Barylyak Liliya G., Tsymbryla Volodymyr V., Zukow Walery, Popovych Igor L. Relationships between parameters of plasma lipoproteines profile and heart rate variability. Journal of Education, Health and Sport. 2019;9(12):238-253. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2019.09.12.025
https://apcz.umk.pl/czasopisma/index.php/JEHS/article/view/JEHS.2019.09.12.025
https://zenodo.org/record/3739169

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

Received: 15.12.2019. Revised: 20.12.2019. Accepted: 31.12.2019.

RELATIONSHIPS BETWEEN PARAMETERS OF PLASMA LIPOPROTEINES PROFILE AND HEART RATE VARIABILITY

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Summary

Background. Relationships between parameters of plasma lipoproteines profile and heart rate variability (HRV) are one of the subjects of research at the Truskavetsian Scientific School of Balneology. The contradictions and ambiguities obtained results indicate that research in this area remains relevant. The **purpose** of this study is to analyze the canonical correlation between HRV parameters, on the one hand, and plasma lipoproteins profile parameters, on the other. **Material and Methods.** The object of observation were 20 volunteers: ten women and ten men aged 33-76 years without clinical diagnose but with dysfunction of neuro-endocrine-immune complex and metabolism, characteristic for premorbid state. We recorded twice electrocardiogram to assess the parameters of HRV (software and hardware complex "CardioLab+HRV"). Then we estimated plasma lipoproteines spectrum: High-, Law- and Very Law-Density Lipoproteines Cholesterol levels. **Results.** Found that plasma level of HD LP Cholesterol is upregulated by vagal influences, whereas sympathetic influences causes a downregulation. Constellation of HRV parameters determines its level by 17%. The VLD LP Cholesterol plasma level is upregulated by sympathetic influences and downregulated by vagal tone; determination rate is 22%. The maximum degree of sympathetic (directly) and vagus (inversely) determination was found in relation to LD LP Cholesterol plasma level (31%). In general, the state of autonomic nerve regulation determines the plasma lipid profile by 63%. **Conclusion.** The content of Cholesterol in the composition of lipoproteins of different density substantially subject to the regulatory influence of the autonomic nervous system.

Key words: High-, Law- and Very Law-Density Lipoproteines Cholesterol, HRV, Relationships.

INTRODUCTION

There is a panel of metabolic diseases including dyslipidemia, obesity, hypertension, insulin resistance/type 2 diabetes and cardiovascular diseases [3]. The sympathetic nervous system directly innervates peripheral fat depots including both brown (BAT) and white adipose tissue (WAT) and plays a key role in BAT thermogenesis and WAT lipolysis [11,24,25,35]. On the other hand, cholesterol is affected on sympathetic neurons [9,23]. Data on the effects of adrenoblockers on lipid profiles in patients with hypertension [6,31,36] as well as in animals with experimental atherosclerosis [4] are mixed.

Relationships between parameters of plasma lipoproteines profile and heart rate variability (HRV) are one of the subjects of research at the Truskavetsian Scientific School of Balneology.

SV Ruzhylo et al [30], compared with histograms of HRV and plasma lipid profile of spa patients, found normal sympathetic tone (by AMo) in 35,7% of individuals, decreased by 38,1%, and increased by 26,2%. Normal vagus tone (by MxDMn) was also found in 35,7%, increased in 42,9%, and decreased in 21,4%. Humoral canal (by Mo) within the norm was found in 59,9% of people, vagotonic shift in 19,0%, and sympathotonic shift in 21,5%. Baevskiy's Stress Index (BSI), as an integral expression of autonomic homeostasis, was found in 35,7% of the surveyed in the eitonia range, in vagotonia in 38,1%, and in sympathotonia in 26,2%. On the other hand, with respect to the plasma lipid profile, 54,8% of patients showed low high-density lipoproteins cholesterol (HD LP Cholesterol) still 16,7% lower than the average, but only 9,6% showed higher than the average and 2,4% high level. The high incidence of low levels of anti-atherogenic lipoproteins is accompanied by a high incidence of very low-density lipoproteins (VLD LP) – 50,0%, in 7,1% of patients higher than average VLD LP levels are found, while low levels are only 7,1%, lower than average in 19,0% of people. However, the low-density lipoproteins (LD LP) cholesterol content in 59,5% of subjects was within the normal range and 40,5% was low. The Klimov's coefficient of atherogenicity calculated by these parameters was high in 61,5% of patients, within the norm in 31,0%, while low level only in 7,1%.

BYa Huchko [13], influenced by the concept of lipid-mobilizing action of major stress-releasing hormones (catecholamines and corticosterone), found that a day after 4 hours of immobilization-cold stress, in 51% of rats in both sexes, BSI increased 61%. This was due to an increase in sympathetic tone (by AMo) in combination with a decrease in vagus tone (by MxDMn) in the absence of changes in the humoral canal of regulation (by Mo). However, such a vegetative response was accompanied, contrary to expectations, by a 39% decrease in plasma LD LP Cholesterol levels in the absence of significant changes in both VLD and HD LP Cholesterol. In 30% of rats in both sexes, a more pronounced sympathotonic shift in sympatho-vagal balance (+94%) was accompanied by an expected significant decrease in HD LP Cholesterol by 10% combined with an unexpected tendency to decrease LD LP Cholesterol in the absence of significant changes in VLD LP Cholesterol changes. And in the remaining 9 (19%) rats, mainly females (Sex-index=1,89, when females=2, males=1), a 26% decrease in HD LP Cholesterol (in the absence of changes in other compartments) was observed on the back of trend only to increase BSI by 24%.

The following experiment, conducted in our laboratory OV Kozyavkina [19,20,21] by a similar design, found that in the post-stress period in vagotonic rats in both sexes increase BSI by 36% is accompanied by a decrease in LD LP Cholesterol by 23%, HD LP by 2%, and VLD LP by 2%. In contrast, in sympathotonic rats increase in BSI was 32% higher, HD LP decreased by 7%, LD LP increased by 14%, and VLD LP increased by 3%.

BYa Huchko and LG Barylyak [14] in an experiment on female rats showed that the opposite changes in the components of the plasma lipid spectrum (under the influence of the course of the introduction through the tube of bioactive Naftussya water) occur regardless of the nature of the changes in autonomous nervous system tone.

A similar conclusion was reached by NV Kozyavkina [18], finding that sympathotonic shift of vegetative homeostasis in females is accompanied by an increase in LDLP level only in cases of simultaneous inhibitory thyrotropic effect. On the other hand, in cases of stimulating effect of bioactive Naftussya water, LD LP level decreases despite a similar sympathotonic shift of autonomous regulation. The same author has shown that in males, changes in the plasma lipid spectrum are even less related to the vegetotropic effects of Naftussya, mainly determined by its thyrotropic effects [17].

In the observation of women HI Vis'tak et al [22,34] found that for all variants of the vegetotropic effects of course use of bioactive Naftussya water (vagotonic, neutral, sympathotonic) levels of HD LP and VLD LP do not change naturally, and the level of LD LP tends to decrease regardless of changes in HRV parameters.

