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FEATURES OF HUMAN METABOLISM CHANGES WITH LONG-TERM HERMETIC SEALING IN ARGON-CONTAINING HYPOXIC GAS-AIR ENVIRONMENT

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The objective of the present study was an in-depth assessment of the main human metabolic parameters upon long-term (60 days) hermetic sealing in a normobaric argon-containing hypoxic gaseous environment (ArHGE) for checking the possibility to generate such gaseous environments able to reduce the risk of ignitions and fires in inhabited hermetically sealed objects, such as submarines. Study group included six male subjects aged 20 to 51 years and cleared to sail in a submarine for up to 90 days. Continuing containment in the test environment comprising 30–35% V/V argon, 13.3–14.5% V/V oxygen, and up to 0.8% V/V, the rest being nitrogen, lasted for 60 days. During this time the subject were engaged in typical physical activities and operator routines. Venous blood samples were taken before, every 15 days in the course of, and 5 days after containment. This regimen has been found to be associated with the gradual accumulation of under-oxidized products of carbohydrate, protein and cholesterol metabolism in the blood and with increasing atherogenicity index.

Adaptation to this regimen was manifested as decreases in the magnitudes of the above changes suggesting that metabolism may be tuned to increase body tolerance to hypoxia. Within 5 days after containment, virtually complete normalization of parameters studied was observed. The data confirm that it is possible to make such gaseous environments for improving fire safety of inhabited hermetically sealed objects, in particular submarines.

Key words: marine medicine, fire safety of hermetically sealed objects, argon-containing hypoxic gaseous environment, metabolism.

Introduction

One of the promising areas for increasing the fire safety of hermetic inhabited objects, in particular submarines, is creation of hypoxic gas-air environments (HGE), suitable for breathing and at the same time significantly reducing the probability of occurrence and development of ignitions and fires [1, p. 115; 2, p. 5]. The most frequent and simple way to create such an environment is to replace some of the oxygen in the air with nitrogen. An assessment of the fire-fighting efficiency of nitrogen-containing HGE has shown that combustion of the main structural materials used in constructing a submarine ceases with an oxygen content in the HGE less than 13-14% (partial pressure below 14 kPa) [3, p. 39]. However, it is known that prolonged stay of a person in such conditions is difficult and can lead to unacceptable violations of his functional state [4, p. 39]. One of the solutions to the problem of the safety of such a HGS for humans was its generation under the conditions of moderate (up to 0.15 mPa) increase in the total barometric pressure in the submarine. In this case, at a concentration of oxygen in the environment at a level of 13-14%, its partial pressure corresponds to "normoxic" values (about 21 kPa). Conducting tests to assess the possibility of prolonged (up to 45 days) human presence under such conditions has shown the absence of unacceptable deviations in the functional state and performance [5, p. 1]. However, such an increase in the total barometric pressure, which is 1.5 times greater than the atmospheric pressure, is unacceptable for most of the equipment, so this method of generating a GSE in the submarine is still difficult.

The writing committee directed by B.N. Pavlov [6, p. 369; 7, p. 33] substantiated the concept of the physiological activity of "metabolically indifferent gases" (helium, argon, xenon) not only at elevated, but also at normal barometric pressure. The essence of the concept is that indifferent gases directly affect the metabolism in the tissues of the body, which allows significant increasing their resistance to hypoxia. Based on this concept, those authors proposed to replace a part of nitrogen with an inert gas when forming fire-safe HGE. However, the only possible solution to the problem of creating such HGE in hermovolumes was the use of an excess of argon, which is one of the components of atmospheric air, in the gaseous environment, where its concentration is about 0.9% (about 1 kPa).

In experimental studies involving human subjects, the presence of an antihypoxic effect of argon was shown when it was added to the HGS, which was confirmed with continuous (up to 10 days) being of subjects in such environments [7, p. 37; 8, p. 20]. On the basis of the results obtained, the authors recommended HGE consisting of 14% oxygen, 53% nitrogen and 33% argon to enhance the fire safety of hermetically sealed objects, in particular, submarines. This HGE, according to the hypothesis of these authors, would have no significant negative effect on the body of specialists and with a longer exposure, which, however, needed an additional verification.

