pharmacology and occupational diseases, Medical Institute, M.K. Ammosov North-Eastern Federal University, krasnova14@mail.ru, http://ORCID: 0000-0002-4811-7801; **FEDOROV A.I.**, Cand.Sci. (Biology), senior researcher, Research center, Medical Institute, associate professor of the Department for public health and health care, general hygiene, and bioethics; **KRAVCHENKO A.F.**, Dr.Sci. (Medicine), Director of Phtisiatry Research-Practice Center, http://ORCID: 0000-0002-9210-3407; **EVDOKIMOVA N.E.**, TB clinician, Phtisiatry Research-Practice Center; **EFREMOVA E.N.**, TB clinician, Pulmonary tuberculosis department, Phtisiatry Research-Practice Center; **CHERTOVSKYKHYA.V.**, chief non-staff clinical pharmacologist of the Ministry of Health of the Sakha Republic (Yakutia), Head of the Center for Personalized Medicine, Republican Hospital No.3; **ALEKSEEVA E.A.**, biologist, Genetic laboratory, Center for Personalized Medicine, Republican Hospital No.3; **RUDYKH Z.A.**, clinical pharmacologist, Center for Personalized Medicine, Republican Hospital No.3; **VASILIEVA O.L.**, clinical pharmacologist, Center for Personalized Medicine, Republican Hospital No.3; Moscow, Russian Federation: **SUVOROVA O.A.**, I.M. Sechenov First Moscow State Medical University; **SYCHEV D.A.**, Dr.Sci.(Medicine), Prof., Corresponding Member of the Russian Academy of Sciences, Professor of the Russian Academy of Sciences, Principal of the Russian Medical Academy of Continuous Professional Education, http://ORCID: 0000-0002-4496-3680.

I.V. Averyanova, S.I. Vdovenko, A.V. Kharin

RESTRUCTURING OF HEART RATE VARIABILITY, GAS EXCHANGE AND MICROCIRCULATION AT CYCLE-ERGOMETRY IN PERSONS WITH DIFFERENT DEGREES OF EXERCISE TOLERANCE

DOI 10.25789/YMJ.2019.68.06

УДК 612.13-15;22-23

An objective criterion for assessing the functional state of the human body, as well as the degree of balance of its physiological systems may be the study of physical performance. The **purpose** of this work was to study the specific features of urgent adaptations of a number of functional systems of the body in response to a cycle-ergometric test, and to identify marker criteria for assessing the level of exercise tolerance.

Based on the study of heart rate variability, indirect calorimetry, capillary blood flow and a modified PWC170 test, a comparative study was carried out on 63 young men aged 17-19 who were students from among Caucasians born in the North in the 1st and 2nd generations. Analysis of the data showed that during the stress test, most values of heart rate variability, microcirculation and metabolism increase as compared with the background level or at different stages of cycle-ergometry. At the same time, these changes are different for people with different degrees of tolerance to the load.

The results of the study made it possible to establish that the most important and informative indices reflecting the degree of tolerance to the load are the heart rate, the concentration of carbon dioxide in the exhaled air, the oxygen utilization factor, and the rate of capillary blood flow. During the performance of the stress test, such criteria are heart rate, MxDMn in relation to heart rate, reflecting the degree of decrease in parasympathetic activation, as well as the level of oxygen consumption, whose values in individuals with normal load resistance continue to increase until the end of the test.

Keywords*:* young men, heart rate variability, gas exchange, microcirculation, exercise test.

AVERYANOVA Inessa Vladislavovna – Senior Researcher, Laboratory for Physiology of Extreme States, Scientiic Research Center “Arktika”, Fareastern Branch of the Russian Academy of Sciences (SRC “Arktika” FEB RAS), 24 Karl Marx street, 24, Magadan, 685000, Ph. D. (Biology), http://orcid.org/0000-0002-4511-6782, Inessa1382@mail.ru, tel.: +7 (924) 691-11-46. **VDOVENKO Sergei Igorevich** – Researcher, Laboratory for Physiology of Extreme States, Scientiic Research Center “Arktika”, Fareastern Branch of the Russian Academy of Sciences (SRC “Arktika” FEB RAS), 24 Karl Marx street, 24, Magadan, 685000, http://orcid.org/0000-0003-4761-5144, Vdovenko.sergei@yandex.ru, tel. +7 (924) 856-55-50. **KHARIN Anton Vladimirovich** – Junior Researcher, Laboratory for Physiology of Extreme States, Scientiic Research Center “Arktika”, Fareastern Branch of the Russian Academy of Sciences (SRC “Arktika” FEB RAS), 24 Karl Marx street, 24, Magadan, 685000, http://orcid.org/0000-0002-8983-2553, Anton-harin@yandex.ru, tel. +7 (964) 455-27-40.

Examination of physical working capacity is an important element of the quantitative assessment of the level of health, and an assessment of the degree of exercise tolerance can serve as a prognostic and objective criterion of the functional state and a quantitative indicator of individual human health [6]. A reduced level of motor activity is accompanied by a decrease in the overall working capacity of the organism and an increase in the "physical cost of the load," which is associated with a high tension of functioning systems involved in response to this load [10]. The autonomic nervous system plays an important role in modulating the cardiovascular system in various situations [16], including physical exercise [17]. To maintain cardiovascular homeostasis during exercise, it is necessary to connect mechanisms based on the rapid action of the autonomic nervous system [17]. Heart rate variability (HRV) characteristics are available and fast in use indicators reflecting changes in cardiovascular homeostasis, and also are indirect indicators of vagal nerve activity of the heart. In doing so, they allow us to determine the relative contribution of the parasympathetic and sympathetic link in the regulation of the rhythm of the heart in stress testing, being an accessible measure of the overall function of the ANS [8, 15].

