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Neuro-immune relationships at patients with chronic pyelonephrite and cholecystite. Communication 2. Correlations between parameters EEG, HRV and Phagocytosis

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Abstracts

Background. Previously, we have shown that blood level of Leukocytes and parameters of Leukocytogram significantly modulated by electrical activity some structures of central and autonomic nervous systems. In this study, we set a goal to analyse the relationships between parameters of EEG and HRV, on the one hand, and the parameters of phagocytosis, on the other hand. **Methods.** In basal conditions in 23 men, patients with chronic pyelonephrite and cholecystite in remission, recorded EEG ("NeuroCom Standard", KhAI Medica, Ukraine) and

HRV (“Cardiolab+VSR”, KhAI Medica, Ukraine). In portion of venous blood estimated parameters of phagocytic function of neutrophils. **Results.** Revealed that canonical correlation between constellation EEG and HRV parameters form with Phagocytic Index 0,94 and 0,93 for E. coli and Staph. aureus respectively. However neural regulation Killing Index as well as Microbial Count significantly distinguished for Gram-negative and Gram-positive Bacteria: R form 0,99 and 0,84 versus 0,66 and 0,69 respectively. Integrated parameter Bactericidity Capacity of blood Neutrophills correlated with EEG and HRV parameters equally: R makes 0,89 and 0,93 respectively. **Conclusion.** Neutrophils phagocytic function subordinate modulation central and autonomic nervous systems.
Keywords: HRV, EEG, Phagocytosis, Escherichia coli, Staph. aureus, correlations.

INTRODUCTION

It is known that all primary and secondary immune organs receive a substantial sympathetic innervation from sympathetic postganglionic neurons. The presence of noradrenergic fibers was demonstrated in the spleen, in the thymus, in lymph nodes and tonsils, in the bone marrow and in mucosa-associated lymphoid tissues. Take place nonsynaptic communication between sympathetic fibers and immune cells. Norepinephrine after released from axon varicosities mediate its effects on target cells via stimulation of adrenergic receptors (ARs). Expression of β_2-ARs was demonstrated on the surface of thymocytes, thymic epithelial cells, B cells, basophils, eosinophils, monocytes and neutrophils as well as Th_1 cells but not Th_2 cells. The presence of α_2-ARs on lymphocytes and monocytes is controversial. There is no neuroanatomical evidence for parasympathetic or vagal nerve supply to any immune organ, with possible exception of the respiratory and the alimentary tracts, which have yet to be demonstrated [reviews: 22,33]. However KJ Tracey and his colleagues as authors of the “cholinergic anti-inflammatory pathway” [7,39,40] believe that at least spleen have vagal input and parasympathetic nervous system, both afferent and efferent, plays the crucial role in immunomodulation. Major vagus nerve neurotransmitter Acetylcholine binds to two major subtypes of receptors - nicotinic and muscarinic cholinergic receptors (AChRs), each of which consists of many different subunits, which provides cellular and tissue specificity cholinergic effects. Both receptors found on immune cells, but nicotine receptors specifically mediate cholinergic anti-inflammatory effects on macrophages. Mainly cholinergic receptors expressed on macrophages, are α7-subunit nicotinic acetylcholine receptor (α7 nAChR). Activation of this receptor on macrophages inhibits NF-κB signaling, thereby inhibiting the production and release of pro-inflammatory cytokines. Acetylcholine also inhibits endotoxin-induced release of pro-inflammatory cytokines (IL-1, IL-6 and TNF-α), but no anti-inflammatory cytokines (IL-10) by macrophages. The effects of the parasympathetic nervous system on the migration of white blood cells is less clear. Thus, Acetylcholine increasing production CCL2 by monocytes, but stimulation of the vagus nerve and acetylcholine agonist, acting through α7-nAChRs, inhibit recruitment of leukocytes to endothelial cells, supressing expression VCAM-1 as well as down-regulate Neutrophils trafficking via CD11b. Taken together, these parasympathetic mechanisms form that was named as the "cholinergic anti-inflammatory mechanism" [7,39,40]. However, adrenal medullary zone and sympathetic nerves also inhibit production of TNF-α by macrophages and systemic inflammation because α7-nAChRs mediate the relationship between spinal preganglionic sympathetic cholinergic neurons and producing catecholamines neurons localized in sympathetic ganglia and adrenal medulla zone. Thus, nicotine stimulates the release of the catecholamines through the activation of α7-nAChRs localized in the peripheral postganglionic sympathetic neurons and

adrenal medulla [reviews: 22,34,38]. It seems that as sympathetic and parasympathetic nervous systems mediates inhibition of TNF-α production and inflammation.

Previously, we have shown that in patients with chronic pyelonephrite and cholecystite in remission blood level of Leukocytes and parameters of Leukocytogram significantly modulated by electrical activity some structures of central and autonomic nervous systems [17,18,30,31]. In this study, we set a **goal** to analyse the relationships between parameters of EEG and HRV (mutually related [32]), on the one hand, and the parameters of Phagocytosis by Neutrophils E. coli and Staph. aureus as mainly pathogens chronic pyelonephrite and cholecystite, on the other hand.

MATERIAL AND RESEARCH METHODS

The object of observation were 23 men aged 24-70 (mean±m: 49,1±2,5) years old, who came to the spa Truskavets' (Ukraine) for the treatment of chronic pyelonephritis combined with cholecystitis in remission. The survey was conducted, as a rule, one time, less two time, before and after balneotherapy.

We recorded firstly during 7 min electrocardiogram in II lead to assess the parameters of heart rate variability (HRV) [1,2,5] (hardware-software complex "CardioLab+HRV" production "KhAI-Medica", Kharkiv, Ukraine). For further analysis the following parameters HRV were selected. 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}), triangulary index (HRV TI) [5]; heart rate (HR), moda (Mo), the amplitude of moda (AMo), variational sweep (MxDMn) [1]. Spectral parameters (Frequency Domain Methods): spectral power density (SPD) components 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). Expectant as classical indexes: LF/HF, LFnu=100%•LF/(LF+HF) and Centralization Index (CI=(VLF+LF)/HF), Baevskiy's Stress Index (BSI=AMo/2•Mo•MxDMn) as well as Baevskiy's Activity Regulatory Systems Index (BARS) [1] both in supine and posture positions.

Then during 25 sec EEG recorded a hardware-software complex "NeuroCom Standard" (KhAI Medica, Kharkiv, Ukraine) monopolar in 16 loci (Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1, O2) by 10-20 international system, with the reference electrodes A and Ref on tassels the ears. Among the options considered the average EEG amplitude (μV), average frequency (Hz), frequency deviation (Hz), index (%), coefficient of asymmetry (%), absolute (μV^2/Hz) and relative (%) SPD of basic rhythms: β (35÷13 Hz), α (13÷8 Hz), θ (8÷4 Hz) and δ (4÷0,5 Hz) in all loci, according to the instructions of the device. In addition, calculated Laterality Index (LI) for SPD each Rhythm using formula [23]:

$$LI, \% = \Sigma [200 \bullet (Right - Left)/(Right + Left)]/8$$

We calculated also for each locus the Entropy (h) of normalized SPD using formula Shannon:

$$h = - [SPD\alpha \bullet \log_2 SPD\alpha + SPD\beta \bullet \log_2 SPD\beta + SPD\theta \bullet \log_2 SPD\theta + SPD\delta \bullet \log_2 SPD\delta]/\log_2 4$$

Parameters of phagocytic function of neutrophils estimated as described by SD Douglas and PG Quie [3] with our (MM Kovbasnyuk) moderately modification. To do this, 5 drops of blood immediately after collection, made in glass centrifuge tubes with 2 ml of 4% solution of sodium citrate. Blood samples were stored in a refrigerator at a temperature of 4^0C. Further samples were centrifuged (5000 rev/min for 5 min). The supernatant was removed with the help of the Pasteur's pipette. We used a fraction of leukocytes with traces of erythrocytes. The objects of

phagocytosis served daily cultures of Staphylococcus aureus (ATCC N 25423 F49) as typical specimen for Gram-positive Bacteria and Escherichia coli (O55 K59) as typical representative of Gram-negative Bacteria. Both cultures obtained from Laboratory of Hydro-Geological Regime-Operational Station JSC "Truskavets'kurort". To prepare the suspension microbes did wipes with relevant shoals sterile saline, immersed tubes in boiling water for 3 seconds, cooled to room temperature. Integrity microbes controlled with the aid of a microscope. To do this, drop the suspension of microbes applied to skimmed substantive piece of glass, fixed in alcohol lamp flame. Ready preparations stained by Papenheim, microscoped during immersion, lense h90, eyepiece x10. The test samples were prepared as follows. In Vidal's plastic tubes made in the following order of 0,05 mL of heparin, 0,05 mL of sterile saline, 0,1 mL suspension of leukocytes, 0,05 mL suspension of microbial bodies. Samples shaked and placed in thermostat at 37^0C for 30 min, shaking them with every 10 mins. Then, to stop phagocytosis, the sample was cooled under running water for 10 min. In further samples are centrifuged (5000 rev/min, for 5 min), the supernatant removed with the help of the Pasteur's pipette. From the suspension of leukocytes (with traces of red blood cells) prepared strokes, dried in air at room temperature and stained by Papenheim. Microscoped during immersion lens h90, x10 eyepiece. Take into account the following parameters of phagocytosis: activity (percentage of neutrophils, in which found microbes - Hamburger's Phagocytic Index), intensity (number of microbes absorbed one phagocytes - Microbial Count or Right's Index) and completeness (percentage of dead microbes - Killing Index). Microbial number and index their digestion is determined for each phagocyte and fixed in phagocytic frame.

