3.88 ± 1.52	1.2 ± 0.5	7.2 ± 1.4	5.55 ± 1.3	12.1 ± 1.1
II, norm	12.6 ± 1.1	3.9 ± 1.54	1.6 ± 0.5	7.1 ± 1.7	5.5 ± 1.1	12.4 ± 0.9
I, after hypoxia	14.1 ± 1.8*	5.2 ± 0.9*	2.1 ± 1.8*	6.84 ± 2.6	5.52 ± 1.3	11.9 ± 0.3
II, after hypoxia	12.9 ± 1.2	4.3 ± 0.4	1.8 ± 0.6	7.0 ± 1.3	5.59 ± 0.8	12.3 ± 0.7
I, after 3 *h*	13.4 ± 0.2	5.11 ± 0.2*	2.2 ± 1.1*	6.2 ± 1.4*	4.91 ± 1.3	10.8 ± 0.2*
II, after 3 *h*	12.8 ±1.3	4.2 ± 0.1	1.8 ± 1.0*	7.1 ± 2.2*	5.4 ± 0.7	12.1 ± 0.3
I, 10 days later	12.2 ± 0.5	3.7 ± 0.71	1.4 ± 0.7	5.02 ± 0.83*	4.2 ± 0.3*	8.3 ± 0.7*
II, 10 days later	12.3 ± 1.3	4.1 ± 1.2*	1.3 ± 0.3	6.9 ± 0.6	5.0 ± 0.5	11.2 ± 1.0

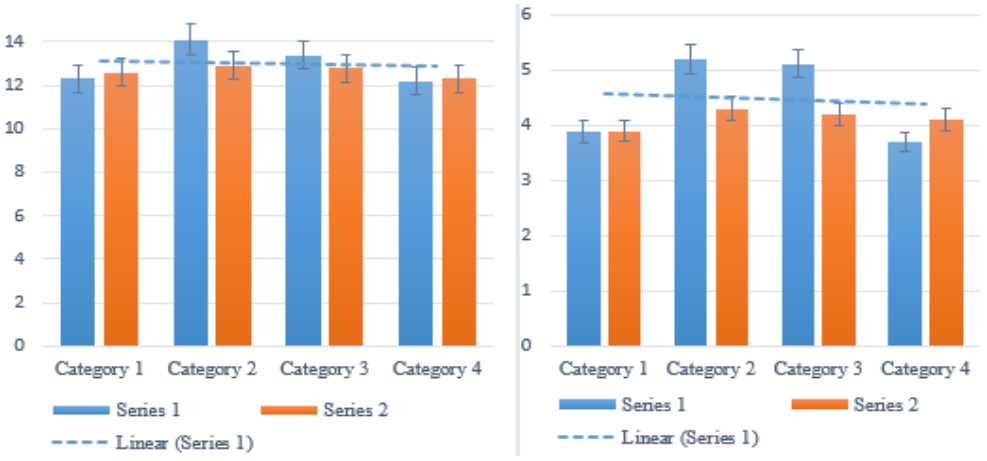
Note: I – untreated animals; II – tocopherol pre-treated animals; * – specifies the degree of accuracy of the changes at least at $p < 0.05$.

Three hours after hypoxic exposure, no essential changes in the absolute number of leukocytes compared to the norm were recorded. An even higher increase in the content of lymphocytes and monocytes was observed, up to 5.11 ± 0.24 and 2.1 ± 1.1 ($\times 10^9/L$) ($p < 0.000$ and $p < 0.05$), correspondingly, which is 32% and 75% more than the norm (Fig. 1.) The number of granular leukocytes decreased by 14% reaching 6.2 ± 1.4 ($\times 10^9/L$) ($p<0.003$) (Tab. 1, Fig. 2).