Cardiovascular reactions, in response to physical exertion, are characterized by a direct expressed decrease in the activity of the parasympathetic link of the autonomic nervous system at the beginning of the test, with an increase in heart rate due to the activation of sympathetic activity. Immediately after the end of exercise, the heart rate decreases due to vagal reactivation [19].

It is important to judge the peculiarities of the changes in metabolic processes during the performance of load tests, preferably using indirect calorimetry, which consists in the fact that the combustion of products generates thermal energy, the value of which can be determined from the results of measuring the body's consumption of oxygen and carbon dioxide [22].

The functional state of the capillary bed and the lability of the dynamic characteristics of microcirculation create conditions for the adaptation of blood flow to external loads [20]. Recent studies have shown that the values of capillary blood flow can differ significantly among comparable groups of people who lead a similar way of life [4].

The purpose of this work was to study the urgent adaptation changes in the indices of cardiorhythm, gas exchange, the characteristics of capillary blood flow in response to the cycle-ergometric test, as well as the identification of marker criteria for assessing the level of exercise tolerance.

Materials and methods. For the purpose, 63 young men were studied - students aged 17 to 19 years from among the Caucasians born in the region in the 1-2 generation who are students of the North-eastern State University (Magadan). The examination was conducted in physical education classes before the load, which implies the presence of medical admission, the absence of chronic diseases in the stage of exacerbation and complaints about the state of health, which was the direct criterion for inclusion in the studies.

Subjects were offered a modified PWC170 test with a standard load, according to which a load of 900 kgm / min (150 W) was set on a cycle-ergometer with a pedaling speed of 60 rpm and duration of 6 minutes. We showed earlier [5] that the degree of load tolerance can be determined on the 3rd minute of the cycle-ergometric load, so that the pedaling time was reduced to 3 minutes. The differentiation of the subjects according to the level of resistance to physical activity was carried out on the basis of the heart rate at the 3 minute of the sample. In the case of an increase in this index above 139 bpm at the peak of the load, the subject was assigned to 1 group with reduced exercise tolerance, whereas at a heart rate of less than 139 bpm, the examinee was assigned to group 2 with normal load resistance. Body length and body weight in the first group were 66.8 ± 1.0 kg, 178.4 ± 0.08 cm, and in the second group they were 72.1 ± 1.1 kg and 180.1 ± 0.9 cm, respectively.

The recording of the heart rate variability was carried out both at rest and during the cycle-ergometric exercise with the help of the Varicard device and the VARICARD-KARDi software and taking into account the methodological recommendations of the group of Russian experts [1]. Further the following HRV parameters were analyzed: the difference between the maximum and minimum values of the cardiointervals (MxDMn, ms); the square root of the sum of the differences in the series of cardiointervals (RMSSD, ms); number of pairs of cardiointervals with a difference of more than 50 ms in % of the total number of cardiointervals (pNN_{50}, ms); standard deviation of the full array of cardiointervals (SDNN, ms); the index of the tension of regulatory systems (SI, unit units); total power of the heart rate spectrum (TP, ms^2), the power of the spectrum of the high-frequency component of the heart rate variability in the range 0.4-0.15 Hz (respiratory waves) (HF, ms^2); power spectrum low-frequency component of heart rate variability in the range of 0.15-0.04 Hz (LF, ms^2); the power of the spectrum of a very low-frequency component of the heart rate variability in the range 0.04-0.015 Hz (VLF, ms^2). The total power of the cardiorhythm spectrum (TP) in the process of rebreathing was calculated without taking into account the ultra-low frequency component (ULF) based on the requirements for the correctness of the application of the analysis of short time series using the Fourier transform method. In addition, the ratio of the low-frequency and high-frequency components of the heart rate variability (LF/HF, conventional units) was determined. To analyze the spectral characteristics of HRV, a 3-minute stretch of the cardio-intervalogram was used to perform the cycle-ergometric exercise, which allowed having more than 250 cardiointervals in the analyzed area, which is a necessary criterion for the analysis of cardiac rhythm [1].

The levels of energy metabolism, as well as the parameters of the external respiration system were studied using the Medgraphics VO2000 (USA) metabolograph. Energy expenditure in the state of rest per minute (Kcal / min, kcal), energy consumption in a state of rest per day (REE day, kcal), respiratory quotient (RQ, conventional units), respiratory rate (RR, cycle / min), total volume of low voluntary ventilation, TV LVV (Vt BTPS, ml), low voluntary ventilation (VE BTPS, L), carbon dioxide emission (VCO_2, mL / min), oxygen consumption (VO_2, mL / min), carbon dioxide concentration and oxygen in the exhaled air (FET CO_2, FET O_2,%), the proportion of carbohydrates and fats in the energy substrate (CHO / REE, Fat / REE,%), oxygen consumption per kilogram weight, OC (Ox. Cons / kg, mL / kg) and oxygen utilization factor (Ox. Util. Fact., mL / L).

The rate of capillary blood flow was measured by the movement of erythrocytes in the capillary in the area of the cutaneous ridge of the nail bed using a computer capillaroscope "Capillaroscan-1" (Russia, LLC "New Energy Technologies"). The software of the device made it possible to evaluate the average speed of the erythrocyte movement over the specifically studied capillaries, as well as the length and diameter of the capillary sections. The temperature in the microcirculation study zone was measured using an infrared receiver built into the capillaroscope.

Examinations of young men were conducted in a room with a temperature of 19-21 °C, mainly in the first half of the day. The study was carried out in accordance with the principles of the Helsinki Declaration (2008). The study protocol was approved by the Ethics Committee of Biomedical Research at the All-Russia Research Center of Far Eastern Branch of the Russian Academy of Sciences (Ethical Protocol No. 004/013, dated December 10, 2013). All subjects were informed of the nature, purpose of the study and gave written consent to participate in it.