Results processed by methods of correlation and canonical analyses, using the software package "Statistica 5.5".

RESULTS AND DISCUSSION

Regarding Staph. aureus we found many, but only moderate in strength connections Phagocytic Index as a measure of the activity of phagocytosis of bacteria by neutrophils.

Among parameters HRV revealed negatively correlation Phagocytic Index with raw SPD LF (r=-0,41) and MxDMn (r=-0,29) as markers of **vagal** tone [1,2,5] while positively correlation with relative SPD VLF (r=0,31). It is speculated that VLF band (0,04÷0,015 Hz) associated with oscillation blood levels of **renin** (0,04 Hz) and **epinephrine** (0,025 Hz), reflects thermoregulatory cycles [cit by: 2,11], cerebral ergotropic and metabolotropic outflows [cit by: 1], **sympathetic** activity [cit by: 10]. In addition, we revealed negatively correlation with Baevskiy's Activity Regulatory Systems Index in posture position (r=-0,33).

Among parameters EEG a regression model with stepwise exclusion included the following 9 (Table 1, Fig. 1).

Table 1. Regression Summary for Dependent Variable: Phagocytic Index for Staph. aureus

R=0,927; R^2=0,859; Adjusted R^2=0,763; $F_{(11,2)}$=8,9; $\chi^2_{(11)}$=35,9; $p<10^{-4}$; Std. Err. of estim.: 0,6%

		Beta	St. Err. of Beta	B	St. Err. of B	n=28 $t_{(16)}$	p-level
Independent Variables	r	Intercpt		96,5	,73	131	10^{-6}
SPD F7-α, %	-0,39	-,540	,219	-,037	,015	-2,46	,026
SPD F8-α, %	-0,32	,658	,244	,045	,017	2,70	,016
SPD Fp2-β, μV^2/Hz	0,38	,767	,215	,020	,006	3,58	,003
SPD F4-β, μV^2/Hz	0,32	-,795	,247	-,016	,005	-3,21	,005
SPD C3-δ, %	0,37	,828	,156	,091	,017	5,33	10^{-4}
SPD Fp1-δ, %	0,29	-,519	,202	-,034	,013	-2,56	,021
δ-rhythm Laterality, %	-0,29	-,359	,111	-,009	,003	-3,23	,005
SPD F7-θ, μV^2/Hz	0,37	,634	,174	,043	,012	3,64	,002
θ-rhythm Deviation, Hz	-0,36	-,298	,109	-,838	,308	-2,72	,015
Baevskiy's ARSI(p), un.	-0,33	-,410	,160	-,160	,063	-2,55	,021
SPD VLF, %	0,31	,366	,125	,027	,009	2,93	,010

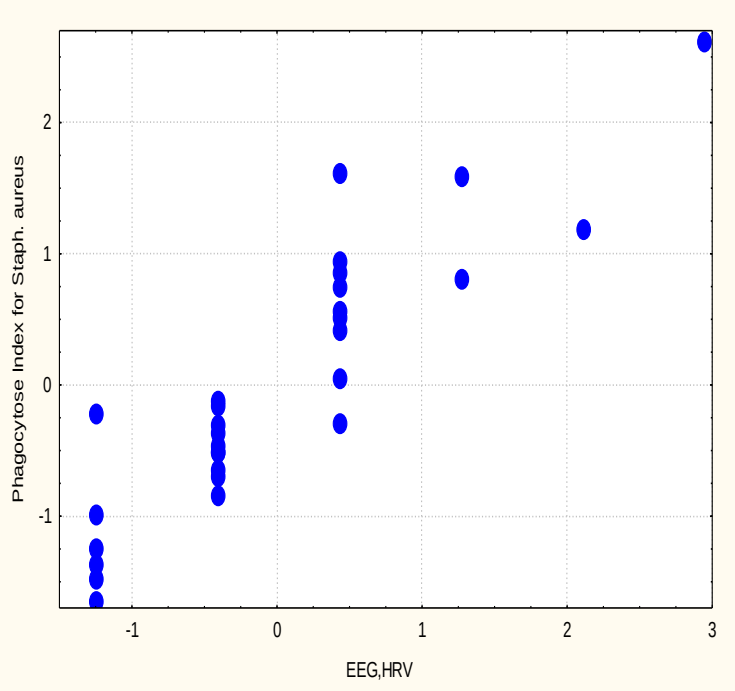


Fig. 1. Canonical correlation between parameters EEG and HRV (X-line) and Activity Phagocytose of Staphylococcus aureus (Y-line)

As you can see, Activity of Phagocytose Staph. aureus downregulated by α-rhythm-generating structures which are projected to both Frontalis Lateralis loci while upregulated by β-rhythm-generating structures which are projected to Rights Frontalis Anterior and Medialis loci, δ-rhythm-generating structures which are projected to Lefts Frontalis Anterior and Centralis loci as well as θ-rhythm-generating structures (hyppocamp? [16]) which are projected to Left Frontalis Lateralis locus. This activating effect θ-rhythm so pronounced, the smaller its Deviation. Probably upregulating outflows realized by means of catecholamines and mineralocorticoids/renin while downregulating outflows realized by means of acetylcholine.

Unlike **Activity** phagocytose its **Intensity** not correlated with parameters HRV but upregulated by some neural structures generating β-, θ- and δ-rhythms (Table 2, Fig. 2). In turn, SPD T5-θ correlated with LF/HF ratio (r=0,31) suggesting role of Sympatho-Vagal balance in upregulation Intensity of phagocytose Staph. aureus.

Table 2. Regression Summary for Dependent Variable: Microbial Count for Staph. aureus
R=0,687; R^2=0,472; Adjusted R^2=0,321; $F_{(6,2)}$=3,1; $\chi^2_{(6)}$=15,1; p=0,024;
Std. Error of estimate: 6,7 Microbes/Phagocyte

		Beta	St. Err. of Beta	B	St. Err. of B	n=28 $t_{(21)}$	p-level
Independent Variables	r	Intercpt		48,9	6,3	7,81	10^{-6}
SPD O2-β, μV^2/Hz	0,45	,372	,167	,091	,041	2,23	,037
SPD T5-θ, μV^2/Hz	0,36	,447	,305	,146	,100	1,47	,157
SPD P3-δ, %	0,30	,313	,186	,249	,148	1,68	,107
SPD F3-δ, μV^2/Hz	0,28	-,441	,317	-,024	,017	-1,39	,179
δ-rhythm Deviation, Hz	0,31	,288	,163	8,61	4,88	1,76	,093
θ-rhythm Deviation, Hz	-0,32	-,251	,166	-4,697	3,109	-1,51	,146

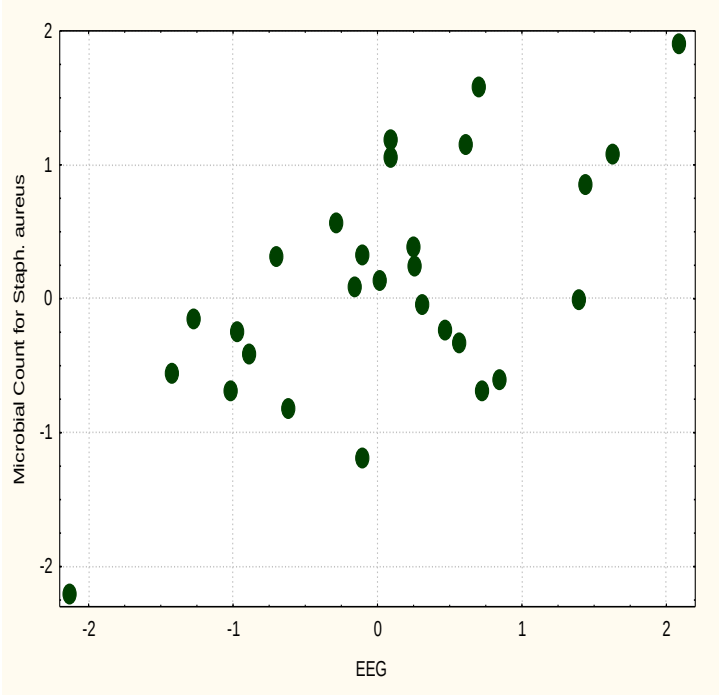


Fig. 2. Canonical correlation between parameters EEG and HRV (X-line) and Intensity Phagocytose of Staphylococcus aureus (Y-line)

Killing Index as a measure of Completeness phagocytose correlated among HRV parameters with Heart Rate and Baevskiy's Vegetative Index of Heart Rhythm as reverse marker of Vagal tone as well as with ULF band (Table 3). It is speculated that ULF band (0,015÷0,003 Hz) associated with oscillation blood level of **norepinephrine** (0,002 Hz) as well as **17-OCS** (0,0019 Hz) [cit by: 11].

