

INDICATORS OF THE ELEMENT RANGE OF RAT'S BLOOD IN TERM ARTIFICIAL HYPOBYOSIS

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Abstract

The promising method of anesthesia and anesthesia is the state of artificial hypobiosis. Hypercapnia is a prerequisite for creating an artificial carbon dioxide hypobiosis, along with hypoxia and hypothermia. Adhering to the conditions under which the state of artificial carbon dioxide hypobiosis is created, animals reduce the level and intensity of metabolic processes both in the body as a whole and in separate organs. In order to investigate the safety of the hypobiological state and evaluate its applicability in clinical practice, it is necessary to investigate the functional characteristics of the blood. One of the most important indicators is the change of elemental composition. After all, the set of micro-and macro-elements is involved in the enzymatic reactions of the organism, its metabolic processes.

Therefore, the aim of the study was to investigate the elemental changes in the blood of rats for artificial hypobiosis. In experiments, white non-breeding male rats weighing 180–200 g were used, which were maintained under standard vivarium conditions. Animals were divided into 2 groups: control and experimental (the state of artificial hypobiosis). Each group had 7 animals. Measurement of the content of macro- and micronutrients was carried out using a mass spectrometric ionization method in an inductively coupled plasma on an IRIS Interband II XSP device manufactured by Thermo Scientific, USA. The results of the study were processed and presented using the methods of statistical analysis, namely: the method of descriptive statistics; Shapiro-Wielka's criterion for choosing a statistical criterion for comparing groups; Student's criterion; Mann-Whitney's criterion. Results of evaluation of dynamics in the experimental (hypobiotic) group using the criterion of sign-marks of Wilcoxon. As a result of the studies, increased levels of Sodium, Ferrum, Calcium were observed, while the content of Nickel and Barium reduced. The results of the analysis of the dynamics of blood parameters in the experimental group by the methods of descriptive statistics showed significant changes in such elements as: Potassium, Sodium, Ferrum, Calcium, Magnesium. The heterogeneity of the results of the experimental and control groups according to the Mann-Whitney criterion was demonstrated in the following elements: Potassium, Sodium, Ferrum, Calcium, Chromium, Strontium.

Keywords: hypobiosis, hypercapnia, hypoxia, blood, macroelements, microelements.

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1. Introduction

The state of artificial hypobiosis is a common concern among scientists, because there is a rather large prospect of using its model in medicine, veterinary and livestock as a way of general anesthesia, canning of biological material, therapeutic method, etc. [1]. The mechanic of biochemical transformations, which undergoes the transition of organisms to the hypometabolic level of vital activity, remains unclear. Also, if it possible to apply this method in clinical practice. Previously, researchers have already studied the biochemical features of this condition in cardiomyocytes, name-

ly, the indicators of oxidative phosphorylation. Analyzing the obtained results, it should be noted that under the conditions of artificial hypobiosis a partial decoupling of oxidative phosphorylation processes in mitochondria of cardiomyocytes of rats is observed for the use of substrate – malate and is not observed for the use of succinate [2]. Therefore, it is possible to suppose the suppression of the functional activity of the first link of the oxidation and phosphorylation of the respiratory chain, taking into account that at the same time no changes in the functional activity of the final link of the conjugation were detected. The obtained results confirm the possibility of endogenous regulation of hypobiosis by modifying the functional activity of individual parts of the respiratory chain of mitochondria, for example, as with the use of inhibitors of the respiratory chain [3]. In addition, the detected increase in succinate-CoQ-oxidoreductase activity of membrane preparations indicates the possibility of switching cardiomyocytes to succinate type of tissue respiration, which results in maintenance of the necessary energy supply, since the heart should function in sufficient mode, including for hypobiosis. Perhaps this also results in the absence of significant changes in ATP-hydrolase activity, which indicates the adequacy of energy formation under such conditions. Partial inhibition of oxidative phosphorylation in cardiomyocytes may be due not to the transition of mitochondria to heat supply [4], but with a decrease in the frequency of cardiac contractions and, correspondingly, to a decrease in the need for ATP.