The obtained results were subjected to statistical processing with application of the package of applied programs Statistica 7.0. The normal distribution of the measured variables was checked based on the Shapiro-Wilk test. The results of nonparametric processing methods are presented as a median (Me) and interquartile range in the form of 25 and 75 percentile (C_{25} and C_{75}), and parametric ones are mean value (M) and its standard error (± SE). For independent samples, the significance level of differences for samples with a distribution not differing from normal was determined using Student's t-test for independent samples and in the case of samples with a distribution different from normal-the Mann-Whitney criterion was used. In dependent samples, the statistical significance of the differences was determined using Student's t-test with parametric distribution and the non-parametric Wilconson criterion for coupled samples with a distribution different from normal. The critical level of significance (p) was assumed to be 0.05; 0.01; 0.001.

Results and discussion. Table 1 presents the main indicators of the frequency characteristics of the heart rate variability at each stage of the cycle-ergometric exercise in representatives of two groups. An analysis of the minute increase in the dynamics of heart rate revealed a number of differences depending on the type of resistance to the load. For example, the boys of the 1st group showed statistically significantly higher HR values at each stage of the load relative to those in the 2nd group, as well as a higher rate of increase in heart rate, reaching 150 beats / min by the 3rd minute, whereas in the group with a normal tolerance to the load, this value was 129 bpm. Obviously, regardless of the type of load resistance, there were qualitatively similar shifts in the dynamics of RMSDD, the indices which, from the third minute, did not differ in the dynamics between the groups studied. But at the same time the RMSDD index had statistically significantly lower values, in the group with a low tolerance at the 3rd minute of the load.

The higher informative value of the degree of assessment of load tolerance can be attributed to the MxDMn and SDNN, in the dynamics of which there were differences in the representatives of the two groups: in persons with normal stability, there was a lack of dynamics in response to the load already in the 2nd minute, whereas in the group with low resistance the decrease in these indicators was fixed until the end of the load. It is necessary to note significantly higher SI indices from the 3rd minute of the load in the representatives of the 1st group. Analysis of the spectral characteristics of HRV (Table 2) revealed a decrease in all parameters in response to the cycle-ergometric test, with a more pronounced dynamics observed in the group with reduced tolerance to the load. Table 3 presents the calculated coefficients reflecting the degree of influence in the provision of the heart rate sympathetic and parasympathetic link of the ANS. The obtained results indicate different dynamics of the estimated coefficients in the representatives of the two groups, which is more pronounced in the group with low resistance to the load.

Table 4 shows the parameters of gas exchange and external respiration against the background and load during the performance of the cycle-ergometric test in young men with different levels of tolerance to the load. In the intergroup comparison of people with different resistance to exercise, it was found that the differences were observed against the background and at the 3rd minute of the sample, in contrast to the 2nd minute, where no significant differences were noted. At rest, the oxygen concentration in the exhaled air was higher in people with low, and carbon dioxide - in people with normal tolerance to the load. In this case, the individuals from the second group had a significantly higher oxygen utilization factor. By the third minute of the load, the number of differing values doubled, affecting the ratio of fats and carbohydrates in the energy substrate, as well as oxygen consumption. At the initial stage of the cycle-ergometric exercise on most indicators, the young men of both groups start to register statistically significant differences. Note that this affects both time intervals: "background - the 2nd minute" and "2-minute - 3-rd minute", while the increase in the indicators for young men of the two groups are observed.

Table 5 presents the indices of blood microcirculation at rest and at the peak of the cycle-ergometric test in young men with different levels of tolerance to the load. In a state of rest, both groups practically did not differ in terms of microcirculation, significant differences were noted only in the rate of blood flow in the arterial part of the capillary against the background. In response to the cycle-ergometric test, when comparing the two groups of subjects, an increase in the diameter of the venous and transitional part of the capillary was detected, and the temperature of the examined area of the skin also increased.

It is known that physical exercise, especially aerobic activity, affects the balance of the autonomic nervous system by increasing parasympathetic tone and reducing sympathetic activity [21] and improves the MOC (maximum oxygen consumption). Thus, our data obtained, along with the results of other authors [11] give us reason to conclude that the values of the heart rate of the background loading period may be a criterion for assessing the level of physical performance, the numerical values of which are known to be due to greater activity of the parasympathetic link of the ANS [21]. The physical load intensity of more than 100 W is now considered as a sufficiently high load leading to physiological stress and to a complete depression of parasympathetic modulation (which results in a significant activation of the sympathetic link of the ANS). An analy-

Table 1

Frequency characteristics of heart rate variability in young men with different levels of exercise tolerance during the cycle-ergometric test performance

Parameter	Cycle test stages				Differences significance between groups		
	Baseline	1st min	2nd min	3rd min	Baseline-1st min	1st -2nd min	2nd -3rd min
Low exercise tolerance group (1)							
HR, BPM	*70.9 (63.7;79.5)	*117.9 (112.4;123.4)	*140.1 (131.8;144.8)	*150.1 (143.2;152.9)	p<0.001	p<0.001	p<0.001
MxDMn, ms	366.1 (277.9;417.3)	207 (174;268)	66 (59;78)	*41 (33;61)	p<0.001	p<0.001	p<0.001
RMSSD, ms	39..9 (33.6;53)	11.2 (8.9;17.5)	5.9 (4.6;7.4)	*5.7 (3.9;8)	p<0.001	p<0.001	p=0.16
SDNN, ms	72 (49.6;83)	45.3 (40.4;57.4)	15.3 (12.5;17.6)	*8.4 (6.2;12.3)	p<0.001	p<0.001	p<0.001
SI., c. u.	51.1 (30.8;82.6)	302.3 (208.6;435.3)	2364.9 (1615;3106.8)	*4757.9 (2447.4;10416)	p<0.001	p<0.001	p<0.001
Normal exercise tolerance group (2)							
HR, BPM	63.1 (58.6;67.7)	106.9 (104.6;112.3)	124.5 (121;129.3)	129.7 (126.5;137.6)	p<0.001	p<0.001	p<0.001
MxDMn, ms	424.4 (312.7;535)	245 (199.8;333.3)	72.6 (48.8;98.8)	52.5 (45.8;76)	p<0.001	p<0.001	p=0.15
RMSSD, ms	52.2 (41.5;64.2)	13.6 (10.3;16.7)	7.1 (4.8;14.1)	7.3 (5.8;15.7)	p<0.001	p<0.05	p=0.20
SDNN, ms	73.9 (53.2;100)	53.9 (45.8;69.2)	15.6 (10.4;19.7)	10.8 (8.8;12.5)	p<0.001	p<0.001	p=0.09
SI., c. u.	34.5 (22.3;71.6)	206.8 (150.5;331.1)	2003.1 (993.4;4324.5)	3901.1 (1794.7;5439.3)	p<0.001	p<0.001	p<0.05

