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RELATIONSHIPS BETWEEN POPOVYCH'S ADAPTATION INDEX AND PARAMETERS OF ONGOIGING HRV AND EEG IN PATIENTS WITH CHRONIC PYELONEPHRITE AND CHOLECYSTITE IN REMISSION

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Abstracts

Background. The conception of general adaptation reactions of organism (GARO), created by Garkavi LKh, Kvakina EB and Ukolova MA in 1977 on the base of Selve H classic conception of stress and developed then by them (1998), and also by Radchenko OM (2004), sufficiently successfully used in medicine and valeology for the estimation of general condition of organism. The downside the concept was qualitative assessment of GIRO. So Popovych IL (2000, 2006) proposed to quantify the various GARO Adaptation Index, which significantly correlated with the levels of key hormones adaptation and HRV parameters as well as phagocytosis. Another disadvantage of the concept is the lack of EEG markers GARO. We set a goal to analyze the relationships Popovych's Adaptation Index with parameters of HRV and EEG. Methods. In basal conditions in 22 men, patients with chronic pyelonephrite and cholecystite in remission, recorded twice during 9-11 days HRV ("Cardiolab+VSR", KhAI Medica, Ukraine) and EEG ("NeuroCom Standard", KhAI Medica, Ukraine). In portion of blood counted up leukocytogram, on the basis of which determined Popovych's Adaptation Index (PAI). Results. Registered 14 normal (harmonious) GARO, 20 premorbidic (disharmonious) GARO and only 9 reactions of superactivation, in the absence stress-reactions. Revealed the closest relationship between PAI and normalized Power Spectral Density (PSD) LF (r=0,44), Baevskiy's Stress Index in Orthostase (r=0,41), Laterality Index PSD θ -Rhythm (r=-0,43), PSD β -Rhythm in Right Occipital locus (r=-0,40). Canonical correlation between PAI, on the one hand, and the parameters of HRV and EEG, on the other hand, is strong: R=0,846; R^2 =0,716; Adjusted R^2 =0,628; $F_{(10)}$ =8,1;

 $\chi^{2}_{(10)}=47.3$; p<10⁻⁵. **Conclusion.** Popovych's Adaptation Index reflects the activity of a number of regulatory nerve structures.

Keywords: general adaptation reactions, leukocytogram, index of adaptation by Popovych, HRV, EEG, correlations.

INRODUCTION

The conception of general adaptation reactions of organism (GARO), created by Garkavi LKh, Kvakina EB and Ukolova MA in 1977 [7] on the base of Selve H classic conception of stress and developed then by them [8], and also by Radchenko OM [23], sufficiently successfully used in medicine and valeology for the estimation of general condition of organism [6,10,16-18]. According to this conception, GARO of training and quiet and heightened activation of high levels of reactivity (HLR, harmonious) represent different gradations of health, but the same GARO of low levels of reactivity (LLR, disharmonious) and stress of HLR (eustress) characterize the premorbide states of organism, while nonspecific nosotropic basis of illness are stress of LLR (distress) and reaction of superactivation. Comparative estimation of the state of the looked after groups of persons and his dynamics under act of pathogenic or sanogenic factors the authors of conception and their numerous followers give after frequentness of separate GARO, id est an estimation has qualitative or semiquantitative character only. The input of index of adaptation as relation lymphocytes/segmentonuclear neutrophiles (L/SNN) quite not decides problems of **quantitative** estimation of the state of adaptation, in fact, after their table [8, p. 361], ranges of quality different GARO is crossing. In particular, ranges of L/SNN-ratio reactions of training of HLR and LLR present accordingly 0,27÷0,52 and 0,26÷1,17, reactions of the quiet activation: $0,45\div0,64$ and $0,44\div1,43$, heightened activation: $0,57\div1,12$ and $0,57\div3,0$. For the decision of problem Popovych IL et al. [6,10,16,21] on results comparative researches of parameters of immunity, hemostase and metabolism and them cross-correlation connections with the parameters of leukocytogram for persons with different GARO fundamentally other index of adaptation, which takes into account the range of both lymphocytosis and other elements of leukocytogram, was offered. A maximal point (7) was appropriated GARO of the quiet activation (QA) of HLR, which appeared the first after a grade. Quantification other GARO it was conducted after a Popovych's formula [16]: $PAI=7 \cdot \Phi^{(1-R)/2}$, where

 Φ is a number of Fibonacci (1,618)

R is a grade of GARO.