Table 3. Regression Summary for Dependent Variable: Killing Index for Staph. aureus
R=0,655; R^2=0,428; Adjusted R^2=0,265; $F_{(6,2)}$=2,6; $\chi^2_{(6)}$=10,6; p=0,047; Std. Err. of estim.: 5,9%

		Beta	St. Err. of Beta	B	St. Err. of B	n=28 $t_{(21)}$	p-level
Independent Variables	r	Intercpt		60,5	13,6	4,45	10^{-3}
β-rhythm Index, %	-0,40	-,190	,183	-,069	,066	-1,04	,309
δ-rhythm Deviation, Hz	-0,32	-,218	,175	-5,509	4,426	-1,24	,227
Heart Rate, beats/min	0,29	-,210	,222	-,010	,010	-0,95	,355
1/Mo•MxDMn, units	0,31	,248	,235	,422	,400	1,05	,304
SPD ULF, %	0,27	,171	,172	,267	,268	1,00	,331
SPD F7-β, %	0,27	,371	,201	,114	,062	1,84	,079

Thus, Completeness phagocytose upregulated probably by **norepinephrine** and **glucocorticoides** release of which connected with β-rhythm generating structures projected in Left Frontalis Lateralis locus (Fig. 3).

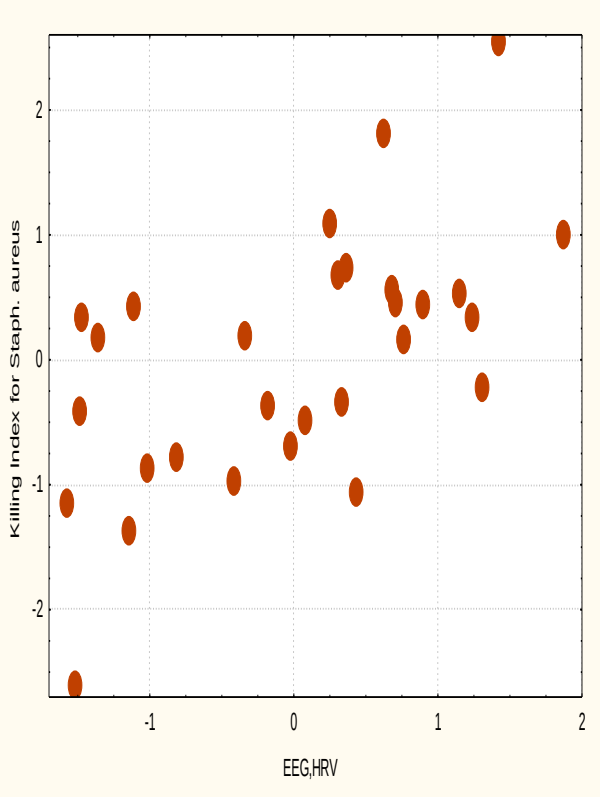


Fig. 3. Canonical correlation between parameters EEG and HRV (X-line) and Completeness Phagocytose of Staphylococcus aureus (Y-line)

Most interesting is the integrated evaluation of phagocytic function of neutrophils by the number of microbes that are able to neutralize neutrophils contained in 1 liter of blood, named as Bactericidity Capacity (BCC) and calculated by formula [28]:

BCC (10^9Bac/L)=Leukocytes (10^9/L)•Neutrophils (%)•PhI (%)•MA (Bac/Phag)•KI (%)/10^6

Interestingly, the integral index of phagocytosis correlated exactly with integrated HRV indices, which reflect Sympatho-Vagal balance (Table 4). In general, Bactericidity Capacity of Neutrophils against Staph. aureus upregulated by Sympathetic outflows while downregulated by

Vagal outflows. Among parameters EEG, included in regression model, various structures generating δ-rhythm upregulated BCC. Among them structures projected in loci O1 and T6 correlated with Baevskiy's Stress Index (r makes 0,68 and 0,66 respectively). The observed negative correlation between BCC and Entropy SPD still waiting for an interpretation from the standpoint of the theory of deterministic chaos. Despite the very moderately rates pairwise correlations canonical correlation between parameters EEG and HRV, on the one hand, and Bactericidity Capacity Neutrophils against Staphylococcus aureus, on the other hand, was very strong (Fig. 4).

Table 4. Regression Summary for Dependent Variable: Bacterocidity Capacity of Neutrophils against Staph. aureus
R=0,700; R^2=0,490; Adjusted R^2=0,320; $F_{(7,2)}$=2,9; p=0,028; Std. Err. of estimate: $28 \cdot 10^9$ Bac/L

		Beta	St. Err. of Beta	B	St. Err. of B	n=29 $t_{(21)}$	p-level
Independent Variables	r	Intercpt		83,5	73,9	1,13	,271
1/Mo•MxDMn, units	0,36	1,625	,716	13,97	6,15	2,27	,034
Baevskiy's SI (p), units	0,33	,365	,234	,048	,030	1,56	,133
AMo/MxDMn, units	0,32	4,005	1,595	,566	,225	2,51	,020
Baevskiy's SI, units	0,30	-5,322	1,832	-1,040	,358	-2,91	,008
SDNN, ms	-0,31	,512	,323	,876	,552	1,59	,128
Moda HRV, ms	-0,30	-,506	,302	-,115	,068	-1,68	,109
SPD ULF, %	-0,28	-,548	,180	-4,281	1,403	-3,05	,006

Table 5. Regression Summary for Dependent Variable: Bacterocidity Capacity Neutrophils against Staph. aureus
R=0,926; R^2=0,857; Adjusted R^2=0,733; $F_{(13,2)}$=6,9; $\chi^2_{(13)}$=39,9; $p<10^{-3}$; SE of est.:$18 \cdot 10^9$ Bac/L

		Beta	St. Err. of Beta	B	St. Err. of B	n=29 $t_{(15)}$	p-level
Independent Variables	r	Intercpt		18,2	38,0	,48	,64
1/Mo•MxDMn, units	0,36	1,824	,579	15,68	4,98	3,15	,007
Baevskiy's SI(p), units	0,33	1,151	,236	,150	,031	4,87	10^{-4}
AMo/MxDMn, units	0,32	2,308	,796	,326	,112	2,90	,011
Baevskiy's SI, units	0,30	-5,255	1,298	-1,027	,254	-4,05	,001
SPD ULF, %	-0,28	-,642	,127	-5,011	,991	-5,06	10^{-4}
SPD F8-δ, μV^2/Hz	0,42	1,214	,379	,083	,026	3,20	,006
SPD Fp2-δ, %	0,32	-,453	,274	-,756	,456	-1,66	,119
SPD T6-δ, μV^2/Hz	0,31	-2,843	1,012	-,219	,078	-2,81	,013
SPD T3-δ, μV^2/Hz	0,29	-,772	,211	-,178	,049	-3,67	,002
SPD O1-δ, μV^2/Hz	0,29	2,608	1,036	,088	,035	2,52	,024
SPD O2-θ, μV^2/Hz	0,37	1,007	,241	1,586	,380	4,17	,001
Entropy SPD T3	-0,48	,474	,183	122,2	47,3	2,59	,021
Entropy SPD T6	-0,35	-,680	,186	-115,6	31,7	-3,65	,002

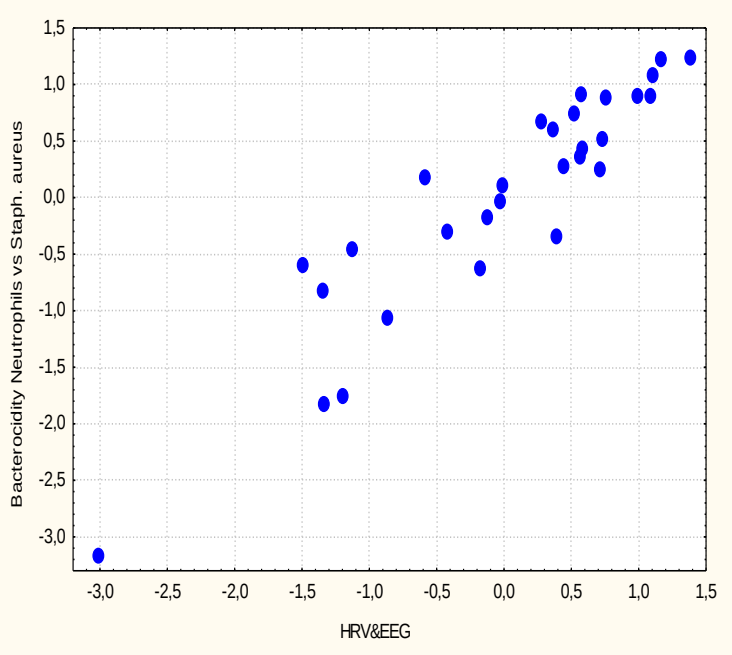


Fig. 4. Canonical correlation between parameters EEG and HRV (X-line) and Bactericidity Capacity Neutrophils against Staphylococcus aureus (Y-line)

Our findings are consistent with long known provisions that sympathetic/adrenergic outflows upregulate phagocytose while vagal/cholinergic outflows downregulate its [review: 9] as well as with data RH Straub et al [35,36] that prior ablation of the Sympathetic nervous system in Mice Female increase dissemination of Staph. aureus from peritoneal cavity, which was caused by reduction in **Sympathetic** and **Corticosterone** tonus followed by reduction IL-4 secretion as well as influx of Lymphocytes into the peritoneal cavity.

However previously in observation of 32 healthy men we found that increased vagal tone (after 80 minutes after drinking bioactive water Naftussya) is accompanied by a significant increase Phagocytic Index vs Staph. aureus in the absence of changes in both Microbial Count and Kiling Index, while sympathotonic effect accompanied by a significant reduction Kiling Index in the absence of changes in both Microbial Count and Phagocytic Index, and in the absence of changes in autonomous regulation stated no change parameters phagocytosis. We found negative correlation Kiling Index with Sympathetic marker AMo (r=-0,38) while positive correlation with Vagal marker Mo (r=0,77) [14,15,29,32].