Note: here and below the * sign denotes statistically significant differences between groups with different exercise tolerance

Table 2

Heart rate variability spectral parameters in young men with different tolerance to exercise during the cycle-ergometric test performance

Parameter	Cycle test stages		Differences significance between groups
	Baseline	1st -3rd min of exercise	
Low exercise tolerance group (1)			
TP, ms²	3242.4 (1889.8;5472.2)	*222.6 (141;389)	p<0.001
HF, ms²	629 (361.1;1771.4)	*32.8 (20.6;70.2)	p<0.001
LF, ms²	1157.1 (898.9;1963.2)	*101.2 (50.6;180)	p<0.001
VLF, ms²	516.1 (361.3;768.8)	*71.1 (46.7;128.1)	p<0.001
LF/HF, c. u.	1.7 (1.1;3.4)	2.2 (2.1;3.7)	p<0.001
Normal exercise tolerance group (2)			
TP, ms²	3506.6 (2107.1;6361.4)	442 (292.5;565.5)	p<0.001
HF, ms²	932.4 (582.2;1421.8)	57 (42.4;103.3)	p<0.001
LF, ms²	1138.735 (715.992;1971.212)	218.6 (120.6;255.1)	p<0.001
VLF, ms²	710.2 (301.0;1129.6)	132 (94.6;152.2)	p<0.001
LF/HF, c. u.	1.3 (1.0;2.3)	2.1 (1.8;3.8)	p<0.001

Table 3

Coefficients reflecting the degree of the parasympathetic and sympathetic link contribution in providing the heart rate at each exercise stage in groups with different exercise tolerance

Parameters studied	Cycle test stages			
	Baseline	1st min	2nd min	3rd min
Heart Rate / MxDMn	0.19	0.61	2.12	3.61
	0.14	0.43	1.71	2.52
Heart Rate / SI * 1000	1387	390	59	32
	1828	516	62	33

Note: in the numerator there are indices of the low exercise tolerance group, in the denominator – normal tolerance group indices

sis of the minute increase in heart rate (Table 1) in response to the cycle-ergometric test showed a more pronounced increase in its degree in the group with low resistance to exercise, reaching 150 bpm to the 3rd minute of the load, whereas in the group with normal exercise tolerance the heart rate was only 129 beats per minute. The rapid increase in HR at the beginning of the load is the result of a sharp parasympathetic decline, whereas sympathetic activation causes a relatively slow increase in heart rate in submaximal performance [9].

Per-minute analysis of changes in the statistical indices of heart rate variability (Table 2) revealed a number of differences in their dynamics, depending on the group of subjects. At the same time, the MxDMn, SDNN parameters were characterized by the highest degree of informativeness with respect to the parasympathetic link of regulation, the significant decrease of which in response to the load reflected the degree of decrease in parasympathetic activity. It should be noted that in the sample with normal exercise tolerance, already from the 2nd minute, the decrease relative to the previous minute segment of the cycle-ergometer was not observed, and the subjects of this group were characterized by higher numerical values of MxDMn, SDNN at the peak of the load. In the group with reduced resistance to physical activity, the SI index, reflecting the degree of assessment of sympathetic effects on autonomic cardiac modulation, had statistically higher values in individuals of the 1st group at the 3rd minute of the load.

To assess the contribution of sympathetic and parasympathetic supply of heart rate, we performed calculations of the ratio of cardiac rhythm and heart rate at rest and at each load minute and analyzed their dynamics, depending on the degree of resistance to physical activity. Considering the high degree of informativeness for the evaluation of the parasympathetic link, the MxDMn index was chosen, and SI for the sympathetic contribution (Table 3). The HR/MxDMn ratio had a more pronounced increase in the group with low resistance to exercise due to high HR values against the background of low MxDMn values. The positive dynamics of this coefficient indicates a decrease in the contribution of parasympathetic modulation in ensuring the level of heart rate at each stage of the load, which is more typical for young men of the 1st group. This fact may indicate a constant decrease in the inhibitory effect of the parasympathetic link at the heart rate, which leads to such high values when the peak load is reached in persons of this group. The coefficient reflecting the degree of activation of the sympathetic link (HR/SI * 1000) did not differ in dynamics and numerical values in the representatives of the two groups, which indicates that there is no difference in the degree of activation of the sympathetic link in providing the loading heart rate. Based on the dynamics of the coefficients analyzed, it can be concluded that even at the 3rd minute of the load it is possible to assess the degree of resistance to the load, while the design coefficients reflecting the degree of decrease in the parasympathetic link of the ANS will be the markers of the autonomic maintenance of the level of the loading heart rate.