Total white blood cell counts, as well as absolute numbers of lymphocytes, monocytes, and granulocytes 10 days after exposure to hypoxia were, respectively, 12.2 ± 0.46 ($p < 0.034$), 3.68 ± 0.71, 1.4 ± 0.7($\times 10^9/L$) and 5.02 ± 0.83 ($\times 10^9/L$) ($p < 0.006$) (Fig. 1). The deviations in all WBC investigated parameters in the dynamics of hypoxic influence of tocopherol-treated animals were no reliable.

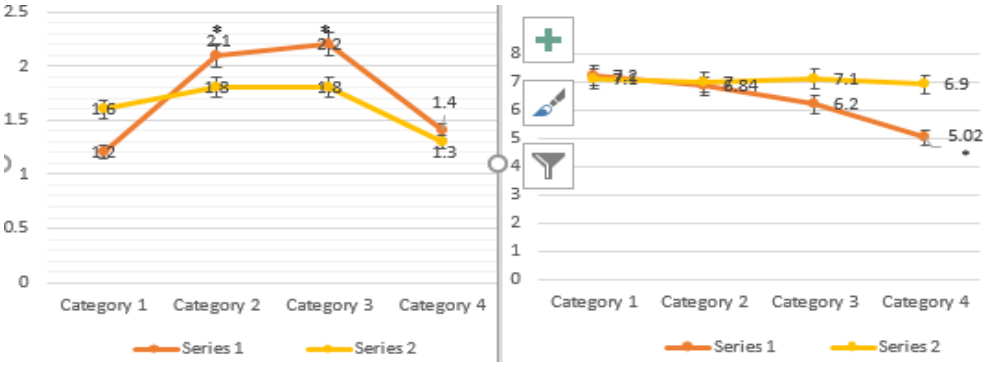
The analysis of deviations of red blood cell indicators showed the following picture. A certain decrease was observed 3 *h* later and after 10 days of hypoxic exposure, compared to the norm by 11.5% and 24%, respectively, making 4.91 ± 1.26 ($\times 10^{12}/L$) and 4.2 ± 0.26 ($\times 10^{12}/L$) ($p < 0.05$) (Tab. 1). Significant changes

in the level of erythrocytes in comparison with the norm were recorded only 10 days after exposure to hypoxia (Fig. 2). No reliable RBC changes in investigated periods of hypoxia compared with initial data occurred in tocopherol-treated animals (Tab. 1, Fig. 3).



WBC, $\times 10^9/L$ LYM, $\times 10^9/L$

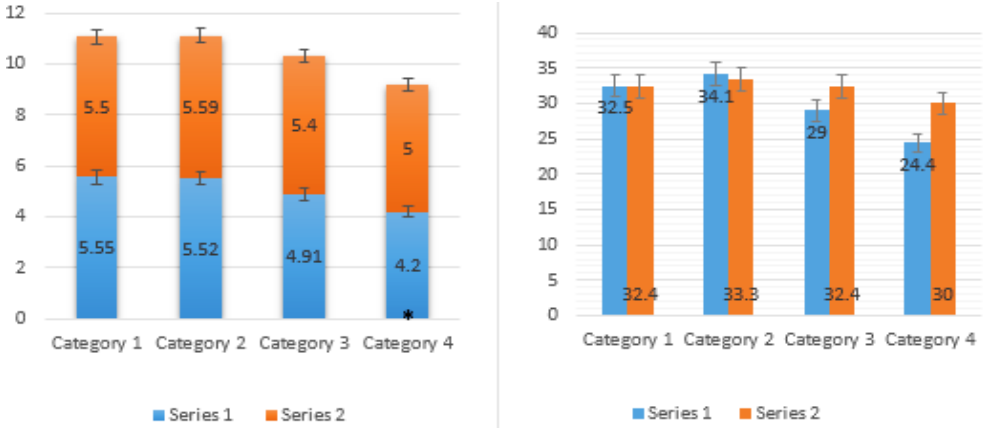
Fig. 1. Effect of alpha-tocopherol on changes of rabbit's white blood cells and lymphocyte count under conditions of 3-day repeated acute hypoxia. Series I – untreated animals; Series II – tocopherol pre-treated animals; Category 1 – norm; Categories 2–4 – 30 *min*, 3 *h*, and 10 days after 3-day repeated hypoxic exposure; * – specifies the degree of accuracy of the changes at least at $p < 0.05$.