In observation of 22 men with chronic pyelonephritis and cholecystitis we [20] found that after 10-12-day cours of balneotherapy on spa Truskavets' decrease LF/HF ratio by 32% and plasma Cortisol by 20% accompanied by increase Kiling Index vs Staph. aureus by 19% without changes in Activity and Intensity phagocytosis.

In another observation of 80 children OV Kozyavkina found weak (r=0,22÷0,33), but statistically significant positive relationships between changes due course balneotherapy on spa Truskavets' indicators phagocytosis Staph. aureus and HRV markers of vagal tone [12,14]. YV Moyiseyenko [21] in patients with "Antarctic syndrome" (a variant of chronic stress) found that reduction of phagocytic activity of neutrophils 30-70% is accompanied by increased urinary excretion of norepinephrine by 37% and increase in power δ-rhythm at 7,1% combined with a decrease in power α-rhythm at 3,8%.

In experiments on female rats [41] we found a weak correlation Microbial Count of Neutrophils/Microphages with vagal markers MxDMn (r=0,33) and Mo (r=0,30) as well as Phagocytic Index of Monocytes/Macrophages with Sympathetic marker AMo (r=-0,29). In another experiment in male rats [13] also found a weak correlation AMo with Phagocytic Index of Monocytes (r=-0,28) and with Kiling Index of Neutrophils (r=-0,35). Instead MxDMn correlate with these parameters the opposite way: r=0,23 and 0,33 respectively.

Previously we [24,25] have been shown that at male rats caused by chronic restraint stress increasing Sympathetic tone and Heart Rate as well as decreasing Vagal Tone accompanied by decrease both Intensity and Activity of Phagocytose Staph. aureus by Neutrophils, while increase Microbial Count for Monocytes of blood and their Bactericidal Capacity against Staphylococcus aureus (despite the decrease in their Phagocytose Index).

In another experiments on female and male rats [37] we found that caused by acute stress Sympathotonic displacement of Sympatho-Vagal Balance evaluated by increasing AMo by 10% and a decreasing MxDMn by 31% and by increasing plasma Ca/K ratio (as its humoral marker [6,27]) by 15%, is accompanied by a decrease Killing Index by 13% but increased Microbial Count by 13% as well as Bactericidal Capacity against Staphylococcus aureus by 24%.

Thus, data on the regulation of phagocytosis of Staphylococcus aureus as a representative of Gram-positive microbes by autonomous nervous system inconsistent. What is the situation regarding Escherichia coli as a representative of Gram-negative bacteria?

Activity Phagocytose of E. coli subordinate suppressor influence vagal tone more than Staph. aureus judging by coefficients correlation with its spectral and temporal HRV markers as well as canonical correlation (Fig. 5 and 6, Table 6).

Among parameters EEG most notable influence on Activity Phagocytose of E. coli SPD α-Rhythm in Frontalis Medialis Left locus (Fig. 7) and SPD β-Rhythm in Occipitalis Right locus (Fig. 8), while the opposite way.

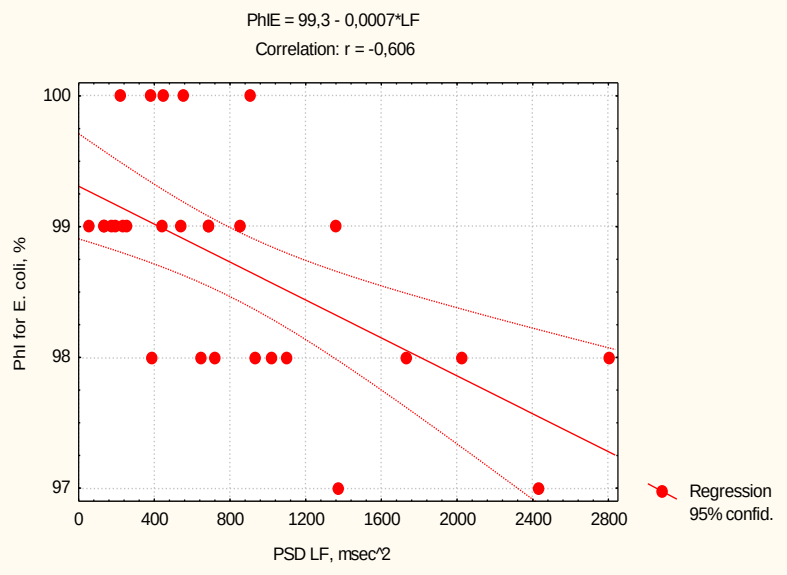


Fig. 5. Correlation between SPD LF HRV (X-line) and Activity Phagocytose E. coli (Y-line)

Table 6. Regression Summary for Dependent Variable: Phagocytic Index for E. coli
R=0,821; R^2=0,674; Adjusted R^2=0,543; $F_{(8,2)}$=5,2; $\chi^2_{(8)}$=25,8; p=0,0014; SE of estimate: 0,6%

		Beta	St. Err. of Beta	B	St. Err. of B	n=29 $t_{(20)}$	p-level
Independent Variables	r	Intercpt		102,5	1,5	69,28	10^{-6}
SPD LF, ms^2	-0,61	-,523	,378	-,0006	,0005	-1,38	,182
Total Power, ms^2	-0,51	2,150	1,043	,0009	,0004	2,06	,052
SDNN, ms	-0,48	-3,872	1,200	-,1616	,0501	-3,23	,004
SPD HF, ms^2	-0,44	-,918	,491	-,0010	,0006	-1,87	,076
pNN_{50}, %	-0,38	-1,359	,709	-,0845	,0441	-1,92	,070
C_V, %	-0,37	,758	,385	,3022	,1533	1,97	,063
RMSSD, ms	-0,32	2,721	,894	,1185	,0389	3,05	,006
AMo HRV, %	0,28	-,649	,269	-,0335	,0139	-2,41	,026

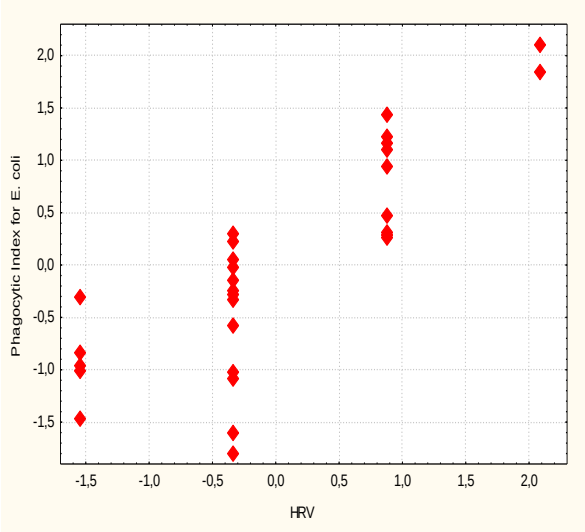


Fig. 6. Canonical correlation between parameters HRV (X-line) and Activity Phagocytose of Escherichia coli (Y-line)

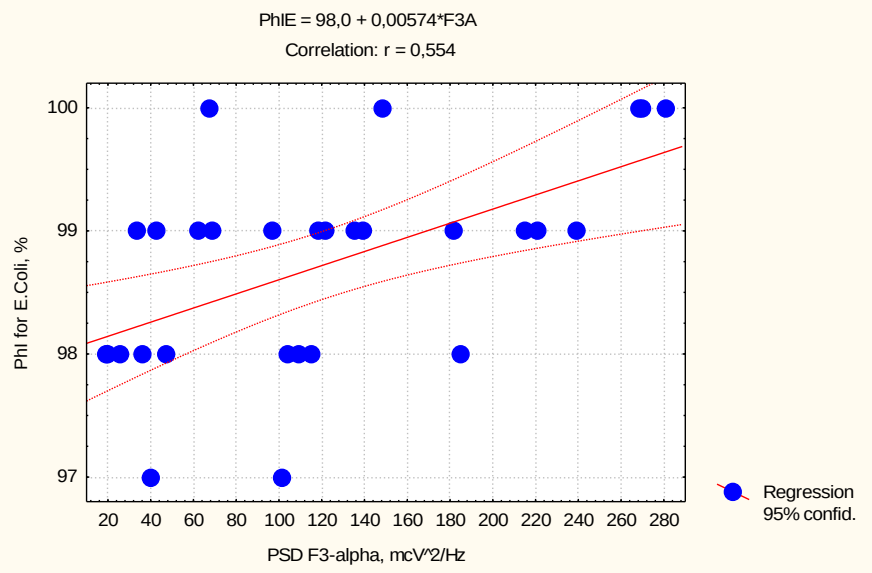


Fig. 7. Correlation between SPD F3-α (X-line) and Activity Phagocytose of Escherichia coli (Y-line)