Analysis of the spectral characteristics of the cardiorhythm (Table 2) in response to the stress test also revealed the presence of a pronounced dynamics of all the studied indicators, but having certain features depending on the degree of resistance to the load. Note that against the background of the absence of statistically significant background intergroup differences between these indicators at the peak of the load, differences were observed due to a more pronounced decrease in the 1st group. A significant decrease in the loading cardiorhythmogram of LF, HF and VLF waves, accompanied by a decrease in the duration of the cardiointervals, indicates a consistent increase in sympathetic and a decrease in parasympathetic influences reaching their poles at maximum heart rate [6]. However, in the group with a low degree of resistance to the load, the shifts to the area of decrease in the activity of the parasympathetic link were more pronounced than in young men with a normal level of tolerance to the cycle-ergometric sample. The balance of sympatho-vagal influences on the heart rhythm (LF/HF) at the peak of the load sharply shifted towards the predominance of activity of the sympathetic link with the same degree of severity in the representatives of the two groups, which is also confirmed by the

Table 4

Indirect calorimetry and external respiration indicators in young men with different exercise tolerance during the cycle-ergometric test performance

Cycle test stages				Differences significance between groups	
Parameter	Baseline	2nd min	3rd min	Baseline -2nd min	2nd-3rd min
Low exercise tolerance group (1)					
REE day, kcal	1975±117.5	12818±166.8	13754±259.6	1.3×10^{-43}	0.01
RQ, c. u.	0.85±0.03	0.93±0.02	1.08±0.02	0.05	3.7×10^{-05}
RR, cycle/min	13.9±0.86	23±1.11	24.2±1.26	5.9×10^{-8}	0.23
Vt BTPS, mL	641±40	1961±96	2222±144.8	8.7×10^{-17}	0.07
VE BTPS, L/min	8.6±0.48	41.9±1.17	50.1±1.09	1×10^{-29}	5.1×10^{-06}
V CO_2, ml/min	240.6±17.5	1660±41.2	1996±43.3	2.3×10^{-33}	1×10^{-06}
V O_2, mL/min	280.4±16.2	1791±23.1	*1858±38.4	9.1×10^{-44}	0.07
FET CO_2, %	*3.5±0.1	5±0.09	5±0.1	2.6×10^{-14}	0.35
FET O_2, %	*16.8±0.15	15.5±0.11	*16±0.11	7.7×10^{-09}	6.9×10^{-04}
CHO/REE, %	50.5±8.7	69.9±5.73	*96.2±2.21	0.05	9.2×10^{-05}
Fat/REE, %	48.9±8.7	37.8±6.21	*3.8±2.21	0.15	4.8×10^{-06}
Ox. Cons/kg, mL/kg	4.1 ±0.25	26.6±1.08	27.5±1.23	6×10^{-25}	0.29
Ox. Util. Fact., mL/L	*33±1.37	43.2±1.06	*37.3±0.98	4.2×10^{-07}	1.5×10^{-04}
Normal exercise tolerance group (2)					
REE day, kcal	2092±67.6	13069±285.5	14362±270.8	1.3×10^{-36}	1.9×10^{-03}
RQ, c. u.	0.84±0.02	0.89±0.02	1.03±0.02	0.05	4.6×10^{-06}
RR, cycle/min	13.6±0.71	21.6±0.95	23.4±1.34	2×10^{-08}	0.13
Vt BTPS, mL	668±30.8	2144±113.4	2286±123.9	1.3×10^{-16}	0.2
VE BTPS, L/min	8.2±0.37	40.9±1.14	49±1.24	1.8×10^{-30}	1.6×10^{-05}
V CO_2, mL/min	249.6±9.42	1635±40.6	1984±41.5	2.7×10^{-34}	2.6×10^{-07}
V O_2, mL/min	298.5±9.52	1843±41.85	1968±41.4	7.3×10^{-36}	0.05
FET CO_2, %	3.9±0.09	5±0.11	5.2±0.1	1.5×10^{-10}	0.17
FET O_2, %	16.3±0.12	15.2±0.12	15.6±0.13	2.1×10^{-07}	0.01
CHO/REE, %	46.8±4.8	61.6±4.5	89.9±2.51	0.05	1.5×10^{-06}
Fat/REE, %	53.5±4.9	41.8±4.2	10.3±2.49	0.05	5.1×10^{-08}
Ox. Cons/kg, mL/kg	4±0.1	24.8±0.72	26.4±0.67	1.7×10^{-31}	0.05
Ox. Util. Fact., mL/L	37.3±1.1	45.6±1.09	40.7±1.1	2.4×10^{-06}	2.9×10^{-03}

Table 5

Blood microcirculation indices in young men with different exercise tolerance before and after performing the cycle-ergometric test

Parameter	baseline	exercise, 3 min	Differences significance
Low exercise tolerance group (1)			Baseline - Exercise
Diameter of arterial department of capillaries, mcm	9.3±0.3	*8.7±0.3	0.10
Venous department diameter, mcm	13.9±0.4	*15.8±0.3	$1.4*10^{-3}$
Transition department diameter, mcm	18.1±0.5	20.7±1.1	0.05
Capillary length, mcm	337.2±17.8	325.0±18.4	0.32
Arterial department speed, mcm/s	*239.0±15.8	*260.8±18.8	0.19
Venous department speed, mcm/s	170.3±14.1	*179.7±13.3	0.32
Transition department speed, mcm/s	189.3±13.0	186.8±16.1	0.45
Frequency of sludges, units	2.7±0.2	2.3±0.2	0.10
Temperature, °C	30.1±0.6	*31.7±0.2	0.01
Normal exercise tolerance group (2)			Baseline - Exercise
Arterial department diameter, mcm	9.0±0.4	9.8±0.3	0.08
Venous department diameter, mcm	12.6±0.5	14.8±0.2	$2.7*10^{-4}$
Transition department diameter, mcm	17.7±0.7	21.9±0.7	$2.4*10^{-4}$
Capillary length, mcm	326.2±14.3	349.2±11.7	0.11
Arterial department speed, mcm/s	374.4±30.0	317.6±11.2	0.05
Venous department speed, mcm/s	217.8±19.7	241.1±13.4	0.39
Transition department speed, mcm/s	222.2±23.1	169.5±9.1	0.05
Frequency of sludges, units	3.0±0.2	2.2±0.3	0.01
Temperature, °C	31.2±0.6	34.1±0.1	$6.9*10^{-5}$

similar dynamics of the calculated heart rate / SI * 1000 (Table 3).