However, changes in mineral metabolism occurring in the state of artificial hypobiosis have not yet been investigated. A detailed study of physiological changes in the main organs of the liver, heart and blood of rats will allow to assess the risks of using this method in clinical practice. Therefore, the purpose of the study was to investigate the elemental blood composition of rats for artificial hypobiosis. As a result of the studies was observed the growth of such elements as: Sodium, Ferrum, Calcium, and the decrease of Nickel, Barium. In the state of artificial hypobiosis in animals, there was a decrease in the frequency of cardiac contractions, a decrease in the intensity of respiration, lack of mobility of the organism.

2. Aim of research

Show elemental changes in the blood of rats in term of artificial hypobiosis. These indicators will make it possible to assess the safety of artificially created hypobiotic conditions and to evaluate the possibility of using this method in medical practice.

3. Materials and methods

The study was conducted on the basis of the State University “Institute of Pharmacology and Toxicology of the National Academy of Medical Sciences of Ukraine”, 2016–2017 years.

In experiments, white non-breeding male rats weighing 180-200 g were used, which were maintained under standard vivarium conditions. Animals were divided into 2 groups: control and experimental (the state of artificial hypobiosis). Each group had 7 animals.

All studies were conducted in accordance with the requirements of the “European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes” (Strasbourg, France, 1985), on the general ethical principles of experiments on animals adopted by the First National Congress of Bioethics in Ukraine (2001) [5].

The results of the study were processed and presented using the following statistical analysis methods, namely:

- method of descriptive statistics;
- results of check the normality of the data distribution using the Shapiro-Wielka criterion for choosing a statistical criterion for comparing groups;
- results of comparison of the experimental and control groups using Student’s criterion;
- results of comparison of experimental and control groups using the Mann-Whitney criterion;
- results of the estimation of dynamics in the experimental (hypopoietic) group using the criterion of Wilcoxon signed-rank test [6].

Animals were placed in a hermetically sealed chamber, which had volume 3 dm³ at ambient temperature 3–4 °C for introduction into the state of artificial hypobiosis. During the stay

of animals in the chamber under such conditions, both the temperature and the composition of the gaseous medium changed: hypercapnia (increased carbon dioxide content) and hypoxia (the level of oxygen decreased). After 3–3.5 hours, depending on the individual characteristics of the animals, there was a decrease in rectal temperature from 37 °C to 16 °C; reduction of heart rate from 380 to 80 beats per minute; the animals completely lost their mobility, the reaction to the pain stimulus and disappeared reflex to the position, indicating the development of the state of artificial hypobiosis [7].

Blood was taken from the heart's aorta of the rat. Sample mineralization and preparation of calibration solutions were carried out using nitric acid. Measurements of the content of macro- and micronutrients were performed by mass spectrometric ionisation in inductively coupled plasma on the IRIS Interband II XSP device, manufactured by Thermo Scientific, USA [8].

4. Results

As a result of the research, it was found that in the state of artificial hypobiosis the content of such elements increases: Sodium, Ferrum, Calcium, but the content of Nickel and Barium decreases, as shown in **Table 1**.

Also, it is enough to note that after exiting from the state of artificial hypobiosis, increased excitability of rats was observed. This is due to the fact that after hypobiotic conditions, which reduces the vital functions of the organism: reduced heart rate, suppressed metabolic processes of the body, there is a complete loss of mobility of the organism.

Table 1

Results of comparative analysis of blood of rats of control and experimental groups by methods of descriptive statistics