Based on the foregoing, we have conducted studies to assess the effect on humans of a prolonged (during 60 days) continuous residence in the specified argon-containing HGE (ArHGE). The overall result of these studies was the conclusion that there were no unacceptable violations on the part of the functional state and performance of all participants in the trials [9, p. 7; 10, p. 13].

The purpose of this study was an in-depth evaluation of dynamics of the main indices of human metabolism during long-term hermetic sealing in ArHGE, reducing the danger of ignition and firs in inhabited hermetically sealed objects.

Materials and methods

The type of study conducted is a prospective cohort. The study was conducted in 2014-2015 on the basis of the test stand (TS) of ASM, JSC (St. Petersburg). The design of the TS allowed modeling the preset normobaric ArHGEs in a closed volume, and also providing the possibility for volunteer testers to carry out in them a long continuous staying and operating. Studies were conducted with the participation of 6 men aged 25-30 years (5 people) and 51 years (1 person). The selection of volunteers for participation in the studies was carried out taking into account a number of criteria: the necessary level of health status (validity to sail to sea at a submarine for 3 months); sufficient level of functional capabilities of the body, allowing to perform physical, mental and other loads; high motivation to participate in the trials; voluntary informed consent to participate in the trials.

During the whole period of thesealing, the following set parameters of the ArHGE were formed in the TS premises: oxygen content 13-14%, argon 30-35%, carbon dioxide 0.03-0.8%, nitrogen the rest, at normal values of atmospheric pressure and other parameters of the microclimate. The duration of the sealing period was 60 days, during which the testers performed a work program that consisted of daily modeling of the intellectual or operator content (work on simulators), as well as intensive multi-modal physical exertion (strength training, exercise bike, individual special exercise programs, etc.). The total duration of daily work and study was about 4 hours a day. As a rule, about 3-4 hours a day functional examinations (that is assessment) took place. In addition, round-the-clock shifts were organized. Thus, the daily activities of the participants in the tests were close to the real activities of the staff at the hermetically sealed objects.

During the follow-up period, all testers underwent in-depth, step-by-step comprehensive studies of functional status and performance. One of the directions of these studies was an in-depth evaluation of the dynamics of metabolism of proteins, fats and carbohydrates, determined in serum. This paper presents the results of these studies.

Sampling of venous blood of the testers was performed on an empty stomach using all the rules of aseptic and antiseptic. Hematological studies were performed in the North-West Center for Evidence-Based Medicine (St. Petersburg) using standard techniques on automated biochemical analyzers.

The primary (background) hematological examination was carried out for several days, before the start of the tests. The control tests at the sealing stage were carried out approximately every 14-15 days of the testers’ stay in the ArHGE. The final examination (that is assessment) was performed on the 5th day after the end of the hermetic sealing.

Statistical processing of the obtained data was carried out according to the existing requirements. Comparison of the data in the assessment dynamics was carried out using the Wilcoxon T-test. The results in the tables were presented as medians (Me), the 1st and 3rd quartiles (Q25, Q75). As statistically significant, differences were taken at a significance level of $p < 0.05$. Analysis and processing of the material was carried out using STATISTICA software packages, v. 10.0 for WINDOWS-8, Microsoft Excel.

The study was organized and conducted in accordance with the provisions and principles of the current international and Russian legislation, in particular the Helsinki Declaration of 1964, taking into account its 1983 and 2013 revisions. The legitimacy of the studies is confirmed by the conclusion of an independent ethical committee at the Northern State Medical University.

Results and discussion

Investigations of the state of the main metabolic processes showed that a long stay in a preset ArHGE was accompanied by such changes, which were typical for all the testers and reflected the development of the hypoxic state in the body and aimed at its compensation.

As follows from the results presented in Table. 1, in the initial state, the main indicators characterizing the metabolism of carbohydrates and proteins were within the reference values, except for lactate content, slightly exceeding the upper limit of the norm in 2 testers. Apparently, this fact was due to the peculiarities of the regime of physical activity and nutrition and was not considered as a contraindication to participation in the trials.

Control tests conducted during the sealing showed that all volunteers had an increase in lactate in the blood without significant dynamics from the concentration of glucose. The peak values of the lactic acid level were fixed approximately in the middle of the tests (on the 30th day), when the values of this parameter exceeded the initial values by approximately 2-2.5 times ($p = 0.014$). However, in the subsequent stages of the tests, the lactate content of all the subjects was gradually reduced, so that at the final (5th) stage of the sealing there were no significant differences compared to the primary examination.

