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RELATIONSHIPS BETWEEN PARAMETERS OF GALLBLADDER MOTILITY AND BRAIN ELECTRICAL ACTIVITY

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Abstract

Objective. Earlier we shown that Cholecystokinetic effect of balneotherapy on spa Truskavets' may be the result of modulation of neuroendocrine-immune complex. The **aim** of present investigation**:** clarification relationships between parameters of gallbladder motility and ongoing Electroencephalogram (EEG) as well as Heart Rate Variability (HRV). **Material and Methods.** At 22 men with chronic cholecystite combined with pyelonephrite we recorded twice basal and postprandial volume of gallbladder (Echoscopy by "Radmir"), EEG ("NeuroCom Standard") and HRV ("CardioLab+HRV"). **Results.** Basal gallbladder volume correlated positively with HRV markers of Vagal tone (HF, RMSSD, pNN_{50}) and relative Power Spectrum Density (PSD) C4-δ while negatively with Amplitude of β-Rhythm and its absolute PSD in loci P3, P4, Fp1, C3, F3, F4 as well as PSD T3-δ and Frequency of α-Rhythm. Canonical correlation is very strong: R=0,96; Adjusted R^2=0,85; $\chi^2_{(15)}$=61; $p<10^{-5}$. Gallbladder volume after 5 min after taking of Cholekinetik (50 ml of 40% solution of xylitol), expressed as portion its basal volume, correlated positively with VLF, Deviation of θ-Rhythm and its relative PSD in loci F4, P4 and P3 while negatively with relative PSD O1-θ and absolute PSD P4-β and T6-β as well as Asymmetry of θ-Rhythm. Canonical correlation is very strong too: R=0,87; Adjusted R^2=0,66; $\chi^2_{(9)}$=38; $p<10^{-4}$. As distinct from early next postprandial volumes significantly less liable to neural regulatory influences: R makes 0,67 (p=0,003) and 0,60 (p=0,009) after 15 and 30 min respectively. In particular, both V_{15} and V_{30} equal positively correlated with HF and Laterality of α-Rhythm, however V_{15} correlated with Asymmetry of θ-Rhythm (r=-0,45) and its PSD in loci F3 (r=0,28) and C4 (r=0,27), while V_{30} correlated with Asymmetry of δ-Rhythm (r=-0,28) and PSD C4-β (r=-0,34). **Conclusion.** Fasting gallbladder volume is strong controlled by Vagal nerves as well as by neural structures generating β-Rhythm, whereas early (5 min) postprandial volume is also strong

controlled by structures generating θ-Rhythm. Next (15 and 30 min) postprandial volumes significantly less liable to neural regulatory influences.

Keywords: gallbladder motility, EEG, HRV, relationships.

INTRODUCTION

It is known that the motility of the gallbladder consists of collection, storage and delivery of bile. Gallbladder motor funtions are controlled by its extrinsic and intrinsic innervation and humoral factor. In the fasting stage, gallbladder motility is associated with phase III of the interdigestive migrating myoelectric complex and increased plasma motilin concentrations. In the fed state cholecystokinin (CCK) is primary mediator of gallbladder contraction. Extrinsic neural control of gallbladder motility appears to play a role in the mediation of cephalic phase of gallbladder emptying. **Vagal** stimulation induces **contraction** whereas **sympathetic** stimulation induces **relaxation** via **cholinergic**, **adrenergic** and noncholinergic, nonadrenergic neurotransmitters [review: 19]. However T Yamasato and S Nakayama [30] have been shown that efferent stimulation of vagus and sympathetic (celiac) nerves caused **contraction** or **inhibition** of the neck, body and fundus of the canine gallbladder. The contractile response induced by vagus nerve stimulation was reduced by subthreshold efferent stimulation of the celiac nerve, while the inhibitory response was neither reduced nor enhanced by subthreshold efferent stimulation of the celiac nerve. The contractile and inhibitory response induced by celiac nerve stimulation was not reduced in the neck, body and fundus by subthreshold efferent stimulation of the vagus nerve. The contractile response to vagus nerve stimulation was reversed to a relaxant response by atropine administration, which was reduced or abolished by hexamethonium. Authors suggested that the vagus nerve-induced contractile response in the canine gallbladder is modulated by sympathetic nerves presynaptically at the vagus nerve endings in the enteric ganglion, but the vagus nerve-induced relaxant response, whith probably was induced by non-adrenergic non-cholinergic inhibitory neurons, is not modulated by the sympathetic nerves. Intrinsic neural control of gallbladder motility is mediated by such neuropeptides as pancreatic polypeptide, somatostatin, bombesin, neuropeptide Y, calcitonin gene-related peptide, vasoactive intestinal polypeptide, CCK, tachykinins and nitric oxide [reviews: 6,8,19].