Microelement	Group	n	M	Me	CB	MIN	MAX	p
K	Control	7	1953.1	1961.0	41.5	1861.0	1981.0	0.038 ^a
	Experiment	7	1979.9	1995.6	42.7	1885.6	2005.6	
Na	Control	7	1794.4	1766.4	50.0	1747.4	1847.4	0.001 ^a
	Experiment	7	1644.9	1702.1	78.7	1502.1	1702.1	
Fe	Control	7	501.4	492.8	36.3	482.8	582.8	0.002 ^a
	Experiment	7	572.6	601.2	48.80	501.2	601.2	
Ca	Control	7	67.13	65.28	4.98	62.28	74.28	0.017 ^a
	Experiment	7	71.19	75.48	5.35	65.44	75.48	
Mg	Control	7	41.20	38.62	5.16	36.62	48.62	0.892 ⁶
	Experiment	7	41.55	39.84	4.53	37.84	47.84	
Zn	Control	7	7.09	6.84	0.85	5.54	7.88	0.128 ^a
	Experiment	7	7.46	7.03	0.53	7.03	8.03	
Cu	Control	7	1.65	1.62	0.09	1.52	1.82	0.318 ^a
	Experiment	7	1.75	1.61	0.38	1.51	2.61	
Cr	Control	7	0.745	0.696	0.0776	0.686	0.886	0.001 ^a
	Experiment	7	0.581	0.568	0.0386	0.558	0.668	
Mn	Control	7	0.713	0.679	0.0522	0.669	0.769	0.128 ^a
	Experiment	7	0.695	0.661	0.0650	0.601	0.761	
Tl	Control	7	0.505	0.484	0.0639	0.404	0.574	0.259 ^a
	Experiment	7	0.442	0.466	0.0744	0.306	0.506	
Ba	Control	7	0.191	0.200	0.0693	0.105	0.309	0.383 ^a
	Experiment	7	0.139	0.129	0.0407	0.109	0.229	
Ni	Control	7	0.190	0.189	0.0090	0.179	0.199	<0.001 ⁶
	Experiment	7	0.080	0.079	0.0068	0.068	0.088	
Sr	Control	7	0.066	0.066	0.0058	0.056	0.076	0.007 ^a
	Experiment	7	0.072	0.068	0.0053	0.068	0.078	

Note: calculated using Mann-Whitney's criterion; calculated using Student's criterion for independent samples

The results of checking the normality of the data distribution of the experimental and control groups using the Shapiro-Wielka criterion are given in **Table 2**. By this criterion, a significant difference from the results of the control group was shown on such elements as: Potassium, Copper, Chromium, Zinc, Barium and Strontium.

Table 2

The results of checking the normality of the data distribution of control and experimental groups using the Shapiro-Wielka criterion

Microelement	Group	Shapiro-Wielka statistics	df	p	Conclusion considering normality	Criterion
K	Control	0.641	7	0.001	Not normal	Mann-Whitney
	Experiment	0.636	7	0.001	Not normal	
Na	Control	0.739	7	0.010	Not normal	Mann-Whitney
	Experiment	0.769	7	0.020	Normal	
Fe	Control	0.565	7	0.000	Not normal	Mann-Whitney
	Experiment	0.600	7	0.000	Not normal	
Ca	Control	0.762	7	0.017	Normal	Mann-Whitney
	Experiment	0.665	7	0.002	Not normal	
Mg	Control	0.751	7	0.013	Normal	Student's
	Experiment	0.783	7	0.028	Normal	
Zn	Control	0.834	7	0.087	Normal	Mann-Whitney
	Experiment	0.665	7	0.002	Not normal	
Cu	Control	0.889	7	0.267	Normal	Mann-Whitney
	Experiment	0.590	7	0.000	Not normal	
Cr	Control	0.792	7	0.034	Normal	Mann-Whitney
	Experiment	0.525	7	0.000	Not normal	
Mn	Control	0.696	7	0.003	Not normal	Mann-Whitney
	Experiment	0.819	7	0.062	Normal	
Tl	Control	0.889	7	0.268	Normal	Student's
	Experiment	0.852	7	0.127	Normal	
Ba	Control	0.875	7	0.204	Normal	Mann-Whitney
	Experiment	0.677	7	0.002	Not normal	
Ni	Control	0.818	7	0.062	Normal	Student's
	Experiment	0.886	7	0.254	Normal	
Sr	Control	0.811	7	0.053	Normal	Mann-Whitney
	Experiment	0.664	7	0.001	Not normal	

Results of the comparison of the elemental blood composition of the rats in the two groups (control and experimental) by some indicators using Student's criterion for independent samples, as shown in **Table 3**, but using the Mann-Whitney criterion in **Table 4, 5**

Table 3

Results of comparison of control and experimental groups using Student's criterion

Variable	t	df	p-meaning	The difference in averages	Conclusion regarding the homogeneity of groups
Mg	-0.138	12	0.892	-0.359	Homogeneous
Ni	25.882	12	<0.001	0.111	Not homogeneous

Note: the conclusion is made at a significance level of 0.05

The heterogeneity of the results of the experimental and control groups according to the Mann-Whitney criterion was demonstrated in the following elements: Potassium, Sodium, Ferrum, Calcium, Chromium, Strontium. Additional rank statistics obtained from the comparison of control and experimental groups using the Mann-Whitney criterion were also demonstrated. The results are shown in the **Table 5**.