Instead, another clinical study found that under similar conditions in both sexes there is a decrease in LDLP and a tendency to increase VLDLP in the absence of HDLP changes [8], with neither BSI nor LF/HF changing naturally [28].

The contradictions and ambiguities obtained results stated here indicate that research in this area remains relevant.

MATERIAL AND RESEARCH METHODS

The object of observation were 20 volunteers: ten women and ten men aged 33-76 years without clinical diagnose but with dysfunction of neuro-endocrine-immune complex and metabolism, characteristic for premorbid (intermediate between health and illness) state [8,32].

We recorded electrocardiogram in II lead to assess the parameters of heart rate variability (HRV) (software and hardware complex "CardioLab+HRV" production "KhAI-MEDICA", Kharkiv, Ukraine). For further analysis the following parameters HRV were selected [1,2,10]. Temporal parameters (Time Domain Methods): the standart deviation of all NN intervals (SDNN), the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), the percent of interval differences of successive NN intervals greater then 50 ms (pNN_{50}); heart rate (HR), the mode (Mo), the amplitude of mode (AMo), variational sweep (MxDMn) as well as triangulary index (TINN). Spectral parameters (Frequency Domain Methods): spectral power (SP) bands of HRV: high-frequency (HF, range 0,4÷0,15 Hz), low-frequency (LF, range 0,15÷0,04 Hz), very low-frequency (VLF, range 0,04÷0,015 Hz) and ultra low-frequency (ULF, range 0,015÷0,003 Hz).

On the basis of these parameters were calculated classical indexes: LF/HF, LFnu=100%•LF/(LF+HF), Centralization Index=(VLF+LF)/HF; Baevskiy's Stress Index (BSI=AMo/2•Mo•MxDMn) and Baevskiy's Activity Regulatory Systems Index (BARSI) [1].

We calculated also for HRV the Entropy (h) of normalized SP bands using formula CE Shannon [26]:

$hHRV=[SPHF \cdot \log_2 SPHF+SPLF \cdot \log_2 SPLF+SPVLF \cdot \log_2 SPVLF+SPULF \cdot \log_2 SPULF]/\log_2 4$

Then we estimated plasma lipoproteines spectrum: total cholesterol (by a direct method after the classic reaction by Zlatkis-Zack) and content of him in composition of High-density Lipoproteins or α-lipoproteins (by the enzyme method by Hiller G. [12] after precipitation of notα-lipoproteins); Very Law-density Lipoproteins or prae-β-lipoproteins (expected by the level of triacylglycerides, by a certain meta-periodate method); Law-density Lipoproteins or β-lipoproteins (expected by a difference between a total cholesterol and cholesterol in composition α-and prae-β-lipoproteins) according to instructions [7] with the use of analyzers "Reflotron" (BRD) and "Pointe-180" (USA) and corresponding sets of reagents.

After testing volunteers within 7 days used bioactive Naftussya water (250 mL one hour before meals three times a day) from Truskavets' or Pomyarky layers [32,33], then repeated the tests listed.

Results processed using the software package "Statistica 5.5".

RESULTS AND DISCUSSION

Preliminary analysis revealed in one observed (Dr) so-called bouncing variable, namely VLF band SP (15667 msec^2) in the initial testing (Fig. 1). Although the maximum sample size for HD LP was consistent with this option, patient Dr was excluded from long-term development (to be more precise, only his primary lipid profile and HRV parameters).

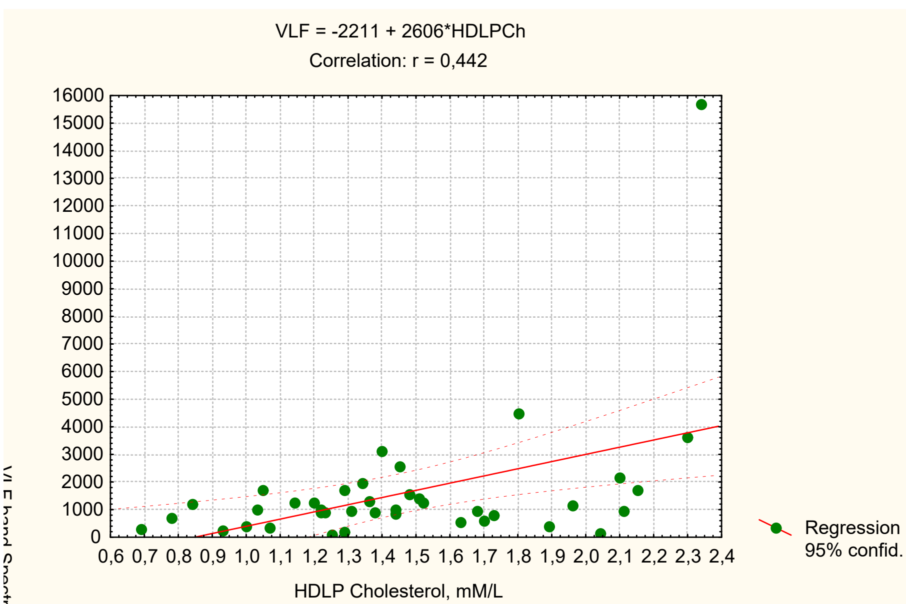


Fig. 1. Scatterplot of correlation between High-density Lipoporoteins Cholesterol plasma level (X-line) and SP VLF band HRV (Y-line)

Interestingly, at the same time, this patient was diagnosed with bouncing ULF band SP (8077 msec^2), HR (138 beats/min), SDNN (148 msec), as well as urinary lithogenicity due to an order of magnitude higher than the average uric acid concentration (11,3 mM/L) in urine collected during the previous day (Fig. 2) [5].

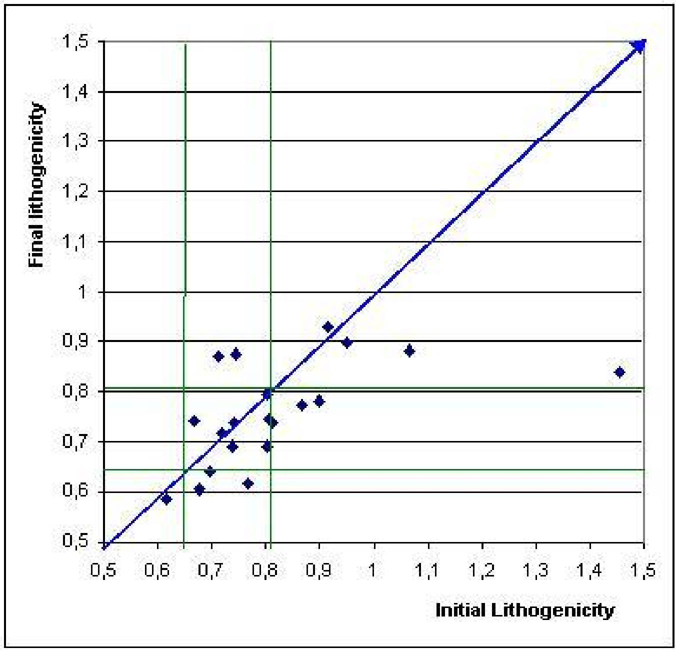


Fig. 2. Individual urine lithogenicity before (axis X) and after (axis Y) a course of drinking bioactive water Naftussya. Green lines show the limits of norm [from: 5].