Approximately the same dynamics turned out to be characteristic for the parameters of protein metabolism. In particular, significant fluctuations in the level of total protein and urea in the blood serum were absent, being during the whole period of testing within the reference values.

Table 1

Indicators of carbohydrate and protein metabolism of blood serum for the testers (n = 6) during the control studies, Me (Q25; Q75)

Stage of assessment	Measurement, unit of measurement (reference values)					
	Glucose, mmol/L (4.1-5.9)	Lactate, mmol/L (0.5-2.22)	Total protein, g/L (66-82)	Urea, mmol/l (2.81-7.21)	Uric acid, µmol/L (208-429)	Creatinine, µmol/L (74-109)
1st stage (initial assessment)	4.88 (4.27; 5.27)	2.35 (1.88; 2.68)	72.0 (71.1; 72.9)	4.08 (3.90; 4.26)	360 (332; 415)	87.3 (81.8; 92.2)
2nd stage (16th day of the sealing)	5.14 (4.65; 5.23)	3.45 (2.92; 4.22) p=0.029	70.9 (69.3; 74.5)	3.55 (3.46; 3.99)	398 (372; 441)	94.7 (84.9; 103.9)
3rd stage (30th day of the sealing)	5.11 (5.05; 5.34)	4.68 (3.95; 5.16) p=0.014	71.0 (67.4; 75.0)	4.41 (3.93; 5.28)	459 (440; 501) p=0.034	102.0 (98.1; 105.2)

						p=0.025
4th stage (45th day of the sealing)	4.77 (4.49; 5.03)	3.46 (3.04; 3.86) p=0.027	73.3 (72.1; 73.5)	4.89 (3.93; 5.45)	432 (406; 490) p=0.044	96.9 (89.9; 101.4) p=0.049
5th stage (59th day of the sealing)	4.64 (4.58; 4.78)	2.90 (2.83; 3.04)	73.9 (70.3; 75.4)	5.15 (4.25; 5.35)	432 (338; 443) p=0.047	97.1 (89.6; 108.0) p=0.045
6th stage (5th day after the sealing)	5.04 (4.37; 5.29)	2.29 (1.97; 2.58)	71.0 (68.7; 72.7)	4.82 (4.45; 5.08)	409 (404; 426)	87.9 (84.4; 103.7)

Note. The level of significance of the differences in indicators compared with the 1st stage is p.

At the same time, there was a progressive increase in protein metabolism catabolites, such as creatinine and uric acid, concentrations of which (like that of lactate) reached a peak around the middle of the tests. Moreover, if the concentration of creatinine did not exceed the upper limits of the norm even at the maximum increment in all testers, then the level of uric acid at this stage of assessment (day 30) exceeded those of all assessed examinees. At the later stage of the sealing (about 45 days) there was a gradual decrease in the level of uric acid in the blood, which led to normalization of the indicator in 3 out of 6 assessed examinees by the end of the test.

These facts, in general, correspond with the results of other similar studies [11, p. 174; 12, p. 262] and, in our opinion, are caused by such a compensatory increase in the activity of anaerobic mechanisms of energy supply of cells, which is associated with a chronic oxygen deficiency, which led to an increase in the content of under-oxidized metabolic products in the circulating blood. At the same time, inadmissible phenomena of metabolic acidosis, judging by the parameters of the acid-base state of the blood that was simultaneously assessed (not shown in the table), none of the testers was detected during the whole period of the study. We considered this fact as an evidence of the effectiveness and safety of the buffer systems functioning in the body, which allowed neutralizing the excess acidity of the cellular metabolites entering the blood.

It is important to note that, already 5 days after the end of the tests, there were obvious tendencies towards normalization from all the catabolites of protein and carbohydrate metabolism, the changes of which occurred during the stay in the conditions of the ArHGE. This fact, in our opinion, is a testament to the preservation of the life-supporting functions of the body of the testers, the reversibility of the compensatory-adaptive reactions that have taken place and, consequently, the permissibility of prolonged continuous human presence under the conditions of the ArgHGS with given parameters.