Table 4

Results of the comparison of the elemental composition of the control and experimental groups of rats using the Mann-Whitney criterion

Variable	Mann-Whitney U*	Wilcoxon W	Z	p-meaning	Homogeneity of groups**
K	8	36	-2.113	0.038	Not homogeneous
Na	0	28	-3.187	0.001	Not homogeneous
Fe	2	30	-2.950	0.002	Not homogeneous
Ca	6	34	-2.398	0.017	Not homogeneous
Zn	12	40	-1.621	0.128	Homogeneous
Cu	16	44	-1.096	0.318	Homogeneous
Cr	0	28	-3.220	0.001	Not homogeneous
Mn	12	40	-1.626	0.128	Homogeneous
Tl	15	43	-1.219	0.259	Homogeneous
Ba	17.5	45.5	-0.897	0.383	Homogeneous
Sr	4	32	-2.691	0.007	Not homogeneous

Note: * – rank statistics are shown in the table. 5; ** – the conclusion is made at the level of significance 0.05

Table 5

Additional rank statistics obtained when comparing control and experimental groups using the Mann-Whitney criterion

Variable	Group	N	Average rank	Sum of ranks
K	Control	7	5.14	36
	Experiment	7	9.86	69
Na	Control	14		
	Experiment	7	11.00	77
Fe	Control	7	4.00	28
	Experiment	14		
Ca	Control	7	4.29	30
	Experiment	7	10.71	75
Zn	Control	14		
	Experiment	7	4.86	34
Cu	Control	7	10.14	71
	Experiment	14		
Cr	Control	7	5.71	40
	Experiment	7	9.29	65
Mn	Control	14		
	Experiment	7	8.71	61
Tl	Control	7	6.29	44
	Experiment	14		
Ba	Control	7	11.00	77
	Experiment	7	4.00	28
Sr	Control	14		
	Experiment	7	9.29	65
	Control	7	5.71	40
	Experiment	14		
	Control	7	8.86	62
	Experiment	7	6.14	43
	Control	14		
	Experiment	7	8.50	59.5
	Control	7	6.50	45.5
	Experiment	14		
	Control	7	4.57	32
	Experiment	7	10.43	73
	Total	14		

The results of the analysis of the dynamics of blood parameters in the experimental group by the methods of descriptive statistics showed significant changes in such elements as: Potassium, Sodium, Ferrum, Calcium, Magnesium. The results are shown in the **Table 6**.

Table 6

Results of analysis of the dynamics of blood parameters in the experimental group by methods of descriptive statistics