Let's reassure readers: when retested after 7 days, these parameters are almost normalized, namely VLF 941 $mces^2$, ULF 48 $mces^2$, HR 58 beats/min, SDNN 23 msec, Uric acid Urine 2,8 mM/L (of course, not under the influence of the miraculous Naftussya, but ...). By the way, Dr's benefactor also found other variables, such as EEG and metabolism, which are significantly, but not as dramatically as mentioned, different from the sample averages. This will be the subject of a separate article in the Case Study, which he kindly agreed to.

But "let's get back to our rams" (this is a winged French expression, not referring to our highly respected observers whom we became friends with during the study).

According to calculations by the formula:

$$|r|=\{\exp[2t/(n - 1,5)^{0,5}] - 1\}/\{\exp[2t/(n - 1,5)^{0,5}] + 1\}$$

for a sample of n=39 critical value |r| at $p<0,05$ ($t>2,02$) is 0,32, at $p<0,02$ ($t>2,42$) is 0,38, at $p<0,01$ ($t>2,70$) is 0,41, at $p<0,001$ ($t>3,55$) is 0,52.

Based on the results of the screening, a matrix (Table 1) is created

Table 1. Correlation matrix for parameters of plasma lipoproteines profile and HRV

N=39	**VLD LPCh**	**HD LPCh**	**LD LPCh**	**Total Chol**
VLD LP Ch	1,00	**-,33**	,14	,24
HD LP Ch	**-,33**	1,00	-,20	,15
LD LP Ch	,14	-,20	1,00	**,91**
Total Chol	,24	,15	**,91**	1,00
N=39	**VLD LPCh**	**HD LPCh**	**LD LPCh**	**Total Chol**
RMSSD	**-,35**	**,31**	-,25	-,20
pNN_{50}	**-,31**	,22	-,26	-,23
HF	**-,31**	,20	-,22	-,21
HF/TP	**-,31**	,22	-,22	-,19
MxDMN	**-,33**	**,30**	-,24	-,18
TNN	**-,32**	**,34**	-,17	-,10
SDNN	-,25	**,33**	-,14	-,06
VLF	-,16	**,35**	-,01	,10
LF	-,18	**,28**	-,24	-,16
AMo	**,36**	**-,34**	,12	,07
BSI	,25	**-,28**	,13	,07
lnBSI	**,30**	**-,36**	,14	,05
LF/HF	,08	**-,35**	,03	-,10
LF/(LF+HF)	,18	-,15	,02	-,01
(VLF+LF)/HF	,16	**-,32**	**,32**	,21
VLF/TP	,26	-,17	**,47**	**,44**
LF/TP	-,09	,03	**-,45**	**-,44**
Entropy HRV	**-,32**	**,28**	**-,37**	**-,31**
Mode	,09	,23	,09	,21
ULF	-,17	,16	,03	,06
ULF/TP	-,08	,07	-,03	-,02

First of all, let us return to Figs. 1 after eliminating the jumping variable (Fig. 2). As you can see, the correlation coefficient decreased by only 0,089, so the question remains about the need to exclude it.

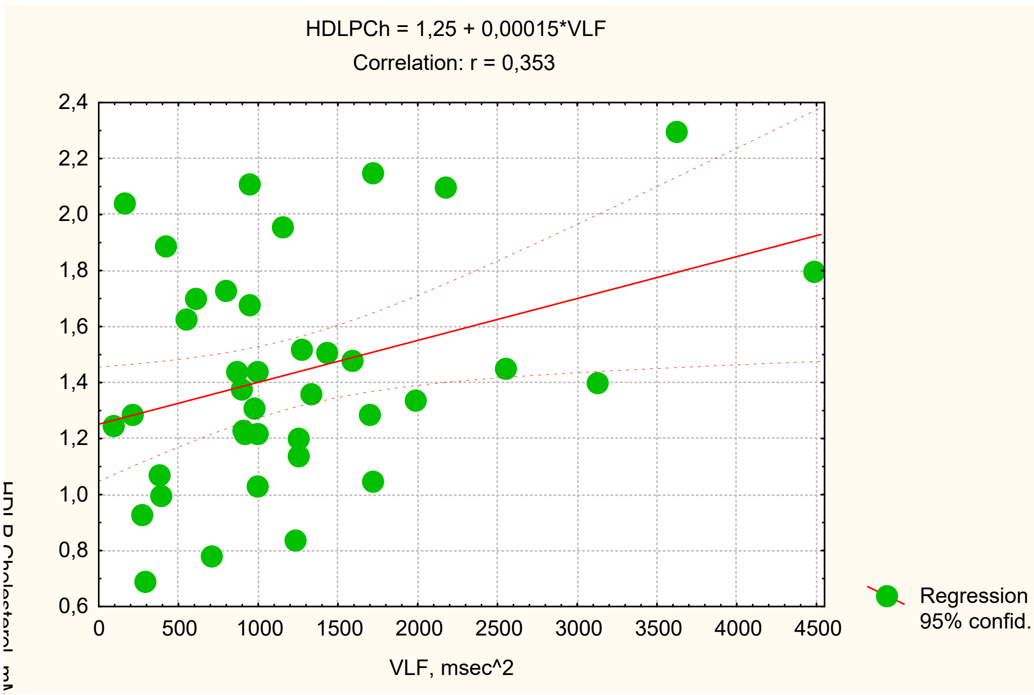


Fig. 3. Scatterplot of correlation between SP VLF band HRV (X-line) and High-Density Lipoproteins Cholesterol plasma level (Y-line) without patient Dr

Another topic of discussion is the interpretation of the nature of the VLF band HRV.

According to various authors, the VLF band (range 0,04÷0,015 Hz) HRV reflects humoral regulation (renin-angiotensin-aldosterone system, circulating catecholamines), cerebral ergotropic effects on subordinate level, the state of neuro-humoral and levels of metabolic regulation and can be used as a reliable marker of the degree of autonomous communication (segmental) levels of suprasegmental regulation of blood circulation, including the pituitary-hypothalamic and cortical levels [1,2,10]. Other authors [15] link VLF band with sympathetic activity. There is speculation that the formation of oscillation in the range of 0,007÷0,003 Hz associated with the activity of the hypothalamic centers suprasegmentary autonomic regulation that generate rhythms transmitted to the heart via the sympathetic nervous system. Assume the relationship VLF rhythms of thermoregulation, asked hypothalamus. Discovered rhythms associated with oscillation blood level of renin (0,04 Hz), epinephrine (0,025 Hz) [16].

Joining the discussion, we present a correlation matrix for the extended sample borrowed from the Truskavetsian School of Balneology database (Table 2).