On this scale the second after the grade of GARO of heightened activation (HA) of HLR is appraised in 5,5 p, GARO of training (T) of HLR in 4,3 p, eustress (stress of HLR) in 3,4 p, GARO of the QA of LLR in 2,67 p, GARO of T of LLR in 2,1 p, GARO of HA of LLR in 1,65 p, reaction of superactivation in 1,3 p and distress (stress of LLR) in 1,0 p.

At the same time, the qualitative-quantitative scale of Baevskiy RM [1] uses for the estimation of the state of adaptation a mass appeal, built on the basis of parameters of hart rate variability. Last, in turn, at a construction scales of Popovych IL et al. [6,10,16,21] not taken into account. Going out expounded, Barylyak LG et al. [2] conducted a comparative estimation based on HRV, endocrine and immune parameters of informativity of leukocytary index of adaptation by Garkavi and by Popovych. An examination of 20 healthy men found that index of adaptation by Popovych that takes into account the relative content in leukocytogram of lymphocytes and deviations of monocytes, eosinophils and stub neutrophils, moderately or significantly correlated with the HRV, endocrine and immune (phagocytose) parameters, whereas links them index of adaptation by Garkavi as the ratio of lymphocytes/segmented neutrophils are weak or absent. However, such an important aspect of GARO as the electrical activity of brain researchers ignored. Therefore we set a goal to analyze the relationships Popovych's Adaptation Index with parameters of HRV and EEG.

MATERIAL AND RESEARCH METHODS

Under a observations were 22 men by age 24-70 years, patients of spa Truskavets' with chronic pyelonephrite and cholecystite in remission. In the morning in basale terms twice during 9-11 days ECG in standard lead II recorded hardware-software complex "Cardiolab+VSR" (KhAI Medica, Kharkiv, Ukraine) [19,20]. For further analysis the following parameters heart rate variability (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 (pNN₅₀) [9]; heart rate (HR), moda (Mo), the amplitude of moda (AMo), variational sweep (MxDMn) [1].

Spectral parameters (Frequency Domain Methods): power spectral density (PSD) 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 Baevskiy's Stress Index (BSI=AMo/2•Mo•MxDMn) as well as Baevskiy's Activity Regulatory Systems Index (BARSI) [1] both in supine and orthostatic positions.

Then 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 tassels on the ears. Among the options considered the average EEG amplitude (μ V), average frequency (Hz), frequency deviation (Hz), index (%), coefficient of asymmetry (%) and absolute (μ V²/Hz) and relative (%) PSD 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 PSD each Rhythm using formula [12]:

LI, $\% = \Sigma [200 \cdot (\text{Right} - \text{Left})/(\text{Right} + \text{Left})]/8$

as well as Entropy (h) for relative PSD each Locus using formula Shannon [cit. by: 17]:

h= - [PSD β•log₂ PSD β + PSD α•log₂ PSD α + PSD θ•log₂ PSD θ + PSD δ•log₂ PSD δ]/log₂ 4

In portion of capillary blood counted up leukocytogram, on the basis of which determined Adaptation Index according Popovych IL scale [6]. For ease of analysis Popovych's Adaptation Index (PAI) expressed in natural logarythmic calculation.