MID, $\times 10^9/L$ GRA, $\times 10^9/L$

Fig. 2. Effect of alpha-tocopherol on changes in rabbit's monocyte count and granulocyte count under conditions of 3-day repeated acute hypoxia. The details are the same as in Fig. 1.

A study of hematocrit in untreated animals showed an increase in the index immediately after exposure to hypoxia to $34.1 \pm 1.04\%$ ($p < 0.00$) (normal $32.5 \pm 1.14\%$), which was by 5%. After 3 *h* and 10 days, compared to the background data, the decrease in the HCT consisted of 11% and 25%, respectively. Under the effect of tocopherol, the deviations of the index were not significant (Tab. 2, Fig. 3).



RBC, $\times 10^{12}/L$ HCT, %

Fig. 3. Effect of alpha-tocopherol on changes in rabbit's red blood cell count and hematocrit under conditions of 3-day repeated acute hypoxia. The details are the same as in Fig. 1.

Total HGB, MCH and MCHC were determined under hypoxia. Hypoxia-induced a gradual decrease in total hemoglobin was observed, which was most pronounced 3 *h* after exposure (by 10.7%) and continued until the 10th day (by 31.4%) ($p < 0.0016$ and 0.009) (Tabs. 1 and 2; Fig. 4).

Deviations in MCH were not reliable after exposure to the factor, but a gradual decrease (compared to the norm) was observed until the 10th day (by 9.2%). Examination of the mean corpuscular hemoglobin concentration showed a decrease in the indicator level, especially after 3 *h* of exposure (by 45%), and consisted of 20.3 ± 0.12 *mg/dL* (normal 37.0 ± 0.4 *mg/dL*) ($p < 0.00$). However, on the 10th day of the study, the level of the index approached the baseline (Tab. 2).

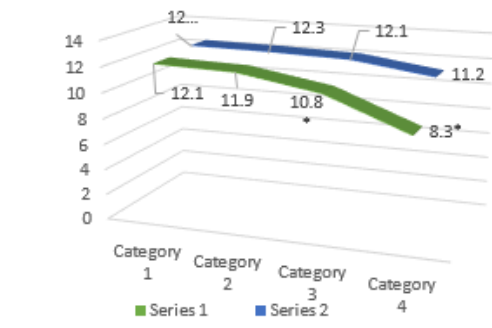
Table 2

Effect of alpha-tocopherol on changes in rabbit's peripheral blood parameters under conditions of acute hypoxia

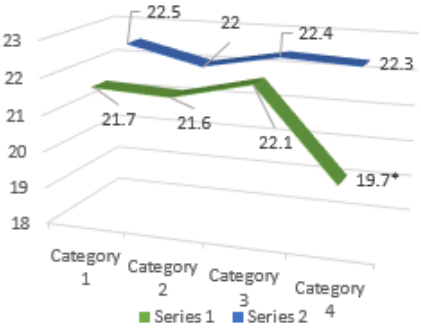
Test	HCT, %	MCV, *fL*	MCH, *pg*	MCHC, *g/dL*	RDW, %	PLT, $\times 10^9/L$
I, norm	32.5 ± 1.1	59.0 ± 1.3	21.7 ± 0.2	37.0 ± 0.4	15.3 ± 0.7	273.0 ± 11.5
II, toc. pre-treated	32.4 ± 1.0	59.0 ± 0.6	22.5 ± 0.3	38.1 ± 0.5	15.4 ± 0.1	279.0 ± 14.4
I, hypoxia 30 *min*	34.1 ± 1.0*	58.0 ± 0.3	21.6 ± 0.2	34.9 ± 0.2	17.0 ± 0.4*	499.0 ± 13.4*
II, hypoxia 30 *min*	33.0 ± 1.0	59.0 ± 0.4	22.0 ± 0.1	37.2 ± 0.6	16.3 ± 0.9	352.0 ± 14.0*
I, 3 *h* later	29.0 ± 1.2*	58.5 ± 1.0	22.1 ± 0.4*	20.3 ± 0.1*	17.3 ± 0.2*	476.0 ± 14.0*
II, 3 *h* later	32.4 ±1.4	59.0 ± 0.4	22.4 ± 0.1	37.3 ± 1.0	16.9 ± 1.2	341.0 ± 15.1*
I, 10 days later	24.4 ± 1.4*	59.0 ± 0.2	19.7 ± 0.1*	34.0 ± 0.1	17.2 ± 0.8*	406.0 ± 12.5*
II, 10 days later	30.0 ± 1.3	60.0 ± 0.1	22.4 ± 0.2	37.3 ± 0.4	16.7 ± 1.1	328.0 ± 12.6*

