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Dynamics of Lipid Metabolism in Volunteers during 120-Day Isolation in a Hermetic Chamber

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Abstract—In the international SIRIUS 19 experiment with a 120-day isolation in a pressurized chamber, conducted at the experimental unit of the Institute of Biomedical Problems, Russian Academy of Sciences, a crew consisting of six subjects of both sexes ranging in age from 27 to 43 years was examined. The levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, apolipoproteins A1 (ApoA1) and B (ApoB), as well as nonesterified (free) fatty acids (NEFA), were determined in the blood serum of the subjects. The concentrations of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) cholesterols, the values of the atherogenicity index, ApoB/ApoA1, and HDL ratios were calculated. A special feature of this experiment was a preventive program that included cycles of daily physical activity of various intensities, as well as regular physical load tests conducted throughout the experimental exposure. In this regard, there were no significant changes in the concentrations of cholesterol or its VLDL fraction, and the contents of lipoproteins A1 and B was at a low level. Due to the action of regular and intense physical exertion, lipolysis was activated for a long time as an additional pathway of energy production, which was characterized by a sharp increase in the content of NEFA in the blood beyond the reference range and led to changes in the synthesis of cholesterol in the liver, expressed in the redistribution of its fractions. Considering the results of this study, the preventive physical loads should be optimized in further experiments.

Keywords: space medicine, isolation in a hermetic volume, lipid metabolism, atherogenesis

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The formation of unfavorable shifts in lipid metabolism indices, a high degree of risk of atherogenesis and the development of damage to the intima of blood vessels during long-term space flights (SFs) have been an urgent problem of space medicine for decades. Suffice it to note that cardiovascular diseases are the main cause of death in Russian cosmonauts [1].

A progressive increase in the concentration of cholesterol in the blood of cosmonauts of the main missions to the Mir orbital station was shown, accompanied by a decrease in the level of high-density lipoprotein (HDL) cholesterol [2]. In some cosmonauts, during flights to the International Space Station (ISS), a more than twofold increase in the concentration of cholesterol relative to the upper limit of the norm was found [3]. After long flights, the crew members of the Salyut 6 and Salyut 7 orbital stations increased the contents of cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol and very low density (VLDL) cholesterol, the value of the atherogenic index (AI), as well as the cholesterol-to-phospholipids ratio increased [4].

State-of-the-art medical technology does not allow for a comprehensive study of lipid metabolism directly during the mission; therefore, it is only possible to obtain data on its features during long-duration flights only in ground-based analog experiments.

Experiments with isolation in a hermetic volume are a model of an SF, in which it is possible to reproduce the effect on the human body of almost all of its factors, with the exception of weightlessness [5].

In isolation for up to 135 days, changes in cholesterol metabolism characteristic of SFs were found: an increase in the content of cholesterol in the blood and redistribution of its fractions towards the predominance of atherogenic forms, but it should be emphasized that no such changes were found during a 240-day isolation in a hermetic volume [6]. In this regard, it should be noted that the risk of atherogenesis is characterized not only by the blood levels of cholesterol and its lipoprotein fractions, HDL, LDL, VLDL cholesterols, but also by the balance of all forms of lipoproteins [7]. The leading role is played by lipids affecting the synthesis and distribution of lipoproteins, primarily apolipoproteins A1 (ApoA1) and B (ApoB). Their ratio indicates the risk of atherogenic changes regardless of the content of lipids associated with cholesterol, even when their levels are normal [8,

9]. The analysis of lipoproteins allows detecting lipid–lipoprotein imbalance, which makes it possible to assess the risk of atherogenesis in cases where the use of traditional indicators of cholesterol metabolism is ineffective [10]. Thus, in the course of an experiment with 17-day isolation in a pressurized volume at almost unchanged levels of the "basic" parameters of cholesterol metabolism (cholesterol, HDL and LDL cholesterols, atherogenic index, phospholipids-to-cholesterol ratio), as early as the first week of exposure, an increase in blood parameters was observed. characterizing changes in the composition of the spectrum of lipoproteins that determine the development of atherogenesis. The content of ApoB increased, the value of the ApoB/ApoA1 index increased, which indicated the development of initial shifts in atherogenic orientation [11].

An increase in the content of nonesterified (free) fatty acids (NEFA) in the liver leads to disruption of cholesterol metabolism, resulting in the formation of hyperatherogenic dense particles of LDL cholesterol along with a sharp decrease in the level of HDL cholesterol [10]. Thus, the availability of information on the state of lipid metabolism, in addition to data on the levels of cholesterol and its fractions, makes it possible to reliably assess the risk of atherogenesis in the subjects.

The goal of this study was to analyze the parameters of lipid metabolism that affect the synthesis and distribution of cholesterol fractions in the course of an experiment with 120-day isolation in a hermetic volume.