Leukocyto-	General	Eosinophiles and Stub	Eosinophiles and Stub
gram	Adaptation	Neutrophiles: 1÷6 %;	Neutrophiles: <1; >6;
Lymphocy-	Reaction of	Monocytes: 4÷7 %;	Monocytes: <4; >7;
tes level, %	Organism	Leukocytes: 4÷8 G/l	Leukocytes: <4; >8 G/l
<21	Stress	1,22	0,02
21÷27	Training	1,46	0,74
28÷33	Quiet Activation	1,95	0,98
34÷43,5	Heightened Activation	1,70	0,50
≥44	Superactivation		0,26

Digital material it is traited by the methods of cross-correlation and canonical analyses, using the package of softwares "Statistica 5.5".

RESULTS AND DISCUSSION

Registered 14 normal (harmonious) GARO (11 HA and 3 QA), 20 premorbidic (disharmonious) GARO (13 HA and 7 QA) and only 9 reactions of superactivation, in the absence stress-reactions, which is consistent with the phase of remission clinical status of patients.

According to calculations by the formula [19]: $|r|=\{\exp[2t/(n-1,5)^{0.5}] - 1\}/\{\exp[2t/(n-1,5)^{0.5}] + 1\}$ for a sample of n=43 critical value |r| at p<0,05 (t>2,02) is 0,30, with p<0,01 (t>2,70) - 0,40, at p<0,001 (t>3,55) - 0,50.

Screening correlations revealed the closest relationship between PAI and normalized PSD LF (Fig. 1) as HRV marker of sympathetic tone.



Fig. 1. Influence on Popovych's Adaptation Index (axis Y) normalized PSD LF HRV (axis X)

Similarly associated with PAI Baevskiy's Stress Index in Orthostase (Fig. 2) but not in Supine (r=0,34).



Fig. 2. Influence on Popovych's Adaptation Index (axis Y) Baevskiy's Stress Index in Orthostase (axis X)

Both factors combine to determine the RAI for 28% (Table 1, Fig. 3)

Table 1. Regression Summary for Dependent Variable PAI from PSD LFnu and BSI(o) R=0,563; R²=0,317; Adjusted R²=0,283; $F_{(2,4)}=9,3$; p<10⁻³; Std. Error of estimate: 0,53

	Beta	St. Err.	В	St. Err.		p-
		of Beta		of B	$t_{(40)}$	level
Intercpt			-,2316	,3130	-,74	,464
LFnu	,387	,132	,0133	,0046	2,93	,006
BSI (o)	,360	,132	,0010	,0004	2,73	,009



Fig. 3. Relationships between normalized PSD LF HRV (axis X), Baevskiy's Stress Index in Orthostase (axis Y) and Popovych's Adaptation Index (axis Z)

Noteworthy also options HRV AMo (r=0,33), LF/HF (r=0,29) and RMSSD (r=-0,25), but they do not affect the coefficient of multiple correlation (Table 2).

Table 2. Regression Summary for Dependent Variable PAI from HRV parameters R=0,585; R²=0,342; Adjusted R²=0,291; $F_{(3,4)}$ =6,75; p<10⁻³; Std. Error of estimate: 0,53

	Beta	St. Err.	В	St. Err.		p-
		of Beta		of B	t ₍₃₉₎	level
Intercpt			-,7857	,5517	-1,42	,162
LFnu	,514	,168	,0178	,0058	3,06	,004
BSI (o)	,417	,139	,0011	,0004	3,00	,005
RMSSD	,215	,177	,0070	,0058	1,22	,231

Among the options of EEG most closely correlated with PAI Laterality Index PSD θ -Rhythm (Fig. 4) and PSD β -Rhythm in Right Occipital locus (Fig. 5).