As we can see, the absolute values of the VLF band correlate significantly with the markers of the **vagus** tone directly, and with the markers of **sympathetic** tone inversely. This gives us reason to believe that VLF (as well as LF) bands are **vagus** markers. Instead, the relative VLF band values are associated with vagus and sympathetic markers in the opposite way, that is, a **sympathetic** marker, as is commonly recognized for LFnu.

Consequently, plasma level of HD LP Cholesterol is upregulated by vagal influences, whereas sympathetic influences causes a downregulation (Table 1, Figs 3-6).

Table 2. Correlation matrix for HRV parameters

$_{0,05}|r|\geq 0,25$; $_{0,02}|r|\geq 0,30$; $_{0,01}|r|\geq 0,33$; $_{0,001}|r|\geq 0,42$

N=60	**VLF**	**VLF/TP**	**LF**	**LF/(LF+HF)**	**LF/TP**
VLF	1,00	,10	,51	-,15	-,17
VLF/TP	,10	1,00	-,41	,07	-,83
LF	,51	-,41	1,00	-,13	,31
LF/(LF+HF)	-,15	,07	-,13	1,00	,39
LF/TP	-,17	**-,83**	,31	,39	1,00
RMSSD	**,63**	**-,39**	**,84**	**-,51**	,09
HF	**,47**	**-,40**	**,88**	**-,45**	,12
TNN	**,52**	**-,42**	**,79**	**-,33**	,18
MxDMN	**,32**	**-,41**	**,75**	**-,36**	,17
AMo	**-,54**	**,36**	**-,61**	**,26**	-,15
lnBSI	**-,29**	**,35**	**-,65**	**,41**	-,07
BSI	-,12	**,26**	**-,34**	**,31**	-,05
LF/HF	-,23	-,08	-,17	**,80**	,42

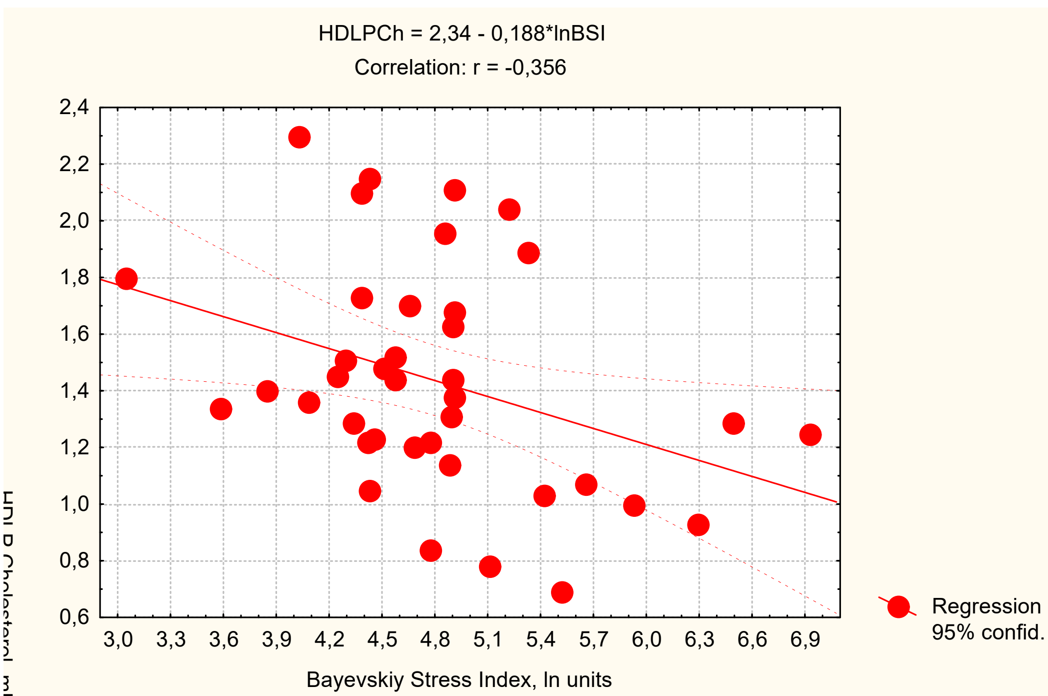


Fig. 4. Scatterplot of correlation between Baevskiy's Stress Index HRV (X-line) and High-density Lipoproteins Cholesterol plasma level (Y-line)

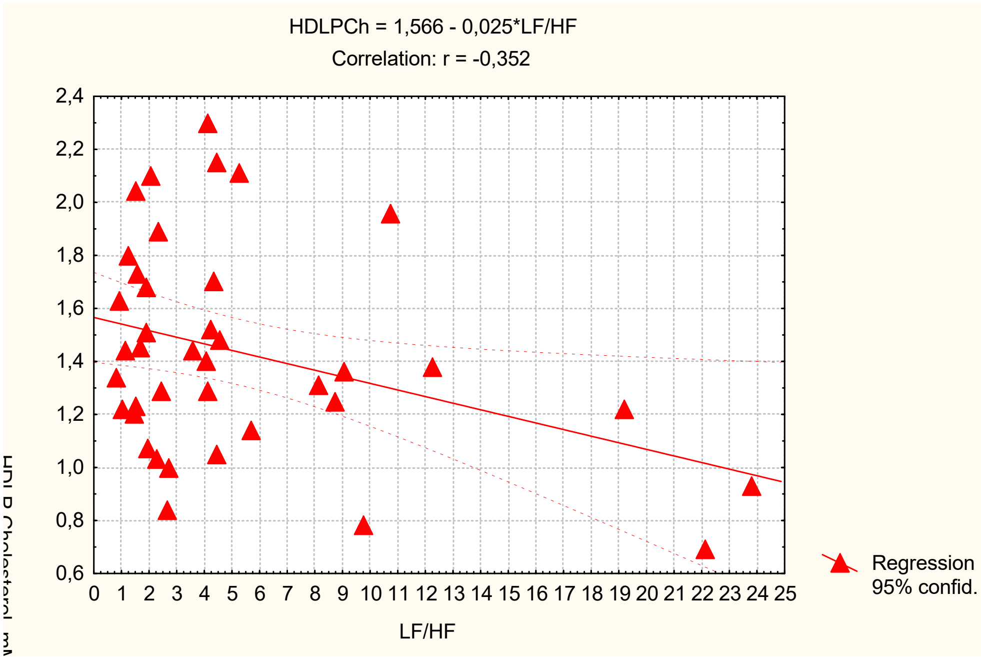
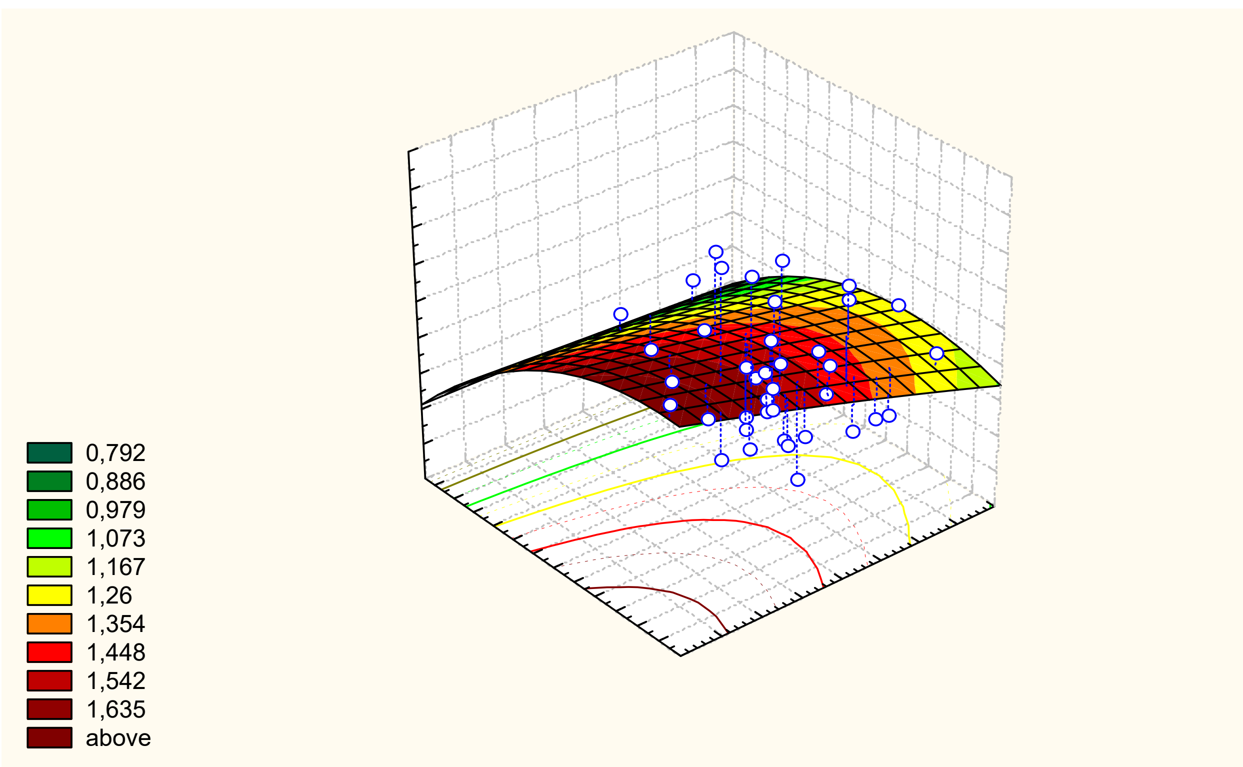