It is known that left insula is predominantly responsible for parasympathetic effects while the right insular cortex is more likely to produce sympathetic responces [18,24]. Functional magnetic resonance imaging studies have identified dorsal and ventral anterior cingulate cortex involvement in autonomic control [4,15]. Ventral anterior cingulate cortex activation correlated significantly with HF HRV, suggesting its control of parasympathetic autonomic activity [15]. 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]. SM Oppenheimer et al. [18] reported the left insula is predominantly responsible for parasympathetic effects while the right insular cortex is more likely to produce sympathetic responces. Functional magnetic resonance imaging studies have identified dorsal and ventral anterior cingulate cortex involvement in

autonomic control [4,15]. Ventral anterior cingulate cortex activation correlated significantly with HF HRV, suggesting its control of parasympathetic autonomic activity [15]. 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]. Vanneste and De Ridder [24] in the study of 21 tinnitus patients also indicated that the dorsal and subgenual anterior cingulate, as well as the left and right insula are important in the central control of HRV. Whereas the sympathovagal balance is controlled by the subgenual and pregenual anterior cingulate cortex, right insula controls sympathetic activity and the left insula the parasympathetic activity. Earlier we shown relationships between parameters of EEG and HRV [22,23]. Just now we received communication from Winkelmann et al. [29]. Authors shown that in a healthy young adult population the amount of resting HRV was positively correlated with the cortical thickness of an area within the right anterior midcingulate cortex, that assotiated with degree of parasympathetic regulation of heart rate. Coefficient correlation between thickness this cortical structure and HF component of HRV form 0,63. Last considered as a biomarker of adaptability and health. Authors concluded that cortical structures forming "Central autonomic network" inhibiting limbic and brainstem structures that are sympathoexcitatory.

It is known also that balneofactors of spa Truskavets' causes modulating influences on gallbladder motility [3] as well as autonomous nervous system at rats and various cohorts of patients [6,9-12,20,21,25-28]. Earlier we shown that Cholecystokinetic effect balneotherapy on spa Truskavets' may be the result of modulation of neuroendocrine-immune complex [13,14].

The **aim** of present investigation**:** clarification relationships between parameters of gallbladder motility and brain electrical activity.

MATERIAL AND METHODS

The object of observation were 22 men aged 24-70 (mean 49,1±2,5) years old, who came to the spa Truskavets' (Ukraine) for the treatment of chronic cholecystite combined with pyelonephrite in remission. The survey was conducted twice, before and after balneotherapy. On the tone and motility of gallbladder judged by its volume on an empty stomach in the morning (fasting) and after 5, 15 and 30 min after ingestion cholekinetic (50 ml of 40% solution of xylitol) (postprandial). The method echoscopy (echocamera "Radmir") applicated [13,14].

For estimation state of autonomous nervous system we recorded ECG in standard lead II hardware-software complex "Cardiolab+VSR" (KhAI Medica, Kharkiv, Ukraine) [22,23]. 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 (pNN_{50}), Triangulary Index (HRV TI) [1,2,7]; 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 Centralization Index (CI=(VLF+LF)/HF), Bayevskiy's Stress Index (BSI=AMo/2•Mo•MxDMn) as well as Bayevskiy's Activity Regulatory Systems Index (BARSI) [1] both in supine and in 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 on tassels of ears. Among the options considered the average EEG amplitude (μV), average frequency (Hz), frequency deviation (Hz), index (%), coefficient of asymmetry (%) and absolute (μV^2/Hz) as well as 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, we calculated Laterality Index (LI) for PSD each Rhythm using formula [17]:

LI, % = Σ [200•(Right – Left)/(Right + Left)]/8

as well as Entropy (h) for relative PSD each locus using formula Shannon [cit. by: 21]:

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

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

Basal (fasting) gallbladder volume correlated strongest with absolute PSD of β-Rhythm in loci F7 (Fig. 1).