Note: I – untreated animals; II – tocopherol pre-treated animals; * – specifies the degree of accuracy of the changes at least at $p < 0.05$.

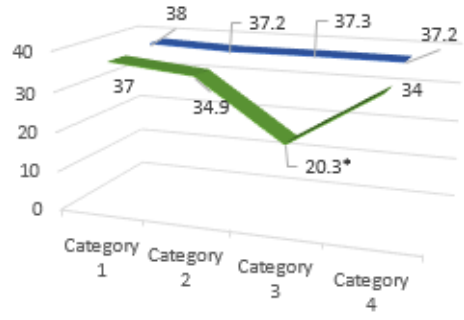
There were no essential changes in all hemoglobin indicators under the conditions of exposure to tocopherol (Fig. 4).



HGB, *g/dL*



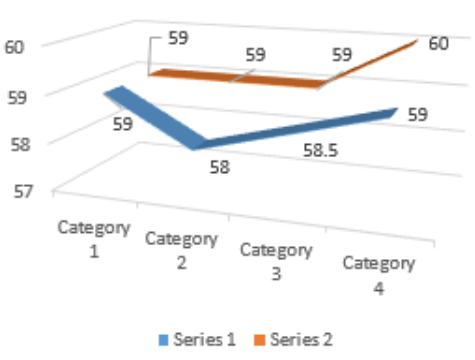
MCH, *pg*



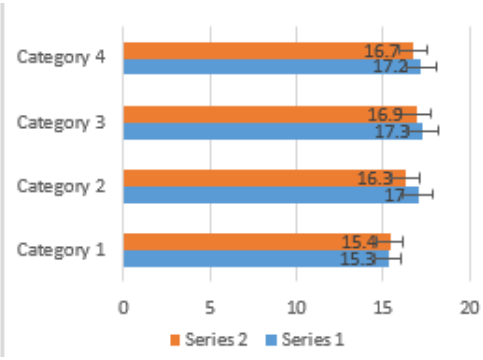
MCHC, *g/dL*

Fig. 4. Effect of alpha-tocopherol on changes in rabbit's total hemoglobin, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration under conditions of 3-day repeated acute hypoxia. The details are the same as in Fig. 1.

Changes in red blood cell mean volume and the heterogeneity index were determined during the specified periods of the factor exposure (Tab. 2; Fig. 5). No significant changes in the average size of erythrocytes were observed in either the normal or the tocopherol pre-treated animals, however an increase in the heterogeneity index was recorded at all time-points of the study (11.1% – immediately after exposure, 13.0% – after 30 *min* and 12% – after 10 days) ($p < 0.01$) (Tab 2; Fig. 5).



MCV, *fL*



RDW, %

Fig. 5. Effect of alpha-tocopherol on changes in rabbit's mean cell volume and red cell distribution width under conditions of 3-day repeated acute hypoxia. The details are the same as in Fig. 1.