Fig. 5. Scatterplot of correlation between LF/HF ratio HRV (X-line) and High-Density Lipoproteins Cholesterol plasma level (Y-line)



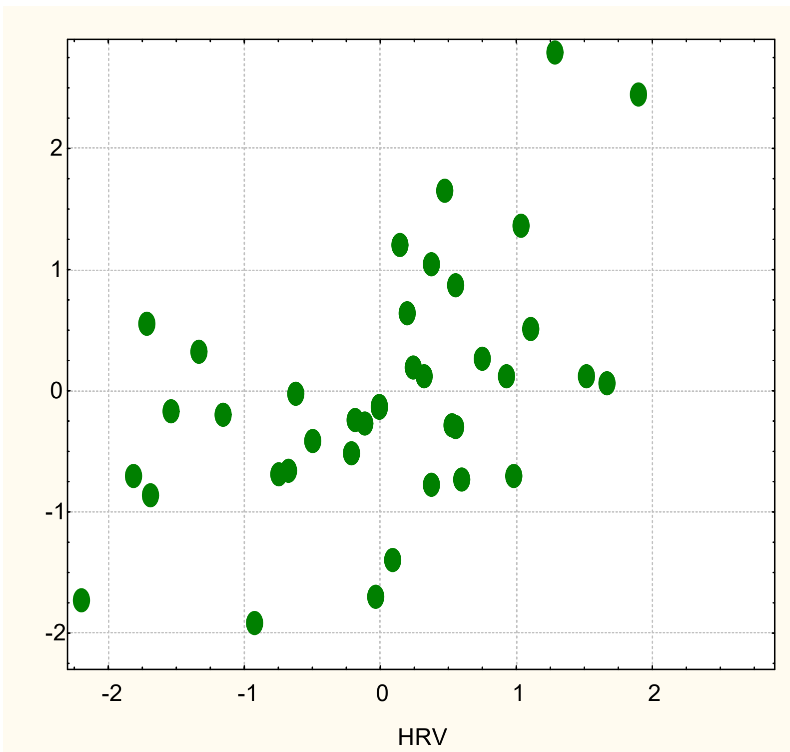
HDLPCh = 2,20 - 0,140•lnBSI - 0,018•LF/HF;
R=0,431; R^2=0,186; Adjusted R^2=0,140; $F_{(2,4)}$=4,1; p=0,025

Fig. 6. Downregulation of High-Density Lipoproteins Cholesterol plasma level (Z-line) by sympathetic HRV markers Baevskiy's Stress Index (X-line) and LF/HF ratio (Y-line)

By stepwise exclusion, 3 HRV parameters as well as its entropy were included in the regression model for HD LP Cholesterol plasma level, while some parameters with significant coefficients were found outside the model. Such constellation of parameters determines HD LP Cholesterol plasma level by 17% (Table 3 and Fig. 7).

Table 3. Regression Summary for Dependent Variable: HD LP Chol
R=0,508; R^2=0,258; Adjusted R^2=0,171; $F_{(4,3)}$=3,0; p=0,033; SE: 0,36 mM/L

		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(34)}$	p-level
Variables	r		Intercpt	,74631	,42191	1,77	,086
VLF	,35	,473	,223	,00020	,00009	2,12	,041
hHRV	,28	,279	,177	,87297	,55233	1,58	,123
pNN_{50}	,22	-,299	,242	-,00971	,00785	-1,24	,224
LF/HF	-,35	-,228	,160	-,01610	,01131	-1,42	,164