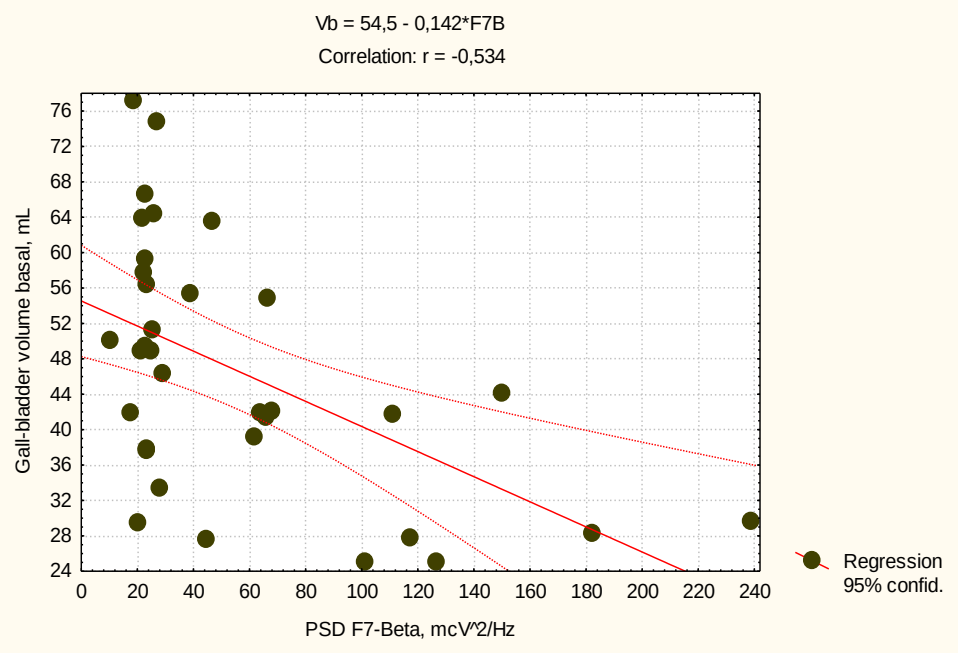

Fig. 1. Correlation between PSD of β-Rhythm in loci F7 (axis X) and basal gallbladder volume (axis Y)

Screening of correlationships between Basal gallbladder volume and EEG as well as HRV parameters detected positively correlation with HRV markers of Vagal tone (HF, RMSSD, pNN_{50}) and relative Power Spectrum Density (PSD) C4-δ while negatively with Amplitude of β-Rhythm and its absolute PSD in loci P3, P4, Fp1, C3, F3, F4 as well as PSD T3-δ and Frequency of α-Rhythm. In summary model of multiple regression with stepwise excluding are currently next parameters (unexpectedly without PSD of β-Rhythm) (Table1, Fig 2).

Table 1. Regression Summary for Dependent Variable Vb and Independent HRV and EEG Variables

R=0,958; R^2=0,918; Adjusted R^2=0,850; $F_{(15)}$=13,4; $\chi^2_{(15)}$=61; $p<10^{-5}$. SE of estimate: 5,5 mL

		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(18)}$	p-level
Variables	r	Intercpt		68,9	13,0	5,30	10^{-4}
pNN_{50}, %	0,46	1,498	,273	1,5211	,2772	5,49	10^{-4}
HF, ms^2	0,37	,401	,207	,0069	,0036	1,94	,068
RMSSD, s	0,33	-1,370	,282	-1,0278	,2116	-4,86	10^{-4}
Laterality of θ-Rhythm, %	0,30	,146	,091	,0443	,0278	1,60	,128
PSD C4-δ, %	0,30	,286	,093	,3483	,1134	3,07	,007
PSD P3-β, μV^2/Hz	-0,43	1,536	,346	,4509	,1015	4,44	10^{-3}
PSD P4-β, μV^2/Hz	-0,43	-,640	,279	-,2362	,1031	-2,29	,034
PSD Fp1-β, μV^2/Hz	-0,41	-,453	,239	-,1689	,0893	-1,89	,075
PSD C3-β, μV^2/Hz	-0,40	-,866	,308	-,2099	,0746	-2,81	,012
PSD F3-β, μV^2/Hz	-0,38	-1,402	,572	-,3328	,1359	-2,45	,025
PSD F4-β, μV^2/Hz	-0,33	1,675	,349	,4076	,0850	4,79	10^{-3}
PSD T6-β, μV^2/Hz	-0,30	-,882	,161	-,1055	,0193	-5,47	10^{-4}
Amplitude of β-Rhythm, μV	-0,33	,459	,179	1,4683	,5716	2,57	,019
PSD T3-δ, μV^2/Hz	-0,32	-,376	,089	-,0371	,0088	-4,22	10^{-3}
Frequency of α-Rhythm, Hz	-0,32	-,133	,089	-1,9862	1,3318	-1,49	,153