Platelets showed quite high reactivity. Immediately after the exposure to hypoxia, the total platelet count increased sharply, reaching 499.0 ± 13.4 ($\times 10^9/L$) ($p < 0.000$), after 3 *h* – 476.0 ± 13.68 ($\times 10^9/L$) ($p < 0.000$), 10 days later – 406.0 ± 12.48 ($\times 10^9/L$) ($p < 0.000$), comparing with the norm (273.0 ± 11.47 ($\times 10^9/L$)). The maximum platelet-reducing effect of tocopherol (25%) was recorded 30 *min* later, and the effect of tocopherol remained the same, reducing the number of platelets by only 11.2% (Tab. 2; Fig. 6).

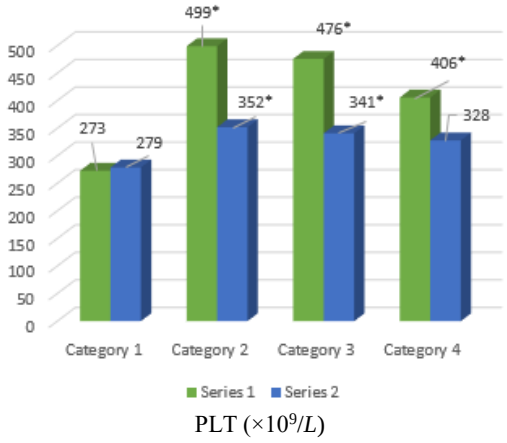


Fig. 6. Effect of alpha-tocopherol on changes in rabbit's platelet count under conditions of 3-day repeated acute hypoxia. The details are the same as in Fig. 1.

Discussion. It is known that hypoxia leads to an insufficient energy supply of cells, as a result of which the vital activity of cells becomes extremely difficult. Methods of experimental hypoxia provide a wide opportunity to search for anti-hypoxic agents in chemical series of different structures.

The results of the experiments undoubtedly indicate the reactivity of blood cells in the body's reactions to general acute hypoxia. The main factor that regulates cell homeostasis is the quantitative density of cells. According to the received data, the effect of acute hypobaric hypoxia leads to a pronounced change in hematological indicators, which coincides with the literature data [15–19]. The increase in the total number of leukocytes and especially in the level of lymphocytes and monocytes in conditions of oxygen deprivation and reoxygenation, even up to the 10^{th} day, is due to hemodynamic disturbances. It should be noted that the maximum changes were observed 3 *h* after exposure to the factor. Leukocytes are characterized by the fact that they actively use oxygen and they constantly generate reactive forms of oxygen, which are necessary for the destruction of pathogens [6, 16].

In the dynamics of the effect of hypoxia, a decrease in the absolute number of red blood cells, hematocrit, and hemoglobin levels was observed, which was most pronounced after 3 *h* of hypoxic exposure. A certain increase was noted in the mean concentration of hemoglobin in the erythrocyte and the levels of heterogeneity indices, the latter indicating the presence of anisocytosis, a large difference between the sizes of the erythrocytes. This fact coincides with the literature data, where it is shown that during various oxidative effects on erythrocytes, hemoglobin oxidation, and transformation (the formation of Heinz bodies) occur, which are accompanied by hem/hemin separation [19]. Exogenous hemin can then be readily incorporated into the membrane, destabilizing it and causing hemolysis.

The analysis of the platelet count showed a reliable increase of the cells, which is considered as an enhanced thrombogenesis factor and an indirect conclusively showing the possibility of development of acute DIC-syndrome during reoxygenation of the organism [17, 20–22]. The structural-functional characteristic of their membranes is also important in the activity of platelets. Its participation in hemostasis presumably depends on the state of the platelet surface. The organs of the cardiovascular and respiratory systems are mainly involved in compensatory reactions aimed at mitigating the effects of hypoxia, as well as the biochemical processes occurring in tissue cells and organ systems due to lack of oxygen. The study of the hematological profile is especially important since compensatory-restorative reactions during hypoxia occur against the background of long-term severe conditions or diseases, and therefore are like persistent changes and deviations from the norm.