Microelement	Time	n	M	Me	CB	MIN	MAX	p
K	T0	7	1979.91	1995.63	42.68	1885.63	2005.63	0.005
	T1	7	1857.63	1842.25	59.66	1800.25	1988.00	
	[T1-T0]	7	-122.28	-153.38	76.29	-198.38	12.38	
Na	T0	7	1644.92	1702.06	78.68	1502.06	1702.06	<0.001
	T1	7	1835.14	1806.00	47.86	1805.00	1905.00	
	[T1-T0]	7	190.22	202.94	66.79	103.94	302.94	
Fe	T0	7	572.62	601.19	48.80	501.19	601.19	0.017
	T1	7	454.32	445.74	36.25	435.74	535.74	
	[T1-T0]	7	-118.31	-155.45	49.57	-165.45	-65.45	
Ca	T0	7	71.19	75.48	5.35	65.44	75.48	0.006
	T1	7	63.32	62.32	3.61	61.32	71.32	
	[T1-T0]	7	-7.87	-4.16	5.00	-14.16	-3.13	
Mg	T0	7	41.55	39.84	4.53	37.84	47.84	0.009
	T1	7	32.59	31.44	3.63	30.44	40.44	
	[T1-T0]	7	-8.97	-7.39	6.24	-16.39	0.61	
Zn	T0	7	7.46	7.03	0.53	7.03	8.03	0.016
	T1	7	6.20	5.77	0.98	4.77	7.77	
	[T1 - T0]	7	-1.26	-1.26	1.00	-3.26	-0.26	
Cu	T0	7	1.75	1.61	0.38	1.51	2.61	0.310
	T1	7	1.70	1.67	0.05	1.67	1.77	
	[T1-T0]	7	-0.051	0.059	0.356	-0.841	0.179	
Cr	T0	7	0.581	0.568	0.039	0.558	0.668	0.017
	T1	7	0.744	0.688	0.096	0.685	0.885	
	[T1-T0]	7	0.163	0.120	0.081	0.117	0.327	
Mn	T0	7	0.695	0.661	0.065	0.601	0.761	0.527
	T1	7	0.664	0.593	0.111	0.592	0.892	
	[T1-T0]	7	-0.032	-0.069	0.125	-0.168	0.231	
Tl	T0	7	0.442	0.466	0.074	0.306	0.506	0.022
	T1	7	0.560	0.503	0.079	0.503	0.703	
	[T1 - T0]	7	0.118	0.097	0.101	-0.003	0.297	
Ba	T0	7	0.139	0.129	0.041	0.109	0.229	0.010
	T1	7	0.259	0.243	0.069	0.143	0.343	
	[T1-T0]	7	0.120	0.114	0.086	0.004	0.224	
Ni	T0	7	0.080	0.079	0.007	0.068	0.088	<0.001
	T1	7	0.177	0.175	0.004	0.175	0.185	
	[T1-T0]	7	0.097	0.097	0.006	0.088	0.107	
Sr	T0	7	0.072	0.068	0.005	0.068	0.078	0.002
	T1	7	0.086	0.083	0.005	0.083	0.093	
	T1	7	0.014	0.015	0.007	0.005	0.025	

Note: calculated using Mann-Whitney's criterion; calculated using Student's criterion for independent samples

The results of checking the normality of the distribution of differences [T1–T0] using the Shapiro-Wielka criterion are given in **Table 7**.

Table 7

The results of checking the normality of the distribution of the differences [T1–T0] with the help of the Shapiro-Wielka criterion for choosing a statistical criterion in order to assess the significance of the dynamics of the experimental group

Microelement	Shapiro-Wielka statistics	df	p	Conclusion on the normality of distribution	Criterion
K [T1–T0]	0.806	7	0.047	Normal	Student's
Na [T1–T0]	0.855	7	0.136	Normal	Student's
Fe [T1–T0]	0.710	7	0.005	Not normal	Уїлкоксонаї
Ca [T1–T0]	0.769	7	0.020	Normal	Student's
Mg [T1–T0]	0.936	7	0.606	Normal	Student's
Zn [T1–T0]	0.787	7	0.030	Normal	Student's
Cu [T1–T0]	0.640	7	0.001	Not normal	Уїлкоксонаї
Cr [T1–T0]	0.672	7	0.002	Not normal	Уїлкоксонаї
Mn [T1–T0]	0.760	7	0.016	Normal	Student's
Tl [T1–T0]	0.911	7	0.402	Normal	Student's
Ba [T1–T0]	0.904	7	0.353	Normal	Student's
Ni [T1–T0]	0.898	7	0.318	Normal	Student's
Sr [T1–T0]	0.840	7	0.099	Normal	Student's

The results of the dynamics evaluation in the experimental group (in the state of artificial hypobiosis) using Student's criterion for pair data are given in **Table 8**.

Table 8

Results of the dynamics evaluation in the experimental group using Student's criterion for pair data

Comparable pair	t	df	p–meaning	Average differences	Conclusion on the significance of differences *
K_1 – K_2	4.241	6	0.005	122.282	Significant
Na_1 – Na_2	–7.535	6	0.000	–190.223	Significant
Ca_1 – Ca_2	4.169	6	0.006	7.871	Significant
Mg_1 – Mg_2	3.804	6	0.009	8.969	Significant
Zn_1 – Zn_2	3.333	6	0.016	1.259	Significant
Mn_1 – Mn_2	0.672	6	0.527	0.032	Not significant
Tl_1 – Tl_2	–3.073	6	0.022	–0.118	Significant
Ba_1 – Ba_2	–3.679	6	0.010	–0.120	Significant
Ni_1 – Ni_2	–45.842	6	0.000	–0.097	Significant
Sr_1 – Sr_2	–5.203	6	0.002	–0.014	Significant

Note: * – The conclusion is made at a significance level of 0.05

The results of assessing the significance of the dynamics in a group using Student's criterion for pair data are given in **Table 8**, and with the help of the Wilcoxon signed-rank (**Table 9, 10**).