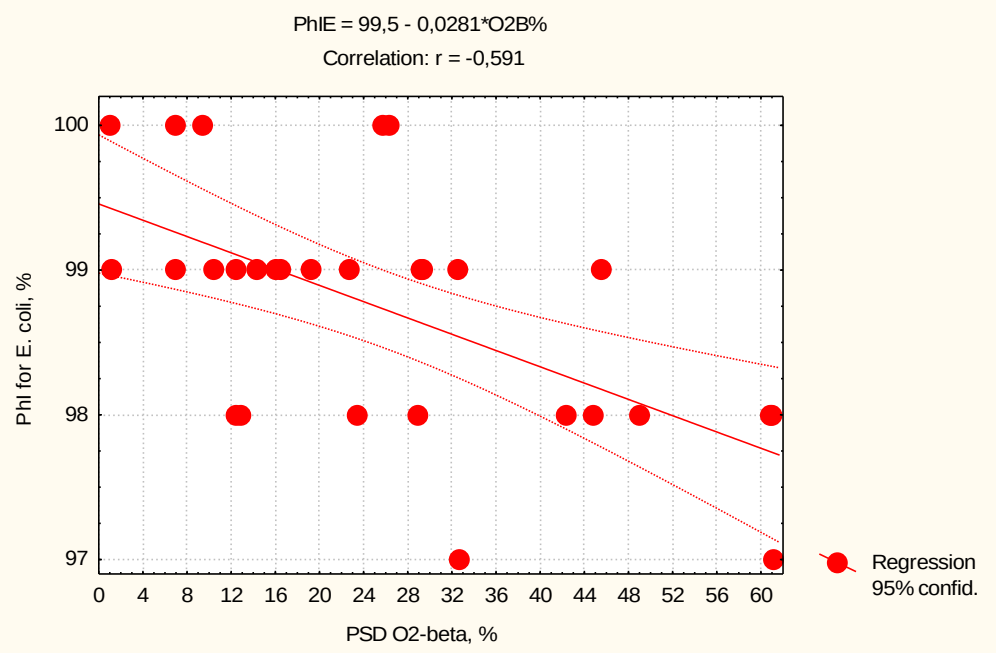
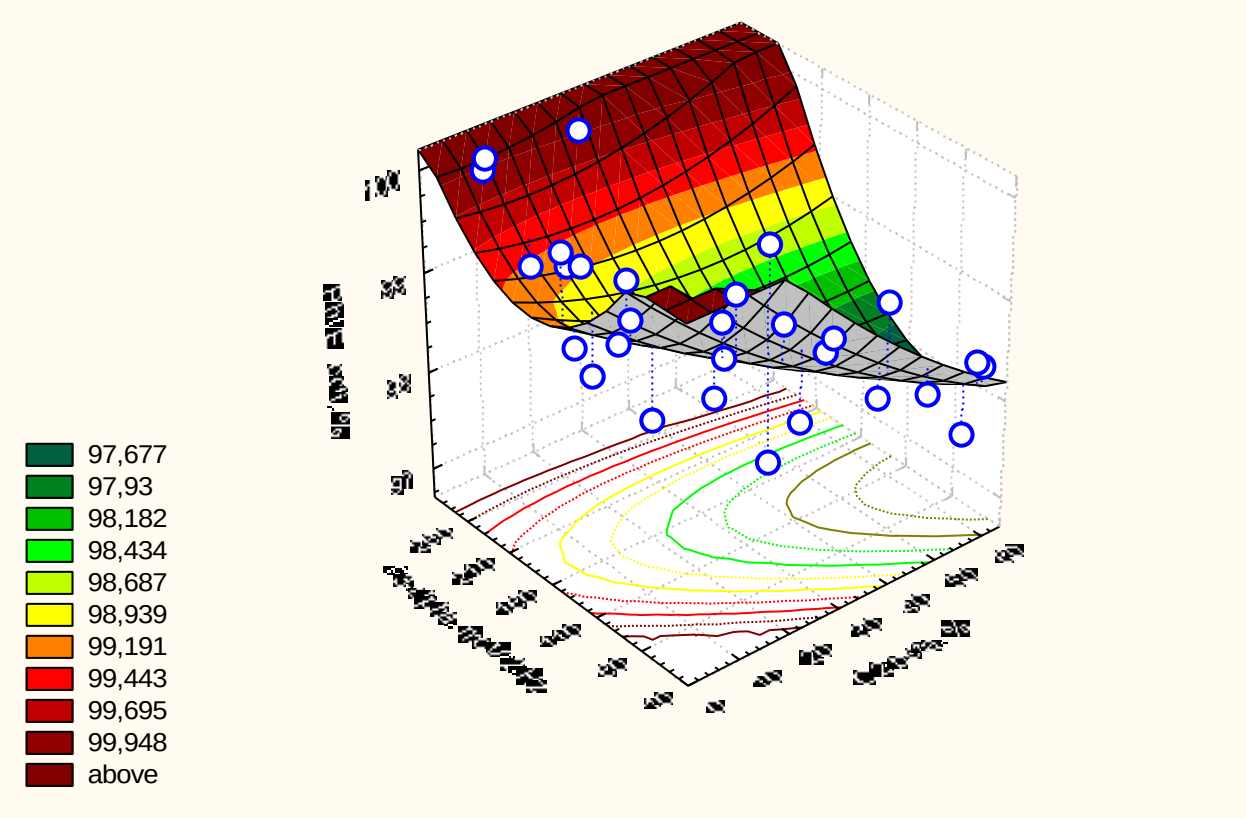


Fig. 8. Correlation between SPD O2-β (X-line) and Activity Phagocytose of Escherichia coli (Y-line)



PhI E. coli (%) = 98,86 – 0,019•O2-β (%) + 0,003•F3-α (μV^2/Hz)
R=0,625; R^2=0,390; Adjusted R^2=0,344; $F_{(2,3)}$=8,3; p<0,002; SE: 0,7%

Fig. 9. Influences SPD O2-β (X-line) and F3-α (Y-line) on Activity Phagocytose of Escherichia coli (Z-line)

Both neural structures together determine the phagocytic index by 34% (Fig. 9). Interestingly, both variables were not included in the final model for unknown reasons, but without them neural influences determine the phagocytic index by 75% (Table 7, Fig. 10).

Table 7. Regression Summary for Dependent Variable: Phagocytic Index for E. coli
R=0,941; R^2=0,886; Adjusted R^2=0,754; $F_{(15,1)}$=6,7; $\chi^2_{(15)}$=42,3; p=0,0007; SE of estimate:0,4%

		Beta	St. Err. of Beta	B	St. Err. of B	n=29 $t_{(13)}$	p-level
Independent Variables	r	Intercpt		103,3	1,3	81,20	10^{-6}
Total Power, ms^2	-0,51	1,774	,828	,0007	,0003	2,14	,051
SPD HF HRV, ms^2	-0,44	-,772	,395	-,0009	,0004	-1,95	,072
SDNN HRV, ms	-0,48	-2,915	1,124	-,1217	,0469	-2,59	,022
pNN_{50}, %	-0,38	-2,170	,522	-,1350	,0325	-4,15	,001
C_V, %	-0,37	,576	,389	,2294	,1549	1,48	,162
RMSSD HRV, ms	-0,32	2,761	,731	,1203	,0318	3,78	,002
AMo HRV, %	0,28	-,538	,219	-,0278	,0113	-2,45	,029
SPD C3-β, %	-0,53	-,539	,237	-,0349	,0153	-2,27	,041
SPD Fp1-α, μV^2/Hz	0,49	-1,925	,573	-,0248	,0074	-3,36	,005
SPD F7-α, μV^2/Hz	0,49	,783	,294	,0185	,0070	2,66	,020
SPD O1-α, μV^2/Hz	0,49	1,110	,457	,0051	,0021	2,43	,031
Amplitude α-Rh, μV	0,45	-,403	,269	-,0475	,0317	-1,50	,158
Asymmetry α-Rh, %	-0,34	-,631	,169	-,0452	,0121	-3,72	,003
SPD F7-θ, μV^2/Hz	0,39	,695	,322	,0327	,0151	2,16	,050
Amplitude δ-Rh, μV	0,32	-,373	,225	-,0170	,0102	-1,66	,121

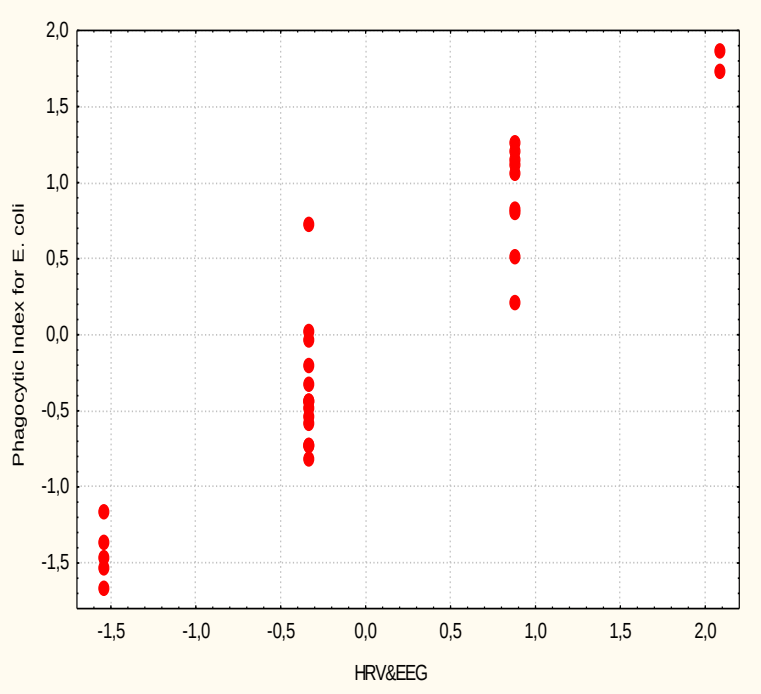


Fig. 10. Canonical correlation between parameters EEG and HRV (X-line) and Activity Phagocytose of Escherichia coli (Y-line)

Thus, Activity Phagocytose of E. coli downregulated by vagal outflows and β-rhythm-generating structures projected in Central Left locus (Hyppocamp? [16]) while apregulated by α-rhythm-generating structures projected in Left Frontal and Occipital loci.