Tocopherol suppresses the activity of phospholipase A_2 of lysosomes, which degrades membrane phospholipids. Damage to the lysosomal membrane leads to the release of proteolytic enzymes into the cytosol and to cell lysis [23].

Tocopherol acts not only as an antioxidant, but also as an anti-hypoxant, which is explained by its ability to stabilize the membrane of mitochondria and save oxygen assimilation by cells. Due to the membrane-stabilizing effect of tocopherol, the coupling of oxidative phosphorylation, the generation of ATP and creatine phosphate in mitochondria is enhanced [9, 12, 14, 15, 19, 23]. On the other hand, tocopherol controls heme synthesis, thereby enhancing hemopoiesis, hemoglobin, and myoglobin synthesis.

Conclusion. The use of tocopherol in conditions of 3-day repeated acute hypoxia on blood cells can be considered effective, since, according to the results obtained, it, as a powerful antioxidant and anti-hypoxia agent, led to significant mitigation of deviations caused by the effects of acute hypoxia and reoxygenation in almost all studied indicators and, most likely, contributed to the biological creation and regulation of favorable conditions for oxidation processes.

The findings highlight the importance of antioxidants, in particular alpha-tocopherol, which plays an important preventing role in the cellular response to severe hypoxia, which would be useful for increasing knowledge on this important issue.

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ԱԼՖԱ-ՏՈԿՈՖԵՐՈԼ ՆԱԽԱՊԵՍ ԸՆԴՈՒՆԱԾ ՃԱԳԱՐՆԵՐԻ ԱՐՅՈՒՆԱԲԱՆԱԿԱՆ ՊԱՏԿԵՐԸ ՍՈՒՐ ՀԻՊՕՔՍԻԱՅԻ ԲԱԶՄԱԿԻ ԱԶԴԵՑՈՒԹՅԱՆ ՊԱՅՄԱՆՆԵՐՈՒՄ

Հոդվածում քննարկվում է արյան համակարգի ուսումնասիրության դերն ու անհրաժեշտությունը՝ որպես հիպոքսիայի ժամանակ օրգանիզմի կարևորագույն ֆունկցիոնալ համակարգերից մեկը: Հիպոբարիկ սուր թթվածնաքաղցի բազմակի (3-օրյա) ազդեցության պայմաններում բացահայտվել են ճագարների արյունաբանական ցուցանիշների էական փոփոխություններ: Ֆիզիոլոգիական մեխանիզմների ուսումնասիրությունը և, հատկապես կանխարգելիչ միջոցների, այդ թվում՝ հակաօքսիդանտների կիրառումը, հնարավորություն է տալիս ապահովել մարմնի անվտանգ գործունեությունը անբարենպաստ հիպօքսիկ պայմաններում: Հոդվածում քննարկվում է α-տոկոֆերոլի օգտագործումը, որպես ուժեղ իմունոմոդուլատոր՝ արյան համակարգում հիպօքսիայի ազդեցությամբ առաջացած բացասական փոփոխությունները մեղմելու համար:

С. Г. СААКЯН

ГЕМАТОЛОГИЧЕСКИЙ ПРОФИЛЬ КРОЛИКОВ, ПРЕДВАРИТЕЛЬНО ОБРАБОТАННЫХ АЛЬФА-ТОКОФЕРОЛОМ, ПРИ МНОГОКРАТНОМ ГИПОКСИЧЕСКОМ ВОЗДЕЙСТВИИ

В статье обсуждается роль и необходимость изучения системы крови как одной из важнейших функциональных систем организма при гипоксии. В условиях повторяющейся (в течение 3-х дней) острой гипобарической гипоксии выявлены сдвиги гематологических показателей кроликов, изучение физиологических механизмов которых, а также применение профилактических мер, в частности антиоксидантов, позволяет обеспечить безопасное функционирование организма в неблагоприятных гипоксических условиях. В статье рассмотрено применение α-токоферола как сильного иммуномодулятора с целью смягчения возможных негативных изменений в гематологической системе, вызванных гипоксией.