Table 9

Results of evaluation of dynamics in the experimental (hypopoietic) group using the Wilcoxon signed-rank criteria

Comparable pair	Z	p-meaning	Conclusion on the significance of differences*
Fe_2 – Fe_1	–2.388	0.017	Significant
Cu_2 – Cu_1	–1.016	0.310	Not significant
Cr_2 – Cr_1	–2.384	0.017	Significant

Note: the conclusion is made at a significance level of 0.05

Table 10

Rank statistics derived from the application of the Wilcoxon signed-rank criteria

Pair of variables, which are compared	Statistical indicators	n	Average rank	Sum of ranks
Fe [T0] & Fe [T1]	Negative ranks	22	21.18	466
	Additional ranks	17	18.47	314
	Connections	1		
	Total	40		
Cu [T0] & Cu [T1]	Negative ranks	14	15.14	212
	Additional ranks	20	19.15	383
	Connections	6		
	Total	40		
Cr [T0] & Cr [T1]	Negative ranks	21	23.21	487.5
	Additional ranks	19	17.50	332.5
	Connections	0		
	Total	40		

Note: parameter [T1]<parameter [T0]; parameter [T1]>parameter [T0]; parameter [T1]=parameter [T0]

5. Discussion

As it is known from previous studies, in the state of artificial hypobiosis, the inhibition of the vital activity of a living organism occurs: the intensity of cardiac contractions decreases, rectal body temperature decreases to –16 °C, mobility of the body completely disappears.

As a result of the studies, the growth of sodium was also found. The reasons for this are likely to be the support of the water-salt balance, because it provides for the conservation of mineral substances in the blood in the soluble state [9].

Also, the experiment showed that the state of artificial hypobiosis decreases the content of Nickel. This, probably, can be explained by the decrease in oxidative-reducing processes in the tissues of the body, which is explained by hypoxia [10].

Causes of sodium growth may be fluid retention in the body, since under artificially-created hypotonic conditions fluidity of the fluid in the body decreases, which is quite positive when conducting short-term surgical interventions. It should be noted that after the release of hypobiosis, increased excitability of rats was observed [11].

At the same time, there was an increase in the level of iron (Ferrum). This is due to oxygen starvation – hypoxia, it is obvious that in this case, the body tries to compensate for the lack of oxygen by the increased production of haemoglobin [12].

Investigations of the elemental blood composition in general showed that changes occurring in the body under hypothetical conditions are not critical to the organism, but only characterize the physiological changes occurring in hypoxia, hypercapnia, hypothermia [13].

It is also necessary to study the micro- and macro-elemental composition of the liver and heart of rats, since these two organs play an important role in maintaining the steady homeostasis of the organism [14]. Therefore, this will give an opportunity to more broadly assess the safety of hypobiosis.

6. Conclusions

1. As a result of the study, it was found that artificial hypobiosis suppress metabolic processes of the body, reduces the frequency of heart contractions, mobility, painful sensations also disappear, which suggests that it is in this state that short-term surgical interventions are possible [15].

2. It was found that changes in the elemental composition of the rat heart in the experimental group are not critical, which can negatively affect the vital activity of the organism. Based on these conclusions, we can assume that hypobiosis - as a general anaesthetic method can be used in clinical practice [16].

3. The heterogeneity of the statistical data of the results of the experimental hypobiotic groups according to the Mann-Whitney criterion was demonstrated in such elements as: Potassium, Sodium, Ferrum, Calcium, Chromium, Strontium.

4. Investigation of the elemental blood composition of rats by artificial hypobiosis will allow to understand the differences in micro- and macro-elemental changes occurring in the body and thus will enable to assess the safety of the use of hypobiosis in clinical practice [17].

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