The results of the survey show that of the 13 indicators characterizing the state of gas exchange and external respiration, background differences in the young men of the two groups were observed only in 3 values characterizing metabolic processes in the body (Table 4). Thus, the value of the carbon dioxide content in the exhaled air (FET CO_2) and the oxygen utilization factor (Ox. Util. Fact.) were higher for young men resistant to the load. At the same time, the oxygen level in the exhaled air (FET O_2) was statistically significantly higher in non-load resistant individuals, reaching 16.8%. The obtained results indicate a more intensive course of energy processes in young men from group 2. At the peak of the stress test, the oxygen consumption (VO_2), carbon dioxide (VCO_2) and oxygen consumption (Ox. Cons / kg) were significantly increased in them, which indicates a more intensive flow energy exchange processes in the body, whose values (REE) were significantly higher than the normative values [14]. It should also be noted that these individuals had a higher fat content as an energy substratum - 10%, while in the other group almost all the energy in the body was produced by the metabolism of carbohydrates. It is known that in a few minutes after the beginning of the cyclic loading the anaerobic processes of providing work begin to give way to a much more efficient aerobic stage of energy production - oxidative phosphorylation. Strengthening lipolysis makes it possible to optimize the energy supply of muscle tissue, allowing more than an order to increase the amount of synthesized ATP. Previous studies have shown that people with a high level of performance during physical work, there is an accelerated transition of carbohydrate metabolism to fat [2].

In this connection, attention is drawn to the fact that in young men with a low tolerance to the load, a higher value of the respiratory quotient (RQ) was observed, which also reflects the utilization of one or another energy substratum. The increase of this indicator is higher than one, due to the increase in the ratio of VCO_2 to VO_2, signals an increase in the anaerobic nature of metabolic processes, in which the only way to regenerate ATP is an energy-poor glycolysis process [7].

One of the main compensatory mechanisms aimed at maintaining the level of oxygen in the blood, as well as satisfying the oxygen demand of the body in muscle activity is activation of the respiratory function [3]. In previous studies by other authors, it was shown that in the cycle-ergometry, the indicators of the LVV of the young men increased more largely due to the increase in TV LVV than in the RR, compared with those of the younger age groups, which is explained by the completion of the morphofunctional formation of the external respiration system [3]. In our studies, during a stress test, the black hole increased by less than 70% compared to the background indicators, while the TV LVV increased almost 3.5 times. When comparing the 2nd and 3rd minutes of the load, this picture only increased, and the growth of the RR practically ceased.

It can also be seen that, during the sample, individuals with normal tolerance to the load, as well as the background, were significantly higher than the oxygen utilization factor. Considering the practically identical fan supply of the organism (LVV) in persons of both groups, this may indicate an increase in the diffusion of oxygen between the alveolar air and blood and the improvement of the oxygen transport function in the body of the boys from the 2nd group.

Since the important function of blood circulation during muscular activity is thermoregulation, it is likely that an increase in temperature in the idle parts of the body is associated with an intensification of heat transfer during physical exertion. These data are confirmed in the studies of other authors [12, 13].

Analysis of the record of erythrocyte movement showed that a statistically significant change in the rate of blood flow occurred only in a group with a normal level of resistance. Apparently, the decrease in the blood flow velocity in the skin of the distal phalanges of the fingers observed at the peak of the sample is due to the outflow of blood to the actively working muscles. This redistribution of blood flow is necessary to meet the metabolic needs of the body [18]. The groups under comparison were also characterized by a more pronounced degree of dilatation of the capillary among boys with a normal level of resistance. Apparently, the observed changes are associated with an increase in the mass transfer of erythrocytes in the capillary bed. The lack of blood flow dynamics in the group with a low tolerance to physical activity indicates the rigidity of the vascular bed, which may be a factor in reducing resistance to physical stress.

Conclusion. Given that the specific task of our research was the selection and justification of the most informative indicators reflecting the degree of tolerance to the load, we can say the following: the most important indicator reflecting the degree of resistance to the cycle-ergometric test is the HR index both at rest and during execution cycle-ergometry.

Analysis of the HRV parameters allowed us to conclude that the cardiac rhythm parameters at rest, with the exception of the heart rate, cannot be the criteria for assessing the degree of resistance to physical activity, whereas the pattern of changes in the characteristics of the heart rate variability in the course of the sample is already at the 2nd minute of the load can give an estimate of the degree of resistance to the load. The most informative criterion will be the MxDMn index in relation to the heart rate, reflecting the degree of decrease in parasympathetic activation in response to the submaximal power load. The pronounced dynamics of the characteristics described above in the two groups examined reflects a decrease in the activity of the parasympathetic link in the regulation of the heart rhythm, which is more pronounced in the group of persons with low resistance to exercise.

When considering the gas exchange parameters, it can be concluded that the marker values can be the values of the concentration of carbon dioxide in the exhaled air and the oxygen utilization factor (Ox. Util. Fact) at rest, which are higher in persons with normal tolerance to the load.

During the test, oxygen consumption (OC) can serve as such a criterion, the values of which in individuals with normal resistance continue to increase, while those with low tolerance go to the "plateau" and do not change by the 3rd minute of the load.

The noted changes in microcirculation indices indicate a different degree of reactivity of the vascular bed, depending on the level of tolerance to physical activity. It is shown that the rate of capillary blood flow can be considered as one of the indicators characterizing the functional state of the organism as a whole and determining the level of efficiency.