The intensity of phagocytosis of E. coli associated with HRV parameters poorly (Table 8).

Table 8. Regression Summary for Dependent Variable: Microbial Count for E. coli
R=0,571; R^2=0,326; Adjusted R^2=0,245; $F_{(3,3)}$=4,0; p=0,018; SE: 6,6 Bacter/Phagocyte

		Beta	St. Err. of Beta	B	St. Err. of B	n=29;$t_{(25)}$	p
Independent Variables	r	Intercpt		79,6	5,9	13,54	10^{-6}
SPD ULF, ms^2	-0,35	-,353	,226	-,015	,010	-1,56	,131
SPD ULF, %	-0,35	-,270	,220	-,465	,379	-1,23	,231
SPD LFnu, %	-0,23	-,457	,179	-,195	,076	-2,55	,017

Among the options EEG greatest infleence on the intensity of phagocytosis of E. coli has SPD θ-Rhythm in Frontalis Lateralis Right locus (Fig. 11).

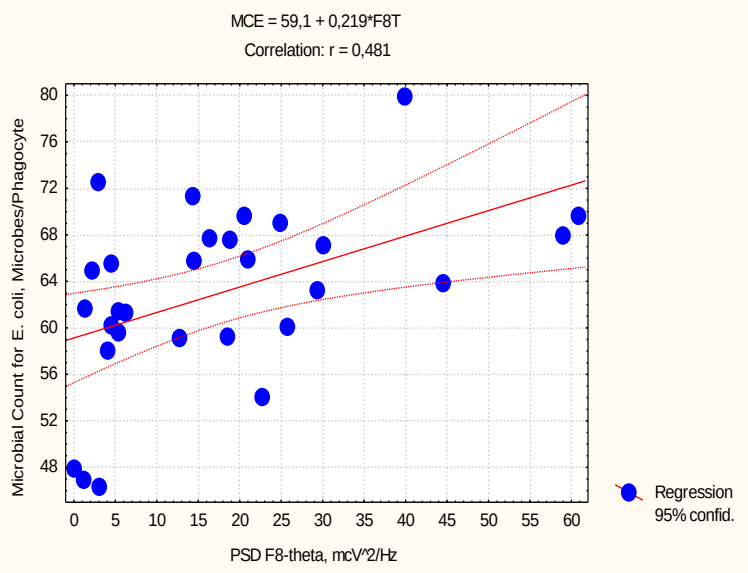


Fig. 11. Correlation between SPD F8-θ (X-line) and Intensity Phagocytose of E. coli (Y-line)

Table 9. Regression Summary for Dependent Variable: Microbial Count for E. coli
R=0,842; R^2=0,708; Adjusted R^2=0,570; $F_{(9,2)}$=5,1; $\chi^2_{(9)}$=27,7; p=0,0013;
SE of estimate: 5,0 Bacteria/Phagocyte

		Beta	St. Err. of Beta	B	St. Err. of B	n=29 $t_{(19)}$	p-level
Independent Variables	r	Intercpt		99,0	8,6	11,5	10^{-6}
SPD O1-θ, μV^2/Hz	0,39	,804	,260	,134	,044	3,09	,006
SPD T5-θ, μV^2/Hz	0,32	-,510	,310	-,158	,096	-1,64	,117
SPD F8-α, μV^2/Hz	0,32	-,542	,193	-,142	,051	-2,81	,011
SPD F3-δ, μV^2/Hz	0,31	-,423	,268	-,022	,014	-1,58	,131
SPD F8-β, μV^2/Hz	0,32	,632	,198	,143	,045	3,19	,005
Frequency β-Rh, Hz	-0,39	-,496	,152	-,871	,267	-3,27	,004
SPD F8-β, %	-0,31	-,562	,201	-,190	,068	-2,79	,012
SPD ULF, ms^2	-0,35	-,557	,180	-,024	,008	-3,10	,006
SPD LFnu, %	-0,23	-,414	,164	-,176	,070	-2,52	,021

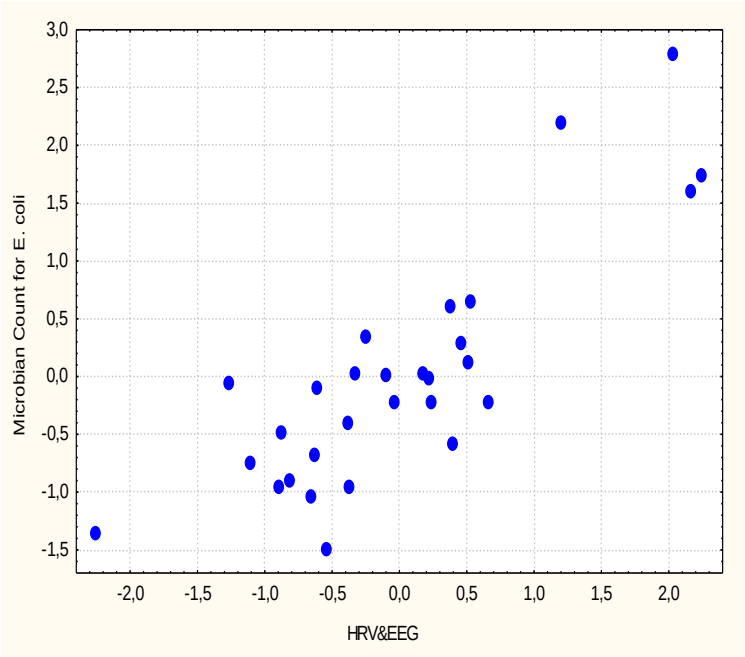


Fig. 12. Canonical correlation between parameters EEG and HRV (X-line) and Intensity Phagocytose of Escherichia coli (Y-line)

But this variables not included in the final regression model, according to which a constellation of neural influences determines Microbial Count for E. coli at 57% (Table 9, Fig. 12). This greatly exceeds the extent of neural determination regarding Staph. aureus (32%).

Completeness Phagocytose also upregulated by SPD ULF (Fig. 13) as marker plasma levels of norepinephrine and glucocorticoides while downregulated by markers of sympathetic neural outflows. Autonomous and hormonal factors together determinate Killing Index vs E. coli at 23% (Table 10, Fig. 14).

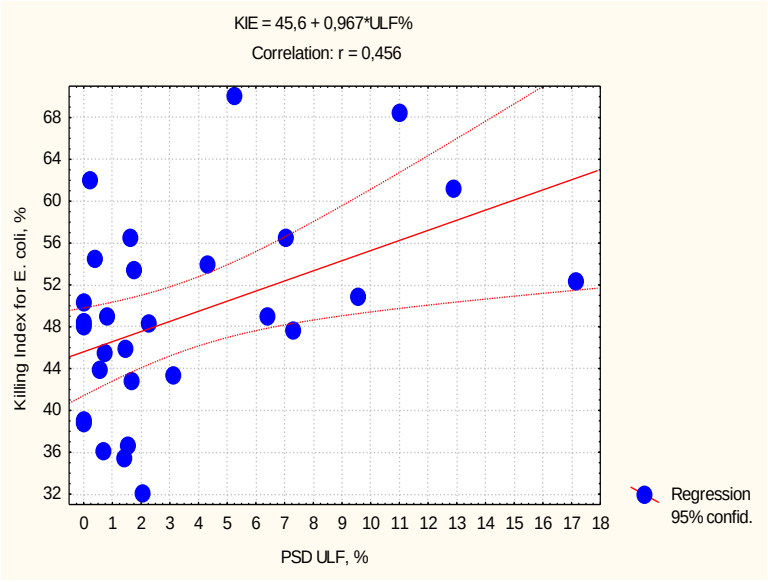


Fig. 13. Correlation between ULF (X-line) and Completeness Phagocytose of E. coli (Y-line)

Table 10. Regression Summary for Dependent Variable: Killing Index for E. coli
R=0,585; R^2=0,342; Adjusted R^2=0,232; $F_{(4,2)}$=3,1; $\chi^2_{(4)}$=10,5; p=0,034; SE of estimate: 8,2%

		Beta	St. Err. of Beta	B	St. Err. of B	n=29 $t_{(24)}$	p-level
Independent Variables	r	Intercpt		43,2	9,7	4,45	,0002
SPD ULF, %	0,46	,370	,181	,784	,384	2,04	,052
SPD LF, %	-0,43	-,248	,218	-,160	,141	-1,14	,267
LF/HF HRV	-0,38	-,421	,301	-,964	,689	-1,40	,175
SPD LFnu, %	-0,26	,352	,301	,185	,158	1,17	,254

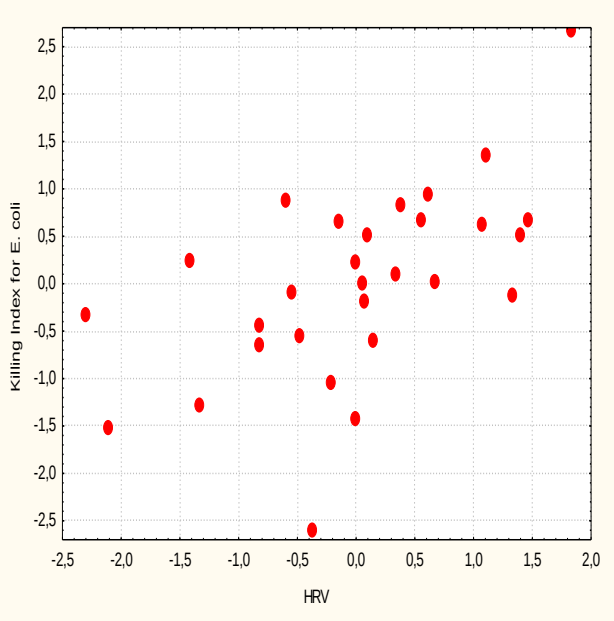


Fig. 14. Canonical correlation between parameters HRV (X-line) and Completeness Phagocytose of Escherichia coli (Y-line)

Killing Index for E. coli downregulated besides sympathetic outflows also by neural structures generating θ-, δ- and α-Rhythm while upregulated by neural structures generating β-Rhythm (Table 11). Among them SPD O1-θ positively correlated with relative PSD LF band as marker of Sympathetic tone (r=0,37) while α-rhythm Index and SPD F3-α correlated with LF/HF ratio as marker of Sympatho-Vagal balance negatively (r makes -0,32 and -0,31 respectively) while SPD T5-θ correlated positively (r=0,31). In addition δ-rhythm Frequency correlated positively with SPD ULF (r=0,25) as marker plasma levels of norepinephrine and glucocorticoides.