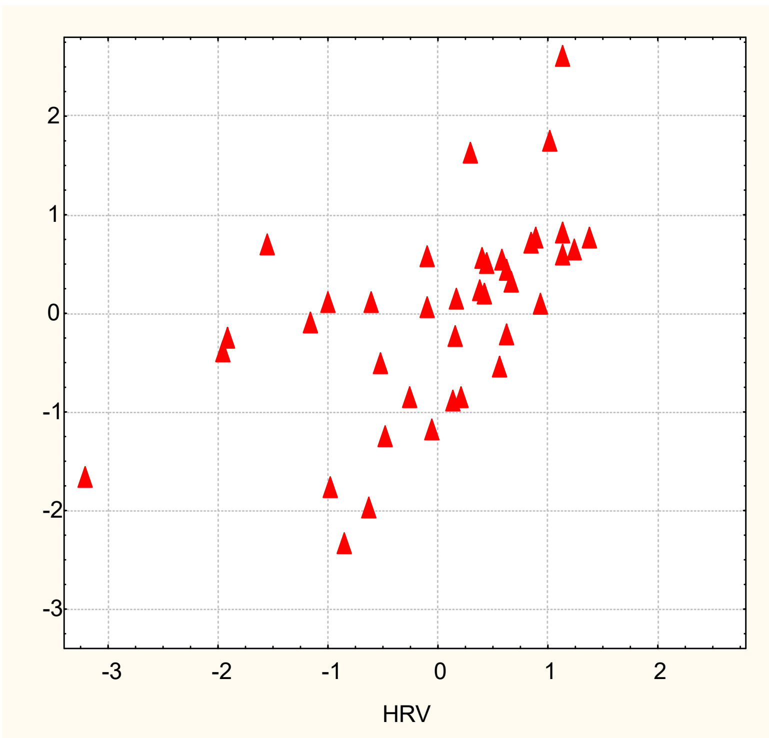


R=0,508; R^2=0,258; $\chi^2_{(4)}$=10,5; p=0,033; Λ Prime=0,742
Fig. 7. Scatterplot of canonical correlation between HRV parameters (X-line) and High-Density Lipoproteins Cholesterol plasma level (Y-line)

The VLD LP Cholesterol plasma level is upregulated by sympathetic influences and downregulated by vagal tone. Determination rate is 22% (Table 4 and Fig. 8).

Table 4. Regression Summary for Dependent Variable: VLD LP Chol
R=0,568; R^2=0,323; Adjusted R^2=0,220; $F_{(5,3)}$=3,1; p=0,020; SE: 0,20 mM/L

		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(33)}$	p-level
	r		Intercpt	1,5359	,9984	1,54	,134
AMo	,36	1,429	,512	,0211	,0076	2,79	,009
lnBSI	,30	-1,324	,690	-,3977	,2074	-1,92	,064
MxDMN	-,33	-,692	,439	-,0021	,0013	-1,57	,125
pNN_{50}	-,31	-,669	,273	-,0123	,0050	-2,45	,020
SDNN	-,25	,917	,438	,0100	,0048	2,09	,044



R=0,568; R^2=0,323; $\chi^2_{(5)}$=13,4; p=0,020; Λ Prime=0,678

Fig. 8. Scatterplot of canonical correlation between HRV parameters (X-line) and Very Law-Density Lipoproteins Cholesterol plasma level (Y-line)

Plasma level of LD LP Cholesterol is upregulated by sympathetic influences (Fig. 9), whereas vagal influences causes a downregulation. Determination rate is 31% (Table 5 and Fig. 10).

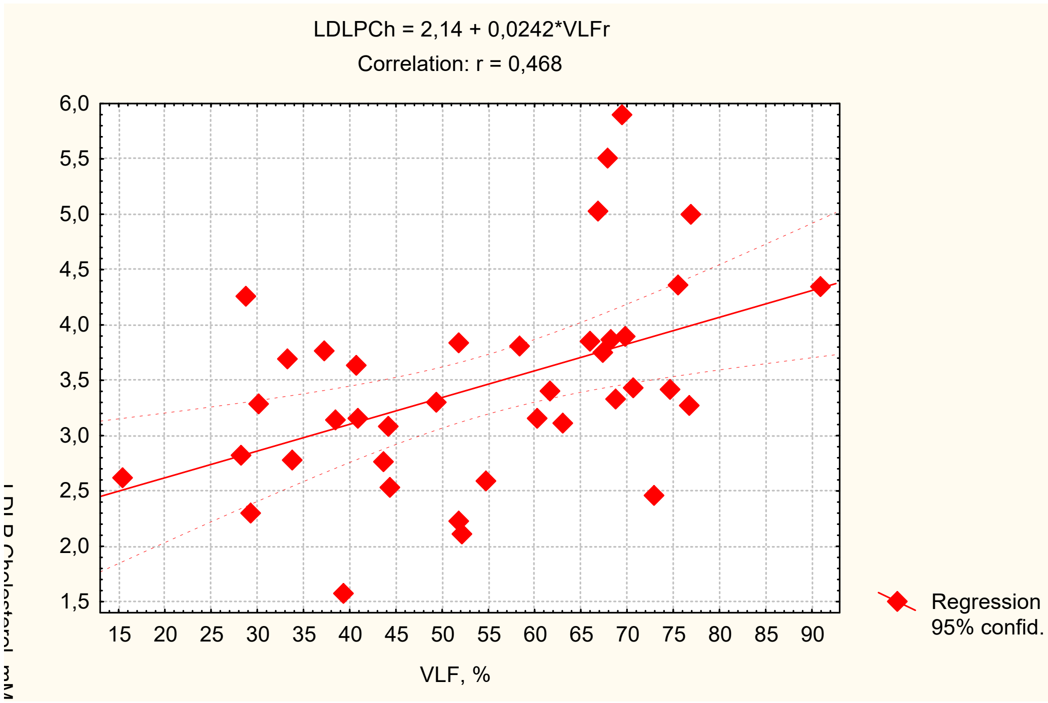
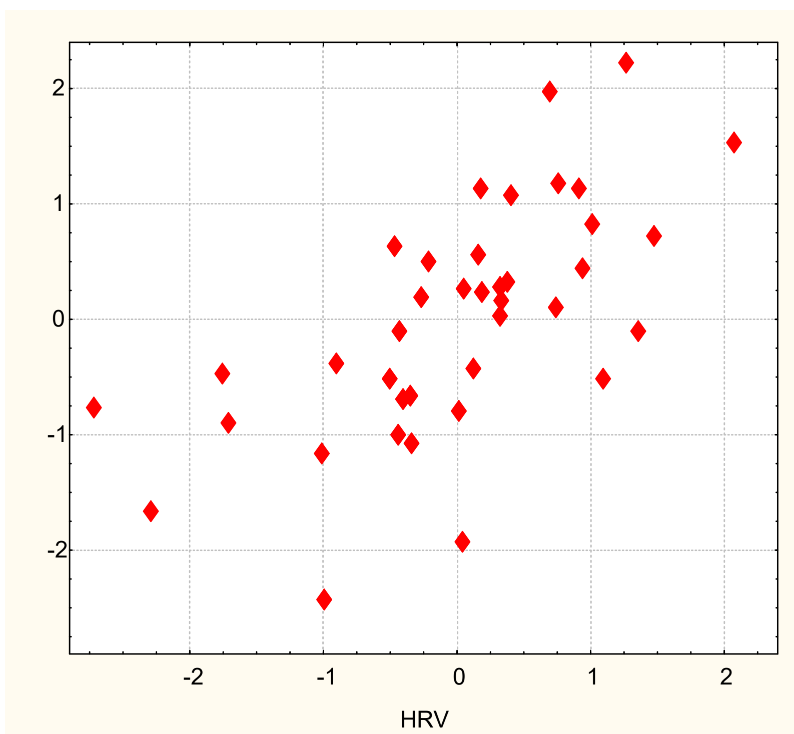


Fig. 9. Scatterplot of correlation between relative SP of VLF band HRV (X-line) and Low-Density Lipoproteins Cholesterol plasma level (Y-line)



