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 Truskavsian 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 Ruzhylko 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 sympatno-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 standard 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 (pNN50); heart rate (HR), the mode (Mo), the amplitude of mode (AMo), variational sweep (MxDMn) as well as triangular 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 (BARSIf) [1].

We calculated also for HRV the Entropy (h) of normalized SP bands using formula CE Shannon [26]:
hHRV=[SPHF•\log_{2}SPHF+SPLF•\log_{2}SPLF+SPVLF•\log_{2}SPVLF+SPULF•\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 msec²) 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).

![Graph](image)

Fig. 1. Scatterplot of correlation between High-density Lipoproteins 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 msec²), 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].
Let's reassure readers: when retested after 7 days, these parameters are almost normalized, namely VLF 941 mces², ULF 48 mces², 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:

\[ |r| = \frac{\exp[2t/(n - 1,5)^{0.5}] - 1}{\exp[2t/(n - 1,5)^{0.5}] + 1} \]

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     | -0.33    | 0.14    | 0.24    |            |
| HD LP Ch  | -0.33    | 1.00     | -0.20   | 0.15    |            |
| LD LP Ch  | 0.14     | -0.20    | 1.00    | 0.91    |            |
| Total Chol | 0.24    | 0.15     | 0.91    | 1.00    |            |

|        | N=39     | VLD LPCh | HD LPCh | LD LPCh | Total Chol |
|--------|----------|----------|---------|---------|------------|
| RMSSD  | -0.35    | 0.31     | -0.25   | -0.20   |            |
| pNN50  | -0.31    | 0.22     | -0.26   | -0.23   |            |
| HF     | -0.31    | 0.20     | -0.22   | -0.21   |            |
| HF/TP  | -0.31    | 0.22     | -0.22   | -0.19   |            |
| MxDMN  | -0.33    | 0.30     | -0.24   | -0.18   |            |
| TNN    | -0.32    | 0.34     | -0.17   | -0.10   |            |
| SDNN   | -0.25    | 0.33     | -0.14   | -0.06   |            |
| VLF    | -0.16    | 0.35     | -0.01   | 0.10    |            |
| LF     | -0.18    | 0.28     | -0.24   | -0.16   |            |
| AMo    | 0.36     | -0.34    | 0.12    | 0.07    |            |
| BSI    | 0.25     | -0.28    | 0.13    | 0.07    |            |
| lnBSI  | 0.30     | -0.36    | 0.14    | 0.05    |            |
| LF/HF  | 0.08     | -0.35    | 0.03    | -0.10   |            |
| LF/(LF+HF) | 0.18 | -0.15 | 0.02 | -0.01 |            |
| (VLF+LF)/HF | 0.16 | -0.32 | 0.32 | 0.21 |            |
| VLF/TP | 0.26     | -0.17    | 0.47    | 0.44    |            |
| LF/TP  | -0.09    | 0.03     | -0.45   | -0.44   |            |
| Entropy HRV | -0.32 | 0.28 | -0.37 | -0.31 |            |
| Mode   | 0.09     | 0.23     | 0.09    | 0.21    |            |
| ULF    | -0.17    | 0.16     | 0.03    | 0.06    |            |
| ULF/TP | -0.08    | 0.07     | -0.03   | -0.02   |            |

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.
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| ≥ 0.25; 0.02 |r| ≥ 0.30; 0.01 |r| ≥ 0.33; 0.001 |r| ≥ 0.42

|              | VLF   | VLF/TP | LF    | LF/(LF+HF) | LF/TP |
|--------------|-------|--------|-------|------------|-------|
| N=60         | VLF   |        | LF    | LF/(LF+HF) | LF/TP |
| VLF/TP       | .10   | .10    | .51   | -.15       | -.17  |
| 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  |
| InBSI        | .29   | .35    | -.65  | .41        | -.07  |
| BSI          | -.12  | .26    | -.34  | .31        | -.05  |
| LF/HF        | -.23  | -.08   | -.17  | .80        | .42   |

**HDLP Cholesterol, mM/L**

| 3,0 | 3,3 | 3,6 | 3,9 | 4,2 | 4,5 | 4,8 | 5,1 | 5,4 | 5,7 | 6,0 | 6,3 | 6,6 | 6,9 |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 0,6 | 0,7 | 0,8 | 0,9 | 1,0 | 1,1 | 1,2 | 1,3 | 1,4 | 1,5 | 1,6 | 1,7 | 1,8 | 1,9 |

**Regression 95% confid.**

**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 = 1,566 - 0,025*LF/HF;
R=0,431; R²=0,186; Adjusted R²=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; R²=0.258; Adjusted R²=0.171; F(4,3)=3.0; p=0.033; SE: 0.36 mM/L

| Variables | Beta | St. Err. of Beta | B     | St. Err. of B | t(34) | p-level |
|-----------|------|------------------|-------|---------------|-------|---------|
| VLF       | .35  | .473             | .223  | .0020         | 2.12  | .041    |
| hHRV      | .28  | .279             | .177  | .0160         | 1.58  | .123    |
| pNN₉₀     | .22  | -.299            | .242  | -.00971       | -1.24 | .224    |
| LF/HF     | -.35 | -.228            | .160  | -.01610       | -1.42 | .164    |

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; R²=0.323; Adjusted R²=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        | .36   | 1.429            | .512 | .0211         | 1.54  | .134    |
| AMo      | .30   | -.1324           | .690 | -.3977        | 1.92  | .064    |
| lnBSI    | -.33  | -.692            | .439 | -.0021        | 1.57  | .125    |
| MxDMN    | -.31  | -.669            | .273 | -.0123        | 2.45  | .020    |
| pNN50    | -.25  | .917             | .438 | .0100         | 2.09  | .044    |

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)

LDLPCh = 2,14 + 0.0242*VLFr
Correlation: r = 0.468

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

R=0.647; R²=0.418; χ²(6)=18.4; p=0.005; Λ Prime=0.582
Table 5. Regression Summary for Dependent Variable: LD LP Chol
R=0.647; R²=0.418; Adjusted R²=0.309; F(6,3)=3.8; p=0.005; SE: 0.76 mM/L

| Variables | Beta | St. Err. of Beta | B | St. Err. of B | t(32) | p-level |
|-----------|------|----------------|---|--------------|-------|---------|
| Intercept | -1.298 | 1.218 | -1,07 | 0.294 |
| VLF/TP    | 0.47 | 0.836 | ,229 | 0.0432 | 3.64 | 0.001 |
| (VLF+LF)/HF | 0.32 | 0.549 | ,212 | 0.0290 | 2.59 | 0.014 |
| HF/TP     | -0.45 | 0.672 | ,312 | 0.0623 | 2.15 | 0.039 |
| pNN 50    | -0.26 | -1.602 | ,631 | -1.193 | 2.54 | 0.016 |
| RMSSD     | -0.25 | 1.244 | ,733 | 0.0671 | 1.70 | 0.100 |
| LF        | -0.24 | 0.454 | ,291 | 0.0004 | 1.56 | 0.129 |

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 lipoproteins profile (left set)

| Right set | R   |
|-----------|-----|
| VLF/TP    | .598|
| (VLF+LF)/HF | .304|
| AMo       | .197|
| Bayevskiy’s Stress Ind (In) | .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).
The following article will analyze the relationship of plasma lipid profile parameters with electroencephalogram parameters.

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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.

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