A number of similar regularities are also recorded from the dynamics of the parameters of fat metabolism (Table 2). Thus, in all testers, unidirectional shifts were detected around the middle of the sealing period, consisting of a moderate increase (5-20% of the baseline level) of total cholesterol, triglycerides, and of a change in the ratio of lipoprotein fractions leading to an increase in the circulating blood atherogenic index. We considered this fact as evidence of the development of such compensatory reactions in the body, which aimed at an emergency adaptation to the changed environmental conditions.

It is known that an increase in total cholesterol, triglycerides, as well as a change in the ratio of lipoprotein fractions is a nonspecific response of the body to a long-acting disturbing factor, and this increase, as well as this change, is due to the participation of these substances in the synthesis of so-called “stress and adaptation” hormones and the formation of cell membranes [13, p. 712].

The gradual decrease in the stressogenicity of the action, which occurs with the development of urgent adaptive structural and functional changes in a test body, was accompanied by a decrease in concentration of cholesterol and triglycerides, and by a reduction in the atherogenic index. In this case, in 4 out of 6 examined persons, by the end of the tests, the listed parameters were already within the reference values. In the remaining 2 people, whose initial indication (before the start of the test) of the atherogenic index exceeded the normative values, there was also such a decrease in these parameters (in comparison with the initial stage of the test), which has led to achievement of their background level.

Table 2

Indicators of lipid metabolism of testers (n = 6) in the assessment dynamics [Me (Q25; Q75)]

Stage of assessment	Measurement, unit of measurement (reference values)					
	Cholesterol total, mmol/L (up to 5.2)	Triglycerides, mmol/L (up to 1.7)	Lipids of low density, mmol/L (up to 3,3)	Lipids of high density, mmol L (from 1.03)	Lipids of very low density, mmol/ L (up to 0,7)	Atherogenic index, rel. units (up to 3.5)
1st stage (initial assessment)	4.95 (4.29; 6.29)	1.55 (1.07; 2.29)	3.24 (2.49; 4.24)	1.33 (1.08; 1.42)	0.51 (0.39; 0.82)	3.21 (1.98; 4.82)
2nd stage (16th day of the sealing)	5.00 (4.13; 6.86)	1.19 (0.99; 1.25)	3.36 (2.59; 5.15)	1.23 (1.09; 1.36)	0.37 (0.32; 0.62)	2.96 (2.63; 4.95)
3rd stage (30th day of the sealing)	5.35 (4.17; 7.65) p=0.042	1.50 (1.25; 2.06)	3.70 (2.61; 4.22) p=0.045	1.09 (1.06; 1.19)	0.44 (0.35; 0.72)	3.75 (2.87; 4.13)
4th stage (45th day	4.98 (4.07; 5.92)	1.46 (1.34; 1.88)	3.59 (2.96; 5.60)	1.27 (1.15; 1.33)	0.48 (0.43; 0.84)	3.22 (2.73; 5.32)

of the sealing)						
5th stage (59th day of the sealing)	4.99 (4.11; 6.49)	1.43 (1.14; 2.45)	3.42 (2.78; 4.90)	1.29 (1.15; 1.37)	0.46 (0.36; 0.55)	3.20 (2.96; 4.13)
6th stage (5th day after the sealing)	4.81 (4.43; 6.64)	0.90 (0.80; 1.29) p=0.046	3.36 (2.62; 4.87)	1.37 (1.14; 1.46)	0.35 (0.24; 0.53) p=0.025	3.11 (2.35; 4.49)

Note. The level of significance of the differences in indicators compared with the 1st stage.

Conclusion

Thus, the facts revealed in the study, in our opinion, reflect some regularities of adaptive reactions of a person who for relatively a long time had been staying in the conditions of pronounced lack of oxygen. The general structure of changes in metabolism in the initial period of staying within the HGE looks like some accumulation of under-oxidized products from carbohydrate and protein metabolism, some cholesterolemia, and some increase in the atherogenic index. However, with the development of adaptability (in case of a sufficient adaptive potential for a human tester) to specific livability conditions, the severity of these reactions decreases gradually, which indicates a “transition” of metabolism to a qualitatively new level. In general, the studies carried out have confirmed our statement [9, p. 8; 10, p. 14] and other authors’ [6, p. 378; 8, p. 21] conclusion about admissibility of human presence in similar ArHGE, the formation of which in an encapsulated inhabited object, in particular in a submarine, will significantly reduce the risk of ignition and fire.

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