R=0,647; R^2=0,418; $\chi^2_{(6)}$=18,4; p=0,005; Λ Prime=0,582

Fig. 10. Scatterplot of canonical correlation between HRV parameters (X-line) and Law-Density Lipoproteins Cholesterol plasma level (Y-line)

Table 5. Regression Summary for Dependent Variable: LD LP Chol
$R=0,647$; $R^2=0,418$; Adjusted $R^2=0,309$; $F_{(6,3)}=3,8$; $p=0,005$; SE: 0,76 mM/L

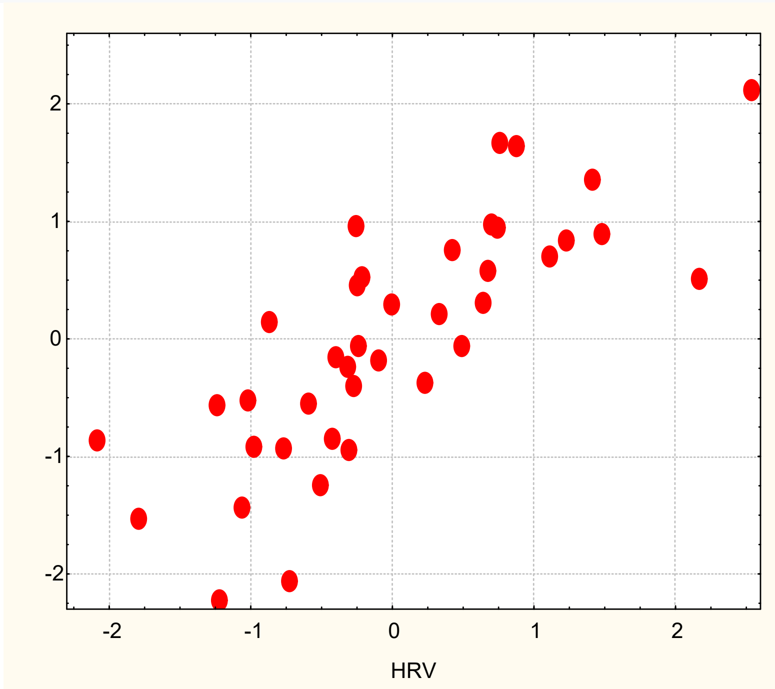
		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(32)}$	p-level
Variables	r		Intercpt	-1,298	1,218	-1,07	,294
VLF/TP	0,47	,836	,229	,0432	,0118	3,64	,001
(VLF+LF)/HF	0,32	,549	,212	,0290	,0112	2,59	,014
HF/TP	-0,45	,672	,312	,0623	,0289	2,15	,039
pNN_{50}	-0,26	-1,602	,631	-,1193	,0470	-2,54	,016
RMSSD	-0,25	1,244	,733	,0671	,0395	1,70	,100
LF	-0,24	,454	,291	,0004	,0003	1,56	,129

Based on the analysis of the canonical correlation between HRV parameters, on the one hand, and plasma lipoprotein profile parameters, on the other, it was found (Table 6) that the root of the autonomic nervous system receives the maximum positive factor load from the relative spectral power of the VLF band, as well as from three more markers of sympathetic tone. Instead, negative loadings give 6 markers of vagus tone as well as HRV entropy. The lipoprotein canonical root receives the maximum positive factor load from the LD LP, twice less from the VLD LP and quite insignificant from the HD LP.

Table 6. Factor structure of canonical correlation between HRV parameters (right set) and parameters of plasma lipoproteines profile (left set)

Right set	R
VLF/TP	**,598**
(VLF+LF)/HF	**,304**
AMo	**,197**
Bayevskiy's Stress Ind (ln)	**,166**
Entropy HRV	**-,464**
pNN_{50}	**-,370**
RMSSD	**-,342**
HF/TP	**-,324**
MxDMn	**-,321**
LF	**-,242**
SDNN	**-,154**
Left set	**R**
LD LP Ch	**,872**
VLD LP Ch	**,470**
HD LP Ch	**,033**

In general, the state of autonomic nerve regulation determines the plasma lipid profile by 63% (Fig. 11).



$R=0{,}793$; $R^2=0{,}629$; $\chi^2_{(33)}=48$; $p=0{,}044$; Λ Prime=0,207

Fig. 11. Scatterplot of canonical correlation between HRV parameters (X-line) and parameters of plasma lipoproteines profile (Y-line)

The following article will analyze the relationship of plasma lipid profile parameters with electroencephalogram parameters.

ACKNOWLEDGMENT

We express sincere gratitude to administration JSC "Truskavets'kurort" and "Truskavets' SPA" as well as clinical sanatorium "Moldova" for help in conducting this investigation.

ACCORDANCE TO ETHICS STANDARDS

Tests in patients are conducted in accordance with positions of Helsinki Declaration 1975, revised and complemented in 2002, and directive of National Committee on ethics of scientific researches. During realization of tests from all participants the informed consent is got and used all measures for providing of anonymity of participants.

REFERENCES

1. Baevskiy RM, Ivanov GG. Heart Rate Variability: theoretical aspects and possibilities of clinical application [in Russian]. Ultrazvukovaya i funktsionalnaya diagnostika. 2001; 3: 106-127.
2. Berntson GG, Bigger JT jr, Eckberg DL, Grossman P, Kaufman PG, Malik M, Nagaraja HN, Porges SW, Saul JP, Stone PH, Van der Molen MW. Heart Rate Variability: Origines, methods, and interpretive caveats. Psychophysiology. 1997; 34: 623-648.
3. Cao Q, Jing J, Cui X, Shi H, Xue B. Sympathetic nerve innervation is required for beigeing in white fat. Physiol Rep. 2019; 7(6): e14031.
4. Chen SJ, Tsui PF, Chuang YP, Chiang DML, Chen LW, Liu ST et al. Carvediol ameliorates

experimental atherosclerosis by regulation cholesterol efflux and exosome functions. Int J Mol Sci. 2019; 20(20): 5202.

5. Flyunt VR, Flyunt I-SS, Fil' VM, Kovbasnyuk MM, Hryvnak RF, Popel SL, Zukow W. Relationships between caused by drinking of bioactive water Naftussya changes in urine lithogenicity and neuro-humoral-immune factors in humans with theirs abnormalities. Journal of Education, Health and Sport. 2017; 7(3): 11-30.

6. Fonarow GC, Deedwania P, Fonseca V, Nesto RW, Watson K, Tarka E et al. Differencial effects of extended-release carvediol and extended-release metoprolol on lipid profiles in patients with hypertension: Results of the Extended-release Carvediol Lipid Trial. J Am Soc Hypertens. 2009; 3(3): 210-220.

7. Goryachkovskiy AM. Clinical biochemi [in Russian]. Odesa. Astroprint; 1998: 608 p.

8. Gozhenko AI, Sydoruk NO, Babelyuk VYe, Dubkowa GI, Flyunt VR, Hubyts'kyi VYo, Zukow W, Barylyak LG, Popovych IL. Modulating effects of bioactive water Naftussya from layers Truskavets' and Pomyarky on some metabolic and biophysic parameters at humans with dysfunction of neuro-endocrine-immune complex. Journal of Education, Health and Sport. 2016; 6(12): 826-842.