Thus, the degree of decrease in activity of the parasympathetic link in response to a functional test, the magnitude of background and exercise heart rate, the concentration of carbon dioxide in the exhaled air and the oxygen utilization factor at rest, the dynamics of oxygen consumption, and the rate of capillary blood flow can be considered as prognostic criteria for assessing the level of physical working capacity.

References

1. Баевский Р.М., Иванов Г.Г., Чирейкин Л.В. [и др.]. Анализ вариабельности сердечного ритма при использовании различных электрокардиографических систем (методические рекомендации). *Вестник аритмологии*. 2001; 24: 65-83. [Baevskij RM, Ivanov GG, Chirejkin LV. [et al.] Heart rate variability analysis when using different electrocardiographic systems (guidelines). *Vestnik aritmologii*. 2001; 24: 65-83. (In Russ.).]

2. Арсеньев Е.Н. Работоспособность и здоровье человека на Севере. Мурманск; 1993. [Arsenyev EN. Human work capacity and health in the North. Murmansk; 1993. (In Russ.).]

3. Ванюшин Ю.С. Елистратов Д.Е. Типологические особенности кровообращения юношей при адаптации к физической нагрузке. *Ульяновский медико-биологический журнал*. 2017; 1: 131-138. [Vanjushin JuS, Elistratov DE. Blood circulation typological peculiarities in young men at adaptation to physical exercise. *Ul'janovskij mediko-biologicheskij zhurnal*. 2017; 1: 131-138. (in Russ.).] DOI: 10.23648/UMBJ.2017.25.5254

4. Максимов А.Л., Аверьянова И.В. Информативность пробы с ререспирацией для оценки устойчисовти организма юношей к сочетанному действию гипоксии и гиперкапнии. *Российский физиологический журнал им. И.М. Сеченова*. 2017; 103(9): 1058-1068. [Maksimov AL, Averyanova IV. The informative nature of the sample with reserpiration for assessing the resistance of young men to the combined effect of hypoxia and hypercapnia. *Rossijskij fiziologicheskij zhurnal im. I.M. Sechenova*. 2001; 103(9): 1058-1068. (in Russ.).]

5. Максимов А.Л., Аверьянова И.В., Харин А.В. Перестройки кардиогемодинамики и микроциркуляции крови при локальной холодовой пробе у юношей уроженцев Севера. *Физиология человека*. 2017; 3: 142-153. [Maksimov AL, Averyanova IV, Kharin AV. Blood cardiohemodynamics, cardiointervalography and microcirculation restructuring in a local cold test in the North-born young men. *Fiziologija cheloveka*. 2017; 3: 142-153. (in Russ.).] DOI: https://doi.org/10.7868/S0131164617030122

6. Похачевский А.Л., Лапкин М.М. Значения изменчивости кардиоинтервалов при нагрузочном тестировании *Физиология человека*. 2017; 43(1): 81-88. [Pohachevskij AL, Lapkin MM. The meaning of cardio intervals variability at exercise testing]. *Fiziologija cheloveka*. 2017; 43(1): 81-88. (in Russ.).] DOI: https://doi.org/10.7868/s0131164616060151

7. Портниченко В.И., Ильин В.Н., Филиппов М.М. Проявление гипометаболического эффекта в реакциях системы дыхания у спортсменов на физическую нагрузку при адаптации в среднегорье. *Ульяновский медико-биологический журнал*. 2017; 2: 117-124. [Portnichenko VI, Ilyin VN, Phillippov MM. Manifestation of hypometabolic effect in athletes' respiratory system reactions for physical exercise during adaptation in the middle mountains. *Ul'janovskij mediko-biologicheskij zhurnal*. 2017; 2: 117-124. (in Russ.).] DOI: https://doi.org/10.23648/UMBJ.2017.26.6226

8. Pichot V, Busso T, Roche F. [et al.]. Autonomic adaptations to intensive and overload training periods: a laboratory study. *Med Sci Sports Exerc*. 2002; 34(10):1660–1666. DOI: https://doi.org/10.1097/00005768-200210000-00019

9. Victor RG, Seals DR, & Mark AL. Differential control of heart rate and sympathetic nerve

activity during dynamic exercise: insight from intraneural recordings in humans. *J Clin Invest*. 1987; 79(2):508–16. DOI: https://doi.org/10.1172/jci112841

10. Luria T, Matsliah Y, Adir Y. [et al.]. Effects of a prolonged submersion on bone strength and metabolism in young healthy submariners. *Calcif. Tissue Int*. 2010; 86(1):8–13. DOI: https://doi.org/10.1007/s00223-009-9308-9

11. Kim MK, Tanaka K, Kim MJ. [et al]. Exercise training-induced changes in heart rate recovery in obese men with metabolic syndrome. *Metab Syndr Relat Disord*. 2009; 7:469–476. DOI: https://doi.org/10.1089/met.2008.0086

12. Gleeson M. Temperature regulation during exercise. *Int. J. Sports Med*. 1998; 19:96–99. DOI: https://doi.org/10.1055/s-2007-971967

13. Gonz'alez-Alonso J. Human thermoregulation and the cardiovascular system. *J. Exp. Physiol.* 2012; 97(3):340–346. DOI: https://doi.org/10.1113/expphysiol.2011.058701

14. Harris J.A., Benedict F.G. "A Biometric Study of Human Basal Metabolism". *Proceedings of the National Academy of Sciences of the United States of America*. 1918; 4(12):370–373. DOI: 10.1073/PNAS.4.12.370

15. Baumert M, Brechtel L, Lock J. [et al.]. Heart rate variability, blood pressure variability, and baroreflex sensitivity in overtrained athletes. *Clin J Sport Med*. 2006; 16(5):412–417. DOI: https://doi.org/10.1097/01.jsm.0000244610.34594.07