Fig. 4. Influence on Popovych's Adaptation Index (axis Y) θ -Rhythm Laterality Index (axis X)



Fig. 5. Influence on Popovych's Adaptation Index (axis Y) PSD β -Rhythm in locus O2 (axis X)

Noteworthy relationships PAI with Laterality Index PSD α - (r=-0,37) and δ - (r=-0,33) Rhythms; absolute PSD β -Rhythm in locus F8 (r=-0,38) and relative in locus T5 (r=-0,37);

relative PSD θ -Rhythm in loci F4 (r=-0,37), Fp2 (r=-0,36), C4 (r=-0,34), F3 (r=-0,33), Fp1 (r=-0,32), C3 (r=-0,32), T4 (r=-0,31), O2 (r=-0,30).

Special attention deserve connections PAI with Entropy of relative PSD all Rhythms. Descending number looks like this: Fp2 (r=-0,38), Fp1 (r=-0,36), F4 (r=-0,33), T4 (r=-0,28), F8 (r=-0,28), C4 (r=-0,28). Interestingly, that with Entropy of Leukocytogram PAI too negative relationship (r=-0,42). It seems that the higher adaptive capacity of the body accompanied by a lesser degree of uncertainty (chaos) as Leukocytogram elements, and Rhythms of EEG.

In the same vein we interpret negative correlation between PAI and deviation (variability) of δ -Rhythm frequency (r=-0,29). Others parameters δ -Rhythm correlated with PAI nonsignificantly: r=0,26 for absolute PSD in loci P3, Fp1, T6.

By stepwise exclusion in the final regression model were included 2 parameters HRV and 8 EEG (Table 3, Fig. 6), which taken together determine PAI on 63%.

Table 3. Regression Summary for Dependent Variable PAI from parameters HRV and EEG

R=0,846; $R^2=0,716$; Adjusted $R^2=0,628$; $F_{(10)}=8,1$; $\chi^2_{(10)}=47,3$; $p<10^{-5}$; Std. Err. of estimate: 0,38

		Beta	St. Err.	В	St. Err.	t ₍₃₂₎	p-
			of Beta		of B		level
Parameters	r			2,648	0,730	3,63	10 ⁻³
PSD LFnu HRV	0,44	0,297	0,109	0,0102	0,0038	2,71	,011
Baevskiy's SI (o)	0,41	,231	,104	,0006	,0003	2,22	,034
PSDa O2-β	-0,40	-0,555	,114	-,0083	,0017	-4,88	10 ⁻⁴
Entropy Fp2 locus	-0,38	,592	,217	2,4571	,9023	2,72	,010
PSDr F4-θ	-0,37	-,671	,302	-,0526	,0236	-2,22	,033
Entropy Fp1 locus	-0,36	-,411	,180	-1,8469	,8091	-2,28	,029
PSDr C4-θ	-0,34	,733	,303	,0725	,0300	2,42	,021
Deviation δ-Rhythm	-0,29	-,231	,101	-,5479	,2391	-2,29	,029
Entropy T4 locus	-0,28	-,563	,157	-3,0949	,8610	-3,59	10^{-3}
PSDa P3-δ	0,26	,458	,111	,0042	,0010	4,12	10^{-3}

It is known that left insula is predominantly responsible for parasympathetic effects while the right insular cortex is more likely to produce sympathetic responces [15,27] Functional magnetic resonance imaging studies have identified dorsal and ventral anterior cingulate cortex involvement in autonomic control [4,11]. Ventral anterior cingulate cortex activation correlated significantly with HF HRV, suggesting its control of parasympathetic autonomic activity [11]. Functionally and anatomically, the subgenual anterior cingulate cortex is more strongly linked to autonomic control centers than the dorsal anterior cingulate cortex. Its activity relates to parasympathetic, rather than the sympathetic autonomic system [5].

Tolkunov D et al. [26] showed strong anticorrelation (r=-0,61) between the amygdala's power spectrum density scaling parameter β and wake HRV, suggesting that sluggish limbic regulation translated down-stream into sluggish autonomic regulation, at both shorter-acting (parasympathetic) and slower-acting (sympathetic) time-domains, as well as suggesting a robust relationship between dysregulated limbic outputs and their autonomic consequences.