9. Guo J, Chi Sh, Xu H, Jiu G, Qui Zh. Effects of cholesterol levels on the excitability of rat hippocampal neurons/ Mol Membr Biol. 2008; 25(3): 216-223.

10. Heart Rate Variability. Standards of Measurement, Physiological Interpretation, and Clinical Use. Task Force of ESC and NASPE. Circulation. 1996; 93(5): 1043-1065.

11. Hill JO, Wyatt HR, Peters JC. Energy balance and obesity. Circulation. 2012; 126:126-132.

12. Hiller G. Test for the quantitative determination of HDL cholesterol in EDTA plasma with Reflotron®. Klin Chem. 1987; 33: 895-898.

13. Huchko BYa. Multialternative poststressory changes in plasma atherogenity and their neuroendocrine and metabolic accompaniments at male and female rats [in Ukrainian]. Medical Hydrology and Rehabilitation. 2008; 6(3): 88-96.

14. Huchko BYa, Barylyak LG. Influence of bioactive water Naftussya on plasma atherogenity and its metabolic and neuroendocrine accompaniments in rats [in Ukrainian]. Medical Hydrology and Rehabilitation. 2009; 7(2): 62-70.

15. Korkushko OV, Pysaruk AV, Shatylo VB. The value of heart rate variability analysis in cardiology: age aspects [in Russian]. Circulation and Hemostase. 2009; 1-2: 127-139.

16. Kotelnikov SA, Nozdrachov AD, Odinak MM, Shustov EB, Kovalenko IYu, Davidenko VYu. Heart rate variability: understanding of the mechanisms [in Russian]. Fiziologiya cheloveka. 2002; 28(1): 130-143.

17. Kozyavkina NV. Variantes of thyrotropic effects of bioactive water Naftussya and their metabolic accompaniment [in Ukrainian]. Medical Hydrology and Rehabilitation. 2008; 6(3): 115-122.

18. Kozyavkina NV. Thyrotropic effects of bioactive water Naftussya at female rats and their metabolic, neuroendocrine and immune accompaniments [in Ukrainian]. Medical Hydrology and Rehabilitation. 2012; 10(4): 91-113.

19. Kozyavkina OV. Post-stress changes in neuro-endocrine status and metabolism in rats with different types of initial vegetative homeostasis induced by Naftussya bioactive water [in Ukrainian]. Medical Hydrology and Rehabilitation. 2009; 7(1): 42-50.

20. Kozyavkina OV. State of post-stress parameters of autonomic homeostasis and endocrine, metabolic and immune status and correlation between them in rats with alternative types of pre-stress vegetative homeostasis induced by bioactive water Naftussya [in Ukrainian]. Medical Hydrology and Rehabilitation. 2009; 7(2): 40-56.

21. Kozyavkina OV, Kozyavkina NV, Gozhenko OA, Gozhenko AI, Barylyak LG, Popovych IL. Bioactive Water Naftussya and Neuroendocrine-Immune Complex [in Ukrainian]. Kyiv: UNESCO-SOCIO; 2015: 349 p.

22. Kozyavkina OV, Vis'tak HI, Popovych IL. Factor, canonical and discriminant analysis of vegetotropic effects and accompanying changes in thyroide, metabolic and haemodynamic parameters at the women, caused by bioactive water Naftussya. Medical Hydrology and Rehabilitation. 2013; 11(3): 4-28.

23. Lee SY, Choi HK, Kim ST, Chung S, Park MK, Cho GJ et al. Cholesterol inhibits M-type K^+ channels via protein kinase C dependent phosphorylation in sympathetic neurons. J Biol Chem. 2010; 285(14): 10939-10950.
24. Nguyen NL, Randall J, Bonfield BW, Bartness TJ. Central sympathetic innervation to visceral and subcutaneous white adipose tissue. Am J Physiol Regul Integr Comp Physiol. 2014; 306: R375-R386.
25. Nguyen NL, Barr CL, Ryu V, Cao Q, Xee B, Bartness TJ. Separate and shared sympathetic outflow to white and brown fat coordinately regulates thermoregulation and adipocyte recruitment. Am J Physiol Regul Integr Comp Physiol. 2017; 312: R132-R145.
26. Popadynets' OO, Gozhenko AI, Zukow W, Popovych IL. Relationships between the entropies of EEG, HRV, immunocytogram and leukocytogram. Journal of Education, Health and Sport. 2019; 9(5): 651-666.
27. Popovych IL, Ruzhylo SV, Ivassivka SV, Aksentiychuk BI (editors). Balneocardioangiology [in Ukrainian]. Kyiv: Computerpress; 2005: 229 p.
28. Popovych IL, Sydoruk NO, Gozhenko AI, Zukow W. Modulating effects of bioactive water Naftussya from layers Truskavets' and Pomyarky on neuro-endocrine parameters at humans with dysadaptation. Journal of Education, Health and Sport. 2017; 7(2): 465-478.
29. Popovych IL, Vis'tak HI, Gumega MD, Ruzhylo SV. Vegetotropic Effects of Bioactive Water Naftussya and their Endocrine-Immune, Metabolic and Hemodynamic Accompaniments [in Ukrainian]. Kyiv: UNESCO-SOCIO; 2014: 163 p.
30. Ruzhylo SV, Tserkovnyuk AV, Popopvych IL. Actotropic Effects of Balneotherapeutic Complex of Truskavets spa [in Ukrainian]. Kyiv: Computerpress; 2003: 131 p.
31. Seguchi H, Nakamura H, Aosaki N, Homma Y, Mikami Y, Takahashi S. Effects of carvediol on serum lipids. Eur J Clin Pharmacol. 1990; 38: S139-S142.
32. Sydoruk NO, Chebanenko OI, Popovych IL, Zukow W. Comparative Investigation of Physiological Activity of Water Naftussya from Truskavets' and Pomyarky Deposits [in Ukrainian]. Kyiv: UNESCO-SOCIO; 2017: 216 p.
33. Sydoruk NO, Gozhenko AI, Zukow W. Modulating effects of bioactive water Naftussya from layers Truskavets' and Pomyarky on neuro-endocrine-immune complex and metabolism at rats exposed to acute stress. Journal of Education, Health and Sport. 2016; 6(11): 715-730.
34. Vis'tak HI, Kozyavkina OV, Popovych IL, Zukow W. Vegetotropic effects of bioactive water Naftussya spa Truskavets' and their thyroide, metabolic and haemodynamic accompaniments at the women. Journal of Health Sciences. 2013; 3(10): 557-582.
35. Wang S, Yang X. Inter-organ regulation of adipose tissue browing. Cell Mol Life Sci. 2017; 74(10): 1765-1776.
36. Wong GWK, Laugerotte A, Wright JM. Blood pressure lowering efficacy dual alpha and beta blockers for primaty hypertension. Cochrane Database Syst Rev. 2015; 8: CD007449.