In the aggregate neural outflows determinate Completeness Phagocytose of Escherichia coli at 93% (Table 11, Fig. 15), while of Staph. aureus at 32% only.

It turns out that vagotonic shift of Sympatho-Vagal balance as well as decrease of Sympathetic tone are good for combating Escherichia coli. Our findings are consistent with data RH Straub et al [35,36] that prior ablation of the Sympathetic nervous system [*leading to vagotonic shift of Sympatho-Vagal balance*] in Mice Female decrease dissemination of Escherichia coli (and Gram-negative P. aeruginosa also) from peritoneal cavity, which was caused by reduction in Sympathetic tonus followed by reduction inhibition [*disinhibition*]

secretion of pro-inflammatory factors (TNF-α, IFN-γ, IL-6) as well as influx of Neutrophils and Monocytes into the peritoneal cavity and Macrophage Phagocytosis.

Table 11. Regression Summary for Dependent Variable: Killing Index for E. coli
R=0,990; R^2=0,981; Adjusted R^2=0,934; $F_{(20,8)}$=20,7; $\chi^2_{(20)}$=67,4; $p<10^{-4}$; SE of estimate: 2,4%

		Beta	St. Err. of Beta	B	St. Err. of B	n=29 $t_{(8)}$	p-level
Independent Variables	r	Intercpt		51,0	6,4	7,97	10^{-4}
LF/HF	-0,38	-,185	,123	-,423	,283	-1,50	,173
SPD T5-θ, μV^2/Hz	-0,44	-2,428	,423	-,926	,161	-5,74	10^{-3}
SPD F7-θ, μV^2/Hz	-0,36	-,439	,163	-,230	,086	-2,69	,027
SPD O1-θ, μV^2/Hz	-0,33	1,044	,219	,215	,045	4,76	,001
SPD F8-θ, μV^2/Hz	-0,30	-1,770	,216	-,995	,122	-8,18	10^{-4}
θ-rhythm Amplitude, μV	-0,32	1,449	,273	3,473	,654	5,31	10^{-3}
SPD C4-δ, μV^2/Hz	-0,42	1,584	,243	,232	,036	6,52	10^{-3}
SPD F3-δ, μV^2/Hz	-0,35	-2,256	,317	-,144	,020	-7,12	10^{-4}
SPD F8-δ, %	-0,30	,720	,134	,226	,042	5,36	10^{-3}
δ-rhythm Frequency, Hz	0,29	,213	,076	11,38	4,05	2,81	,023
SPD F7-α, μV^2/Hz	-0,42	1,210	,294	,319	,077	4,12	,003
SPD F3-α, μV^2/Hz	-0,34	-1,013	,254	-,117	,029	-3,99	,004
SPD FP1-α, μV^2/Hz	-0,33	-9,358	1,047	-1,345	,151	-8,93	10^{-4}
SPD T5-α, μV^2/Hz	-0,31	2,306	,256	,388	,043	9,00	10^{-4}
SPD C4-α, μV^2/Hz	-0,34	-2,838	,372	-,217	,028	-7,63	10^{-4}
SPD FP2-α, μV^2/Hz	-0,28	8,399	,861	1,124	,115	9,75	10^{-5}
α-rhythm Index, %	-0,30	1,058	,236	,328	,073	4,49	,002
SPD F8-β, μV^2/Hz	0,34	-,337	,098	-,094	,027	-3,44	,009
SPD F7-β, %	0,30	-1,157	,210	-,482	,087	-5,52	10^{-3}
SPD C4-β, μV^2/Hz	-0,28	,661	,215	,112	,036	3,08	,015

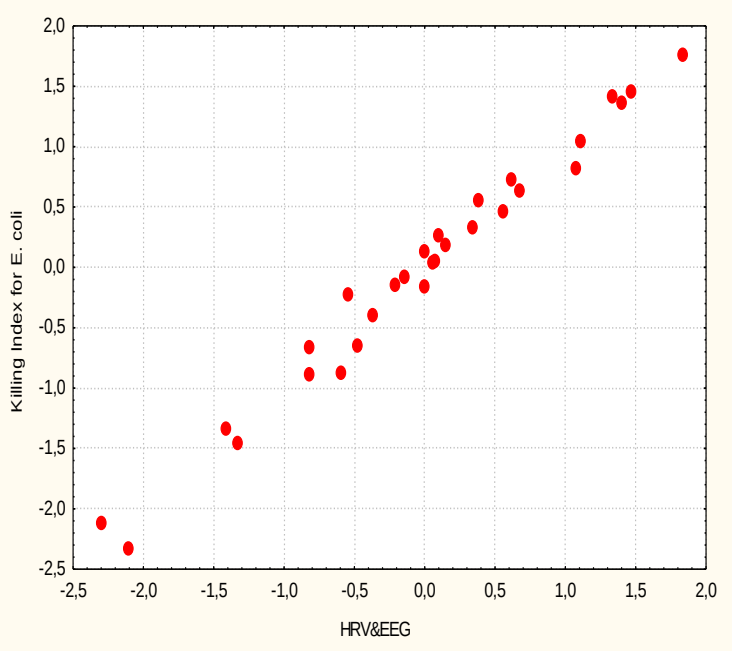


Fig. 15. Canonical correlation between parameters HRV and EEG (X-line) and Completeness Phagocytose of Escherichia coli (Y-line)

But Bactericidity Capacity Neutrophils against E. coli determinated by only autonomous (Table 12) as well as by total neural (Table 13, Fig. 16) outflows same extent as Staph. aureus.

Table 12. Regression Summary for Dependent Variable: Bactericidity Capacity Neutrophils against Escherichia coli

R=0,668; R^2=0,446; Adjusted R^2=0,295; $F_{(6,2)}$=2,9; p=0,029; SE of estimate: $25 \cdot 10^9$ Bac/L

		Beta	St. Err. of Beta	B	St. Err. of B	n=30 $t_{(22)}$	p-level
Independent Variables	r	Intercpt		136,4	65,8	2,07	,050
Baevskiy's SI(p), units	0,41	,607	,226	,068	,025	2,68	,014
1/Mo•MxDMn, units	0,37	1,686	,673	12,52	5,00	2,51	,020
Baevskiy's SI, units	0,33	-1,059	,619	-,179	,105	-1,71	,101
Baevskiy's SI, ln units	0,30	-,800	,455	-29,27	16,6	-1,76	,093
SPD ULF, ms^2	-0,25	-,295	,187	-,050	,031	-1,58	,129
SPD VLF, %	0,25	,363	,171	,654	,308	2,13	,045

Table 13. Regression Summary for Dependent Variable: Bacterocidity Capacity Neutrophils against Escherichia coli

R=0,892; R^2=0,795; Adjusted R^2=0,642; $F_{(12,2)}$=5,2; $\chi^2_{(12)}$=33,3; p=0,0015;
Std. Error of estimate: $18 \cdot 10^9$ Bacter/L

		Beta	St. Err. of Beta	B	St. Err. of B	n=30 $t_{(16)}$	p-level
Independent Variables	r	Intercpt		324	60	5,39	10^{-4}
SPD ULF, ms^2	-0,25	-,238	,177	-,040	,030	-1,35	,197
1/Mo•MxDMn, units	0,37	,955	,353	7,096	2,623	2,71	,016
β-Rh Laterality Index, %	0,31	,393	,152	,445	,172	2,58	,020
Baevskiy's SI, ln units	0,30	-1,117	,383	-40,86	14,01	-2,92	,010
Baevskiy's SI(p), units	0,41	,458	,174	,052	,020	2,63	,018
SPD F8-δ, μV^2/Hz	0,34	-1,774	,747	-,104	,044	-2,37	,030
Entropy SPD in locus T3	-0,45	-,569	,182	-126,8	40,6	-3,13	,006
SPD T3-θ, %	-0,35	,573	,259	2,620	1,186	2,21	,042
SPD T3-θ, μV^2/Hz	-0,37	-,421	,264	-,309	,194	-1,59	,130
SPD C3-θ, μV^2/Hz	-0,28	,998	,354	,492	,175	2,82	,012
SPD P4-θ, μV^2/Hz	-0,30	-1,037	,310	-,816	,244	-3,34	,004
SPD O2-δ, μV^2/Hz	0,30	2,031	,744	,049	,018	2,73	,015