METHOD

In the SIRIUS 19 experiment with a 120-day isolation in a pressurized volume, carried out in the framework of the SIRIUS international project at the ground-based experimental complex of the Institute of Biomedical Problems, Russian Academy of Sciences (Moscow, Russia), a crew of six subjects of both sexes aged from 27 to 43 years was examined. The rationale for combining men and women into a single group was the absence of gender differences in the values of the reference ranges of all the studied indicators, with the exception of ApoA1 and ApoB. However, the difference in the latter does not exceed 10% [12].

A specific characteristic of this experiment was a preventive program that included cycles of daily physical activity of varying intensity, lasting for about a month, with a six-day break between cycles. Physical exercise tests were carried out regularly using a bicycle ergometer and a treadmill track. In addition, emergency situations were simulated twice, consisting of 24-h sleep deprivation for all crew members.

Venous blood was taken in the morning, on an empty stomach, 28 days before the start of the experiment, on days 37, 63, and 120 of isolation, as well as on days 7 and 14 of the recovery period (RP). The sampling points were chosen so that at least three to five days passed from the moment of the last physical activity or emergency situation. In the blood serum, the levels of total cholesterol, HDL cholesterol, ApoA1 and ApoB, triglycerides, and NEFA were determined. The concentrations of LDL cholesterol and VLDL cholesterol, the atherogenic index (IA), and the ApoB/ApoA1 and HDL ratios were calculated using generally accepted equations [13]. The measurements were carried out by means of a Targa BT 3000 biochemical analyzer (Biotecnica Instruments, Italy) using reagent kits from DiaSys (Germany). Statistical processing of the data was carried out by the methods of variation statistics by means of the Statistica for Windows software package (United States), with the use of Student's *t*-test. The exclusion of individual values not belonging to the general sample was carried out using the Dixon test [14].

RESULTS AND DISCUSSION

The results of the study are presented in Table 1.

In the background period, there was a decrease in the concentration of triglycerides beyond the physiological norm (Table 2), which was explained by nutritional reasons.

In all periods of the examination, the concentrations of cholesterol and VLDL cholesterol did not differ significantly from the background level. At the same time, the level of HDL cholesterol significantly decreased on the 63rd and 120th days of isolation by about a third and remained lowered within the physiologically normal range by the 7th day of RP. The reason for this could be a sharp increase in the concentration of NEFA during all periods of isolation, from 37 to 120 days, by 213, 163, and 139%, respectively. As mentioned above, an increase in the content of NEFA in the blood leads to disturbance of the metabolism of cholesterol in the liver and a decrease in the level of HDL cholesterol [10].

A decrease in the content of HDL cholesterol was reflected in a simultaneous significant decrease in the HDL ratio in the range of 45–32%, but within the reference values. On the 120th day of isolation, the level of LDL cholesterol increased significantly, by 26%, while the content of HDL cholesterol was significantly reduced by 30%, which led to a significant increase in the AI value by 26%, its absolute value exceeding the physiological norm.

Against the background of changes in cholesterol metabolism indices, the content of ApoA1 significantly decreased by 15% within 63 days of isolation and by the same amount during the RP. However, due to the fact that the level of ApoB also tended to decrease in all periods of the examination, the value of the ApoB/ApoA1 ratio did not significantly differ from the background values.

Table 1. Indicators of cholesterol metabolism among testers in the course of the experiment with a 120-day isolation in a pressurized chamber ($M \pm m$, $n = 6$)

Indicator	Background	37 s	63 s	120 s	+7 s	+14 s
Cholesterol	4.87 ± 0.28	4.67 ± 0.17	4.53 ± 0.31	5.04 ± 0.16	4.97 ± 0.17	4.70 ± 0.22
HDL cholesterol	1.69 ± 0.11	1.53 ± 0.07	1.20 ± 0.06*	1.19 ± 0.06*	1.41 ± 0.04*	1.48 ± 0.03
LDL cholesterol	2.83 ± 0.23	2.86 ± 0.14	3.05 ± 0.32	3.58 ± 0.16*	3.36 ± 0.16	2.94 ± 0.19
VLDL cholesterol	0.240 ± 0.030(5)	0.280 ± 0.030	0.282 ± 0.035	0.240 ± 0.020(5)	0.210 ± 0.020	0.270 ± 0.010
AI	1.97 ± 0.32	2.07 ± 0.13	2.86 ± 0.36	3.32 ± 0.29*, !	2.53 ± 0.09	2.17 ± 0.10
HDL-rel.	0.620 ± 0.068	0.540 ± 0.030	0.417 ± 0.055*	0.340 ± 0.030*	0.420 ± 0.020*	0.510 ± 0.030
TG	0.528 ± 0.066(5)!	0.620 ± 0.060	0.621 ± 0.076	0.520 ± 0.050(5)!	0.450 ± 0.040!	0.600 ± 0.030
NEFA	380 ± 9(5)	808 ± 145*, !	621 ± 73*, !	529 ± 57*	405 ± 30	288 ± 43
Apo A1	1.72 ± 0.10	1.65 ± 0.08	1.46 ± 0.05*	1.59 ± 0.05	1.45 ± 0.04*	1.46 ± 0.04*
Apo B	0.744 ± 0.078	0.660 ± 0.040	0.504 ± 0.012(5)*	0.600 ± 0.020(5)	0.640 ± 0.050	0.610 ± 0.050
ApoB/ApoA1	0.380 ± 0.027(5)	0.410 ± 0.030	0.342 ± 0.006(5)	0.370 ± 0.010(5)	0.450 ± 0.040	0.420 ± 0.040