16. Malpas S.C. Sympathetic nervous system overactivity and its role in the development of cardiovascular disease. *Physiol Rev*. 2010; 90:513–557. DOI: https://doi.org/10.1152/physrev.00007.2009

17. Williamson JW, Fadel PJ, & Mitchell JH. New insights into central cardiovascular control during exercise in humans: a central command update. *Exp Physiol.* 2006; 091:51–58. DOI: https://doi.org/10.1113/expphysiol.2005.032037

18. Laughlin MH, Davis MJ, Secher NH. [et al.]. Peripheral circulation. *J. Compr. Physiol.* 2012; 2(I):321–447. DOI: https://doi.org/10.1002/cphy.c100048

19. Sato I., Hasegawa Y. K. Hotta Autonomic nervous control of the heart in exercising man. *Pflügers Arch*. 1980; 384:1-7. DOI: https://doi.org/10.1007/bf00589508

20. Gonzalez-Alonso J., Crandall C.G., & Johnson J.M.. The cardiovascular challenge of exercising in the heat. *J. Physiol*. 2008; 586(1):45-53. DOI: https://doi.org/10.1113/jphysiol.2007.142158

21. Tigen K., Karaahmet T., & Gürel E. [et al.]. The utility of heart rate recovery to predict right ventricular systolic dysfunction in patients with obesity. *Anadolu Kardiyol Derg*. 2009; 9:473-479.

22. Walsh T.S. Recent advances in gas exchange measurement in intensive care patients. *Br J Anaesth*. 2003; 91:120–131. DOI: https://doi.org/10.1093/bja/aeg128

I.A.Goldina, E.V.Markova

ENDOGENOUS RETROVIRUS HERV - E *λ 4-1* INFLUENCE ON IMMUNE CELLS FUNCTIONAL ACTIVITY IN MULTIPLE SCLEROSIS PATIENTS

DOI 10.25789/YMJ.2019.68.07

УДК 616.832-004.21

Purpose: a comparative study of the blood immune cells functional activity in multiple sclerosis patients associated with the human endogenous retrovirus HERV - E *λ 4-1* activation, as well as the immunomodulating properties of the homologous to a conservative region of hydrophobic transmembrane protein p15E 17 - amino acid synthetic oligopeptide.

Materials and methods. Human endogenous retrovirus HERV - E *λ 4-1env* gene expression was determined by the method of reverse transcriptase polymerase chain reaction. The spontaneous and mitogen-induced blood mononuclear cells proliferative activity of patients with a progredient course of disease, as well as blood mononuclear cells of central and peripheral organs of the immune system cells and of experimental animals when exposed to retroviral oligopeptide in culture was evaluated by the of tritium-labeled thymidine incorporation.

Results and discussion. We found that multiple sclerosis patients with activated retrovirus HERV - E *λ 4-1* are characterized by a higher blood immune cells functional activity compared with healthy donors, as well as in multiple sclerosis patients, in whose blood mononuclear cells the expression of this retrovirus was not detected. Synthetic 17 - amino acid oligopeptide, homologous to the conservative region of the hydrophobic transmembrane protein p15E of the HERV retrovirus - E *λ 4-1*, increased the functional activity of blood mononuclear cells of multiple sclerosis patients, as well as the immune system central and peripheral organs cells and blood mononuclear cells of experimental animals *in vivo*. This oligopeptide's effect was not genetically restricted.

Conclusion. Human endogenous retrovirus HERV - E *λ 4-1* sequence - specifically increases the immune cells functional activity in multiple sclerosis patients, which determines its role in the disease pathogenesis.

Keywords: multiple sclerosis, progredient course, human endogenous retrovirus HERV - E *λ 4-1*, retroviral oligopeptide, thymocytes, splenocytes, blood mononuclear cells, functional activity, genetic restriction.

GOLDINA Irina Alexandrovna[1]**,** Researcher of Neuroimmunology Laboratory, Federal State Budgetary Scientific Research Institute of Fundamental and Clinical Immunology, 14 Yadrincevskaya str., Novosibirsk, Russian Federation**,** igoldina@mail.ru, +7 905 936 88 80**,** ORCID iD: https://orcid.org/0000-0002-8246-9552**; MARKOVA Evgeniya Valerievna**[1, 2]**,** DM, Professor, Head of Neuroimmunology Laboratory, Chief Researcher of Federal State Budgetary Scientific Research Institute of Fundamental and Clinical Immunology; Professor of Federal State Budgetary Educational Institution of Higher Education "Novosibirsk State Pedagogical University», 28 Viluyskaya str., Novosibirsk, Russian Federation, evgenya_markova@mail.ru, +7 903 934 67 86

Introduction. Multiple sclerosis (MS) is a socially significant polyetiological autoimmune disease of the nervous system with immune-mediated damage to the brain gray and white matter as a result of the inflammatory foci with fibrosis and **gliosis** of the subarachnoid and intracortical regions and secondary neurodegeneration formation [5,7]. Clinically, MS is characterized by progressive neurological dysfunction, cognitive insufficiency and affective disorders [16]. The MS incidence is characterized by a unique geographic distribution, reflecting the significance in the etiology of genetic susceptibility, disturbances of the epigenetic mechanisms of the gene expression regulation, as well as extragenetic factors, in particular, the latitude gradient, with the disease prevalence in the regions near the North and South Poles [1,9,14].

Among the autoimmune inflammation triggers in the nervous system in MS, endogenous retroviruses (ER) are considered to be one of the most significant that can induce polyclonal activation of T lymphocytes [8]. These retroviruses are an integrated as a provirus form of exogenous and are a type of mobile genome elements - RNA retrotransposons, DNA sequences that make up to 8% of the human genome, distributed in more than 700,000 discrete loci [6].

In according to the modern classification, ERs are combined into 3 classes, represented by 50 families of 3173