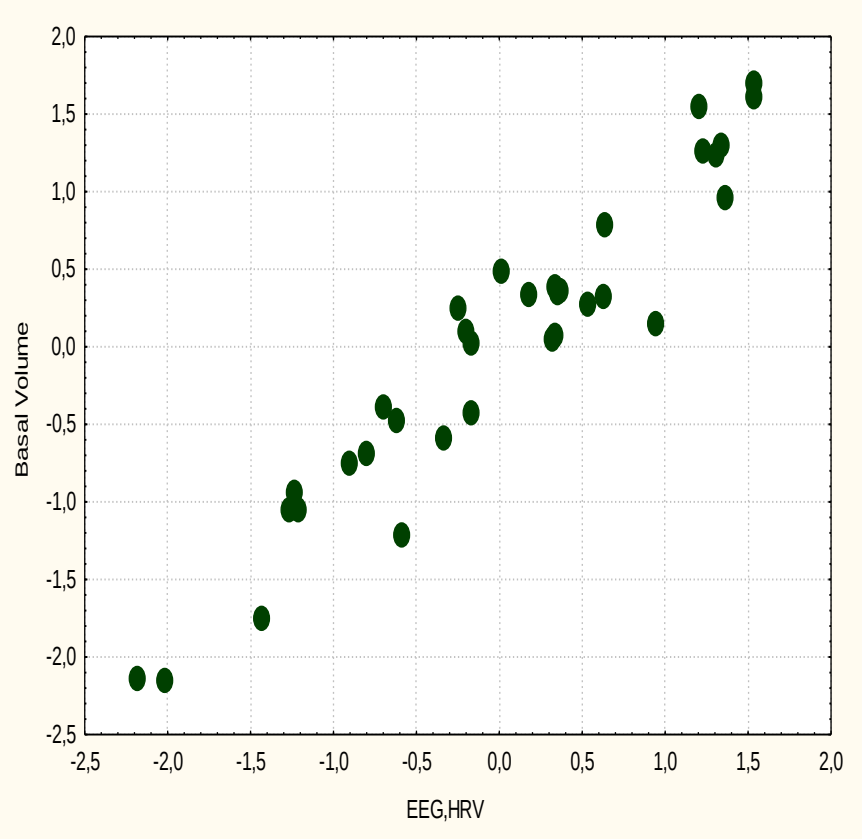

Fig. 2. Canonical correlation between parameters of EEG and HRV (axis X) and basal gallbladder volume (axis Y)

Canonical correlation is very strong. Positively but not negatively as expected relationships

between Basal gallbladder volume and markers of Vagal tone suggested that Basal gallbladder volume is caused by influence of Pancreatic Polypeptide, releasing of whith mediated by vagal stimulation [16].

Gallbladder volume after 5 min after taking of Cholekinetik, expressed as portion its basal volume, correlated positively with VLF, Deviation of θ-Rhythm and its relative PSD in loci F4, P4 and P3 while negatively with relative PSD O1-θ and absolute PSD P4-β and T6-β as well as Asymmetry of θ-Rhythm. Canonical correlation is very strong too (Table 2, Fig. 3). It is created impression that after 5 min after taking of Cholekinetik gallbladder Motility passes from influence of neural structures generating β-Rhythm to structures generating θ-Rhythm.

Table 2. Regression Summary for Dependent Variable V_5 and Independent HRV and EEG Variables

R=0,867; R^2=0,751; Adjusted R^2=0,658; $F_{(9,2)}$=8,0; $\chi^2_{(9)}$=38; $p<10^{-4}$; SE of estimate: 1,1 %

		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(24)}$	p-level
Variables	r	Intercpt		98,4	1,01	96,3	10^{-6}
VLF, ms^2	0,41	,288	,114	,0005	,0002	2,52	,019
Deviation of θ-Rhythm, Hz	0,32	,155	,115	,6486	,4782	1,36	,188
PSD F4- θ, %	0,28	,739	,239	,1638	,0531	3,08	,005
PSD P4- θ, %	0,27	-,671	,322	-,2502	,1201	-2,08	,048
PSD P3- θ, %	0,27	,371	,228	,1617	,0994	1,63	,117
PSD O1-θ, %	-0,37	-,481	,135	-,2225	,0622	-3,58	,002
Asymmetry of θ-Rhythm, %	-0,34	-,288	,141	-,0300	,0147	-2,05	,052
PSD P4-β, μV^2/Hz	-0,29	-,408	,137	-,0192	,0065	-2,97	,007
PSD T6-β, μV^2/Hz	-0,27	-,227	,116	-,0035	,0018	-1,96	,062