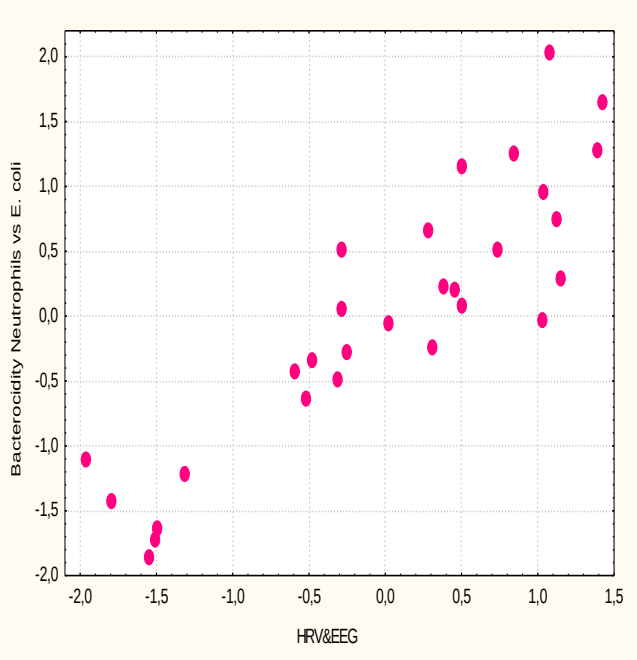


Fig. 16. Canonical correlation between parameters HRV and EEG (X-line) and Bactericidity Capacity Neutrophils against Escherichia coli (Y-line)

In order to clarify the detailed differences in the autonomous regulation of phagocytosis Escherichia coli and Staphylococcus aureus we built profiles of coefficients correlation. It is discovered (Fig. 17), that Activity phagocytose for **Escherichia coli** downregulated more or less by 10 markers of Vagal tone, whereas in respect **Staphylococcus aureus** respectively coefficients correlation, usually insignificant or significantly smaller. This is consistent with the concept "cholinergic antiinflammatory pathway" [7,39,40]. However, upregulation by markers of Sympathetic tone is equal for both bacteria, which is also consistent with the provisions of anti-inflammatory effects sympathetic/adrenergic outflows too [22,34,38].

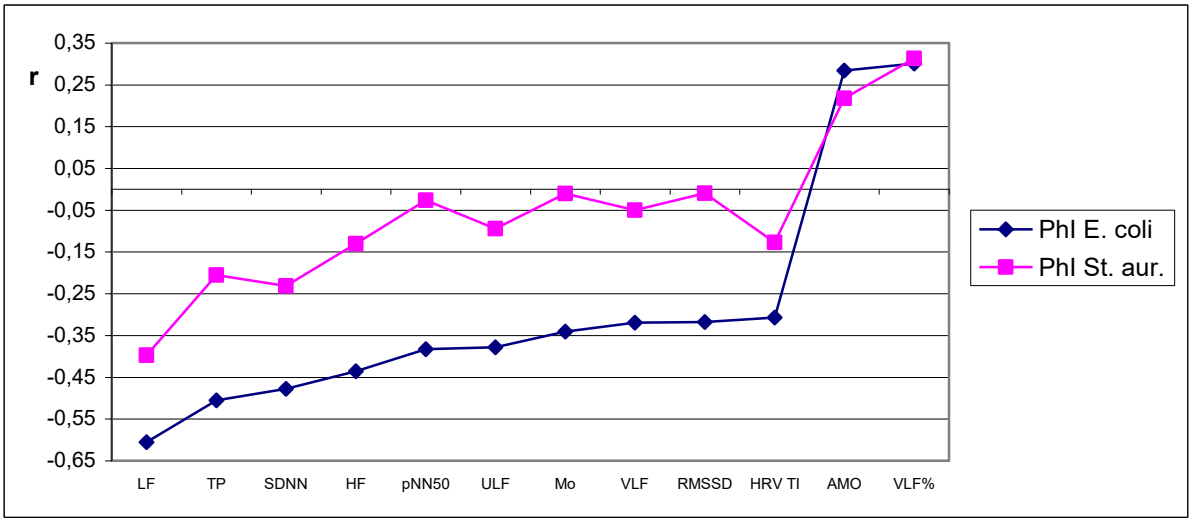


Fig. 17. Profiles of coefficients correlation HRV markers of vagal and sympathetic tone with Phagocytic Index for Escherichia coli and Staphylococcus aureus

Intensity phagocytose for **Escherichia coli** moderately downregulated by sympathetic outflows and upregulated by vagal outflows while for **Staphylococcus aureus** relationships are non significantly (Fig. 18).

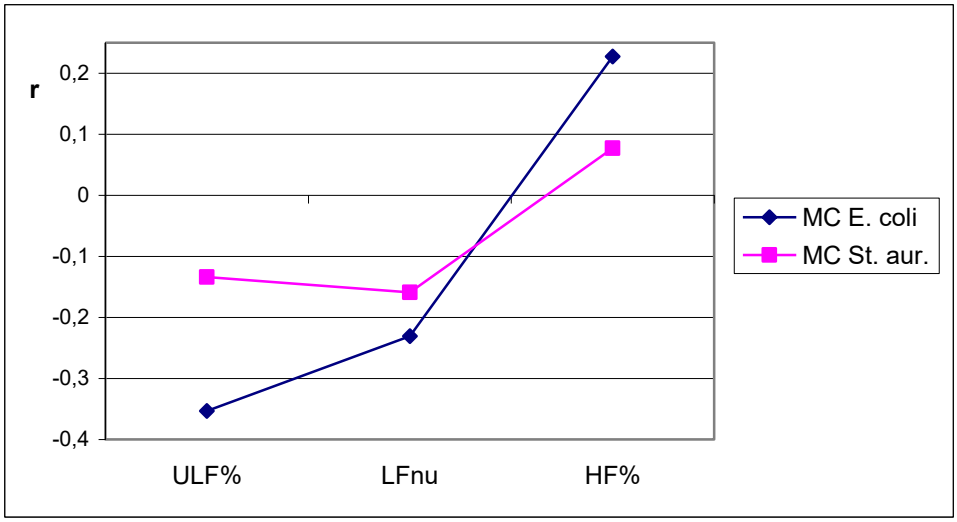


Fig. 18. Profiles of coefficients correlation HRV markers of sympathetic and vagal tone with Microbial Count for Escherichia coli and Staphylococcus aureus

Concerning features regulation of Completeness Phagocytose situation is ambiguous. On the one hand, Killing Index for **Escherichia coli** upregulated by markers of circulating catecholamines and glucocorticoides, on the other hand, it downregulated by markers of sympathetic tone while for **Staphylococcus aureus** relationships are non significantly, except downregulation by Mo as marker of vagal tone (Fig. 19).

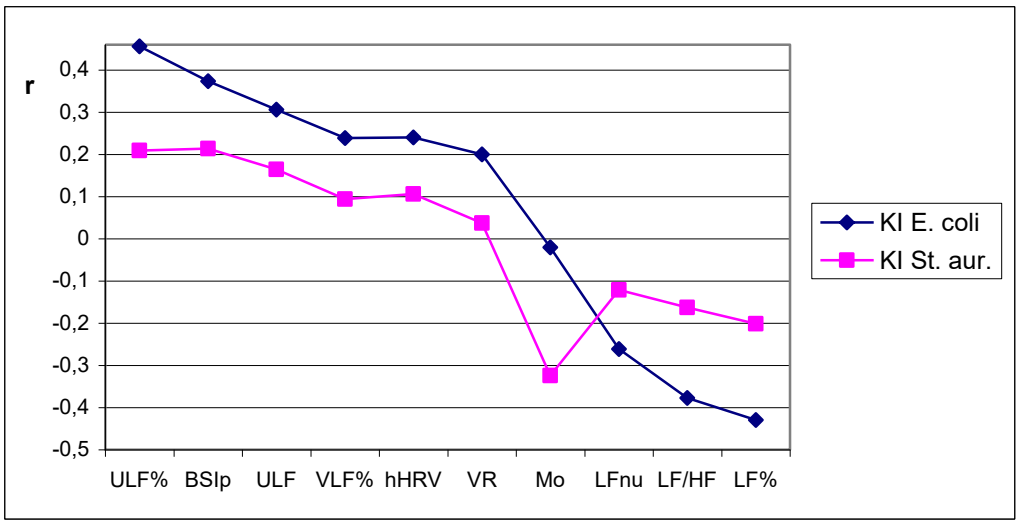


Fig. 19. Profiles of coefficients correlation HRV markers of sympathetic and vagal tone with Killing Index for Escherichia coli and Staphylococcus aureus

We recently discovered that in practically healthy people Bactericidity Neutrophils against E. coli downregulated by Baevskiy's Stress Index significantly (r=-0,39) while against Staph.

aureus nonsignificantly (r=-0,20), while correlation with plasma Cortisol makes -0,20 vs -0,27 respectively [4].

Instead of **conclusion** allow ourselves to announce the following communication, which raised the topic will be continued.

ACKNOWLEDGMENT

We express our sincere gratitude to administration JSC "Truskavets'kurort" for help in conducting immune tests and recording EEG and HRV.

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.

For all authors any conflict of interests is absent.

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