Fig. 6. Canonical correlation between Neural Factors (axis X) and Popovych's Adaptation Index (axis Y)

Yi-Yuan Tang et al. [29] in the study of 42 healthy young males to explore the relationship between brain activity and parasympathetic tone analysed the correlation between the changes in frontal midline θ power (related to generators in the anterior cingulate cortex [3]) and HFnu HRV. After 5 days of integrative body-mind training correlations between HFnu and Fz- θ (r=0,566), FCz- θ (r=0,551) and Cz- θ (r=0,575) were significantly positive. We [20] also found correlations between HFnu and F4- θ (r=0,38) and P4- θ (r=0,45), between HF% and Fp1- θ (r=0,32) and P4- θ (r=0,43), and between indicator of parasympathetic tone RMSSD and P4- θ (r=0,46). However, correlations between HF% and O1- θ were significantly negative (r=-0,42).

Prinsloo GE et al. [22] in the study for eighteen healthy males found that less pronounced changes in HRV, due to work-related stress, accompanied by higher relative PSD Fz- θ , Pz- θ and Cz- θ , lower fronto-central relative β power and higher θ/β ratio. It is also perfectly consistent with our [20] data on a negative correlation LFnu, LF% and LF/HF with F4- θ , P4- θ , F7- θ , F8- θ , F4- θ and positive - with F7- β and F8- β - on the one hand, and a positive correlation with HF% Fp1- θ and P4- θ and negative - from P4- β - on the other side.

Subhani AR et al. [24] in the study of ten healthy participants showed a significant upsurge in the value Fz- θ /Pz- α while mental stress (playing video games). PSD LFnu and LF/HF ratio were significantly increased and HFnu sank during video games. On the other hand, the decrease in 7 healthy elderly individuals LFnu accompanied by a fall in α -wave proportion of EEG [13], whereas in 38 healthy young volunteers during mental arithmetic task were found positive correlation between the percent change from the baseline in slow α -power and that in LF/HF ratio

[14]. Instead, our [20] study found a negative correlation between PSD LFnu and F4- θ (r=-0,38), and P4- θ (r=-0,45) and positive correlation between PSD LFnu and P4- α (r=0,41), and O2- α (r=0,32), the amplitude of α -rhythm (r=0,35) and the index α -rhythm (r=0,46). The above applies to the LF/HF ratio and inverse way - PSD HF. Our [20] data on a negative correlation between PSD HF HRV and α -rhythm consistent with findings Wahbeh H and Oken BS [28] that in patients with posttraumatic stress disorder peak α frequency was higher while peak HF HRV was lower than in patients without posttraumatic stress disorder.

Tiinanen S et al. [25] in children with asperger syndrome found that the increase of sympathetic activity during stress-test, measured by HRV, is accompanied by a decrease in frontal EEG asymmetry index. We have also shown that the LF/HF ratio, LFnu (and VLF) negative, whereas HF% and RMSSD positively correlated with asymmetry β -rhythm [20].

Ohtake Y et al. [14] found that mental arithmetic task induced an increase in slow β -power in the stress responders, whereas it induced a decrease in slow β -power in the stress non responders. According to our own data [20] with PSD β -rhythm LF/HF ratio correlated negatively.

CONCLUSION

Thus, the factors that favourable influence the adaptive capacity of the body, measured at Leukocytary Popovych's Adaptation Index, may be considered Sympathetic tone and activity of neural structures generating δ -Rhythm in Left Parietal locus while activity of neural structures generating β -Rhythm in Right Occipital locus as well as θ -Rhythm in Right Medial Frontal and Central loci affect unfavourable adaptation. Unfavourable factors also appeared Entropy of relative PSD all Rhythms in Anterior Frontal and Right Anterior Temporal loci.

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 (SV Petsyukh, MS Petsyukh, MM Kovbasnyuk, LG Barylyak, W Zukow) any conflict of interests is absent.

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