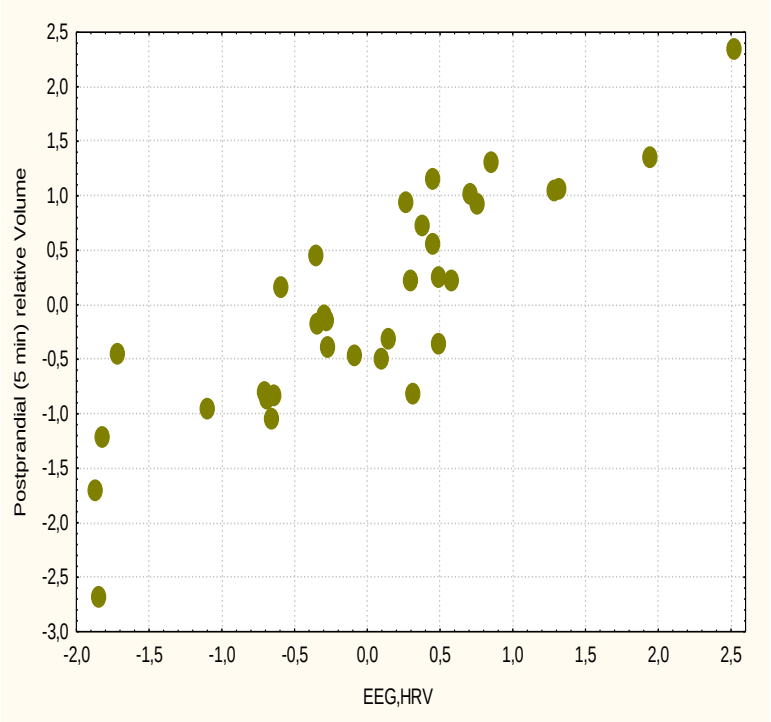

Fig. 3. Canonical correlation between parameters of EEG and HRV (axis X) and gallbladder volume after 5 min after ingestion of Cholekinetic (axis Y)

As distinct from early next postprandial volumes significantly less liable to neural regulatory influences. So, canonical correlation between parameters of EEG and HRV, on the one hand, and gallbladder volume after 15 min after ingestion of Cholekinetic, on the other hand, makes 0,674 only, with prevalence influence from structures generating θ-Rhythm (Table 3, Fig. 4).

Table 3. Regression Summary for Dependent Variable V_{15} and Independent HRV and EEG Variables

R=0,674; R^2=0,454; Adjusted R^2=0,357; $F_{(5,3)}$=4,7; $\chi^2_{(5)}$=17,9; p=,003; SE of estimate: 5,5 %

		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(28)}$	p-level
Variables	r	Intercpt		83,8	3,2	26,6	10^{-6}
Laterality of α-Rhythm, %	0,33	,317	,143	,0869	,0392	2,22	,035
HF, ms^2	0,28	,440	,159	,0036	,0013	2,77	,010
PSD F3-θ, %	0,28	,316	,274	,2670	,2316	1,15	,259
PSD C4-θ, %	0,27	-,401	,296	-,4255	,3137	-1,36	,186
Asymmetry of θ-Rhythm, %	-0,45	-,549	,165	-,2160	,0649	-3,33	,002