* Significant difference from the background, $p < 0.05$, ! the average the value of the indicator goes beyond the boundaries of the physiological norm. The numbers of subjects in the sample that differ from the usual one are indicated in parentheses. For an explanation of the abbreviations of the studied indicators, see the text.

Despite the fact that changes in some parameters of cholesterol metabolism in this experiment resemble those in previous studies [15], the reasons for their occurrence are completely different. In earlier experiments, shifts of cholesterol metabolism occurred due to the development of hypodynamia. In this study, in connection with the implementation of the program of daily preventive physical activity and regular exercise tests, physical inactivity, in all likelihood, did not develop. Moreover, due to the high intensity of physical training, signs of the inclusion of lipolysis as a reserve pathway of energy synthesis in the body were observed. Lipolysis substrates arein some respects lipid analogs of those of glycolysis and glycogenolysis [16]. For example, triglycerides are similar to glycogen, and NEFA, as products of the cleavage of triglycerides, can be considered as lipid analogs of glucose that are used for the synthesis of adenosine triphosphate (ATP) in β-oxidation reactions.

Table 2. The boundaries of the reference ranges of the studied biochemical parameters

Indicator	Reference range
Cholesterol , mmol/L	2.8–5.2
HDL cholesterol, mmol/L	>0.91
LDL cholesterol, mmol/L	<4.0
HDL-rel.	>0.28
AI	2.2–3.0
TG, mmol/L	0.55–2.30
NEFA, μmol/L	100–600
ApoA1, g/L	1.1–1.7
ApoV, g/L	0.80–1.55
ApoB/ApoA1	0.1–0.9

In the SIRIUS 19 experiment, by the end of the exposure and on the 7th day of RP, there was a decrease beyond the reference interval in the mean value of triglyceride concentration after a sharp significant increase in the level of NEFA, sometimes beyond the physiological normal range, on days 37 and 63, which may be associated with increased cleavage of triglycerides as initial substrate of lipolysis reactions. Stably high concentrations of NEFA in the blood is most likely to lead to disturbance of the synthesis of cholesterol in the liver and redistribution of the composition of its fractions.

CONCLUSIONS

The characteristic feature of the experiment was a preventive program, which included cycles of daily physical activity of varying intensity, as well as regular exercise tests carried out throughout the entire experimental exposure. This explains the difference in the nature of changes in lipid metabolism indices observed in this experiment from those observed in previous similar studies. There were no significant changes in cholesterol metabolism of atherogenic nature: the concentrations of cholesterol and its atherogenic LDL (with the exception of one examination period) and VLDL fractions did not change, the levels of lipoproteins A1 and B significantly decreased, while the ApoA1/ApoB ratio remained unchanged. From the middle of the isolation period, a significant decrease in the concentration of HDL cholesterol was observed; however, it was not associated with the development of hypodynamia, as in previous experiments; most likely, it was due to the effect of lipolysis metabolites on its synthesis in the liver.

During isolation, due to the action of regular and intense physical exertion, the process of lipolysis, an

additional pathway of energy synthesis, was activated for a long time, which was accompanied, by the end of isolation and up to the seventh day of the recovery period, by a decrease in the average concentration of triglycerides, a source of free fatty acids, beyond the physiological norm. Their concentration in the blood was characterized by a significant sharp increase, beyond the upper limit of the reference range, in the first half of the experiment, which led to changes in the synthesis of HDL cholesterol in the liver.

Considering the results of this study, it becomes obvious that it is necessary to optimize preventive physical activity in subsequent experiments.

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COMPLIANCE WITH ETHICAL STANDARDS

All studies were carried out in accordance with the principles of biomedical ethics formulated in the 1964 Declaration of Helsinki and its subsequent updates, and approved by the Commission on Biomedical Ethics of the Institute of Biomedical Problems of the Russian Academy of Sciences (Moscow).

INFORMED CONSENT

Each study participant provided a voluntary written informed consent, signed by him after explaining the potential risks and benefits, as well as the nature of the upcoming study.

CONFLICT OF INTEREST

The authors declare no obvious and potential conflicts of interest related to the publication of this article.

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