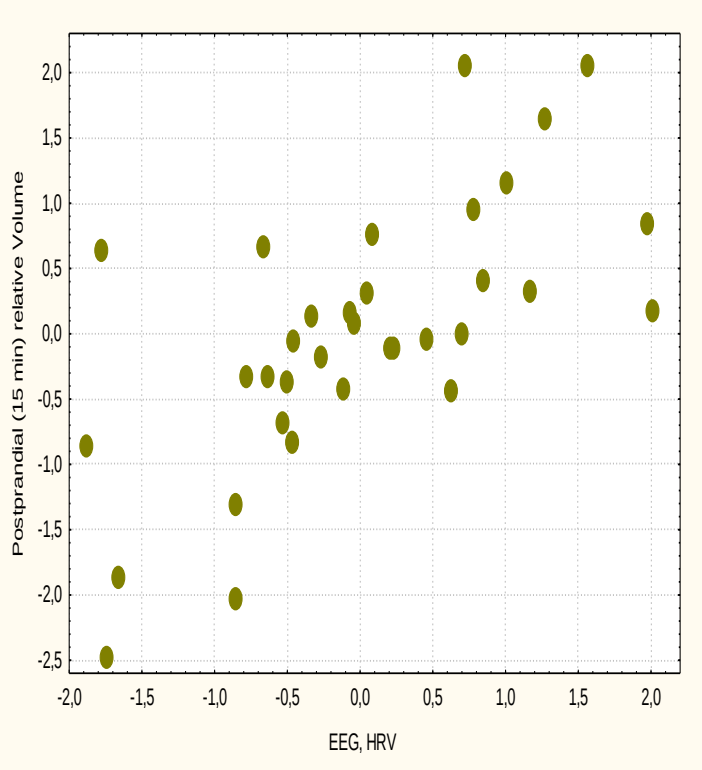

Fig. 4. Canonical correlation between parameters of EEG and HRV (axis X) and gallbladder volume after 15 min after ingestion of Cholekinetic (axis Y)

More less liable to neural regulatory influences detected gallbladder volume after 30 min after ingestion of Cholekinetic (Table 4, Fig. 5).

Table 4. Regression Summary for Dependent Variable V_{30} and Independent HRV and EEG Variables

R=0,603; R^2=0,364; Adjusted R^2=0,276; $F_{(4,3)}$=4,1; $\chi^2_{(4)}$=13,6; p=0,009; SE of estimate: 8,8 %

		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(29)}$	p-level
Variables	r	Intercpt		69,8	4,9	14,3	10^{-6}
Laterality of α-Rhythm, %	0,37	,259	,161	,1073	,0667	1,61	,119
HF, ms^2	0,31	,372	,149	,0046	,0019	2,49	,019
PSD C4-β, %	-0,34	-,280	,158	-,2364	,1333	-1,77	,087
Asymmetry of δ-Rhythm, %	-0,28	-,198	,152	-,1042	,0801	-1,30	,203

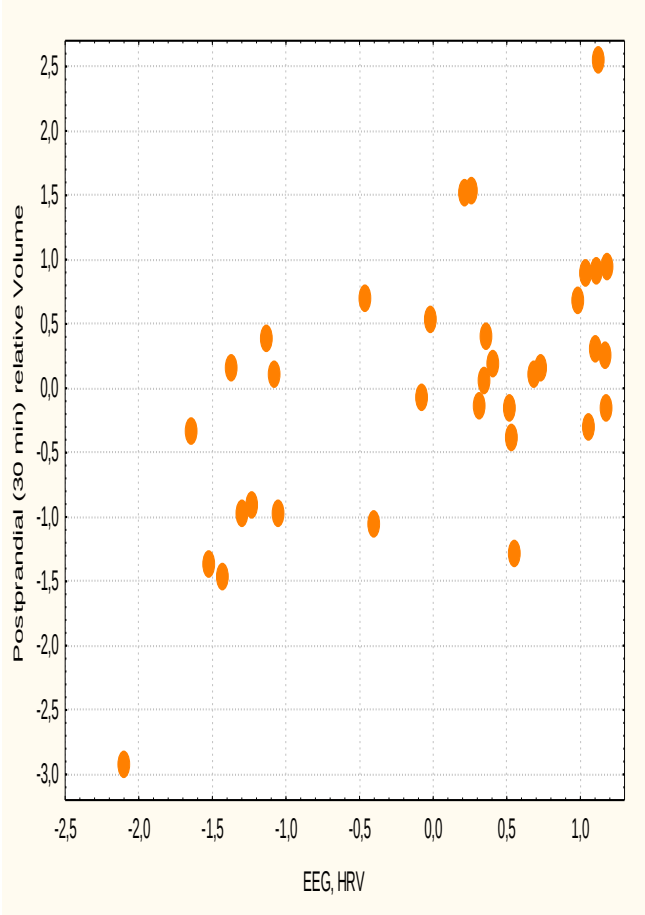

Fig. 5. Canonical correlation between parameters of EEG and HRV (axis X) and gallbladder volume after 30 min after ingestion of Cholekinetic (axis Y)

It is very likely that tardy postprandial gallbladder motility is caused by hormonal (Cholecystokinin, Pancreatic Polypeptide, VIP, Calcitonine etc [8,19]) and metabolic (diurese, body massa, exchange of Phosphates, Sodium and Magnesum [13,14]) influences.

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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