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RELATIONSHIPS BETWEEN CALCIEMIA AND CALCIURIA AND EEG AND HRV PARAMETERS IN PATIENTS WITH CHRONIC PYELONEPHRITIS

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Abstract

Background. This article launches a new project "Relationships between parameters of electrolytes exchange and EEG&HRV in people without kidney disease and patients with chronic pyelonephritis". Calcium was chosen as the first swallow. **Material and methods**. The object of observation were 48 males and 15 females 24-76 years old, who came to the spa Truskavets' (Ukraine) for the treatment of chronic pyelonephritis in remission. We recorded simultaneosly EEG ("NeuroCom Standard") and electrocardiogram ("CardioLab+HRV") in II lead to assess the parameters of HRV. Calcium and creatinine concentration was determined in blood plasma and daily urine. **Results**. The observed sample is characterized by moderate and mild expressed urinary syndrome, ie represents the urological contingent of the Truskavets' spa. It was stated normal or moderately reduced plasma calcium levels in combination with a very wide range of calcium urinary excretion. A very strong canonical correlation was found between calciumemia and EEG/HRV parameters (r=0,910). The correlation with the parameters of the beta rhythm of the EEG and VLF/ULF components of the HRV is positive, while with the parameters of the alpha rhythm of the EEG is negative. The canonical correlation between calciumuria and EEG/HRV parameters is moderate (r=0,571). There was a positive correlation with other parameters of the beta rhythm of the EEG and a negative correlation with the parameters of the delta rhythm of the EEG and LF/VLF components of HRV. **Conclusion**. Parameters of calcium exchange and EEG/HRV are closely related, however the question of the causal nature of correlations remains open.
Key words: calciumemia, calciumuria, EEG, HRV, relationships, chronic pyelonephritis.

INTRODUCTION

This article launches a new project "Relationships between parameters of electrolytes exchange and EEG&HRV in people without kidney disease and patients with chronic pyelonephritis". Calcium was chosen as the first swallow.

Calcium is one of the most important ions, the level of which in the blood plasma is maintained at a relatively stable level. This is achieved primarily through hormonal mechanisms involving parathyroid hormone and calcitonin, which regulate calcium homeostasis through calcium balance between the depot (bone) and the extracellular sector and control of renal excretion [12]. Therewith, there are isolated studies that suggest that the nervous system may be involved in the regulation of calcium homeostasis. However, it is not known which parts of the nervous system (central or autonomic) are involved in the control of calcium metabolism and how they are related to the renal mechanisms of excretion of this ion, especially in patients with renal pathology. The above led to the study of the role of central and autonomic nervous systems in the regulation of calcium homeostasis in patients with chronic pyelonephritis.

MATERIAL AND METHODS

The object of observation were 48 males and 15 females 24-76 years old, who came to the spa Truskavets' (Ukraine) for the treatment of chronic pyelonephritis in remission.

Criteria for inclusion (which are also indications for balneotherapy at the spa [20]) were the presence of moderate bacteriuria (determined by double-seeding) and leukocyturia (defined in the Nechiporenko test) in the absence of hypercreatininemia (over 220 μM/L) and severe hypertension (BP over 180/110 mmHg) (Fig. 1). Exclusion criteria (which are also contraindications for spa balneotherapy [20]): nephrotic syndrome with severe hypoproteinemia, macrohematuria, insipidar syndrome, hydronephrosis, vesicoureteral reflux, significant disorders of urodynamics, the presence of coral stones.

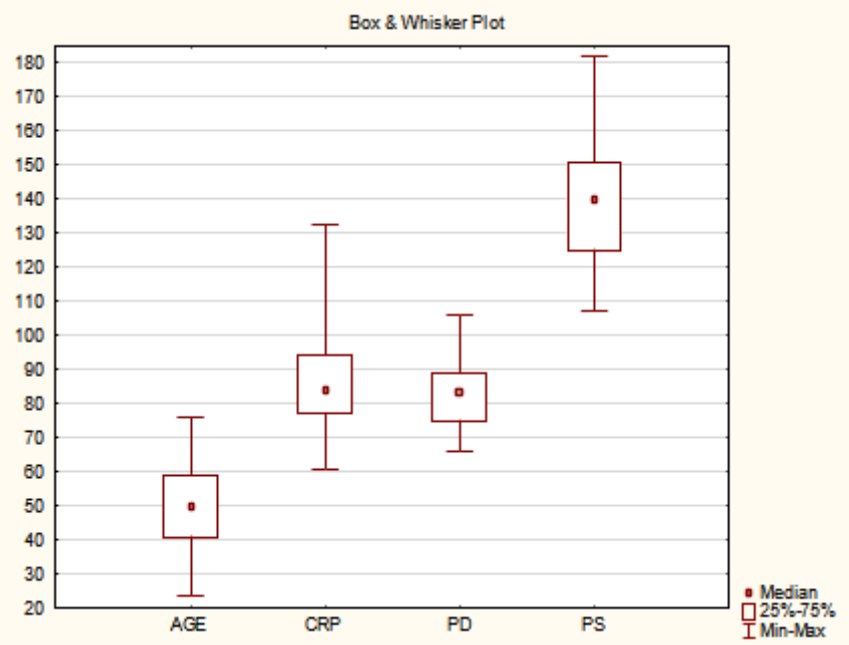


Fig. 1. Parameters of age, creatinine and blood pressure of the observed contingent

To qualitatively assess the manifestations of pyelonephritis, a single-point IL Popovych's [15] scale, built on the basis EC Harrington's desirability function [6], was used.

In particular, bacteriuria over 10^6 CFU/mL is quantified at 0,9 points (strongly expressed), within $(0,3\div1,0)\bullet10^6$ CFU/mL – 0,715 p (more than average, but not strong), 10^5 CFU/mL – 0,5 p (moderately expressed), $(0,2\div0,5)\bullet10^5$ CFU/mL – 0,285 p (weakly expressed), $(0,01\div0,1)\bullet10^5$ CFU/mL - 0,1 p (very weak), less than $0,01\bullet10^5$ CFU/mL - 0 p (absent).

Leukocyturia over 60•10^3/mL - 0,715 p, within (20÷60)•10^3/mL – 0,5 p, (4÷20)•10^3/mL – 0,285 p, (2÷4)•10^3/mL – 0,1 p, less than 2•10^3/mL – 0 p. Erythrocyturia over 30•10^3/mL - 0,715 p, within (10,1÷30)•10^3/mL – 0,5 p, (2,1÷10)•10^3/mL – 0,285 p, (1÷2)•10^3/mL – 0,1 p, less than 10^3/mL – 0 p.

As you can see (Figs. 2 and 3), the observed sample is characterized by moderate and mild expressed urinary syndrome, ie represents the urological contingent of the Truskavets' spa.

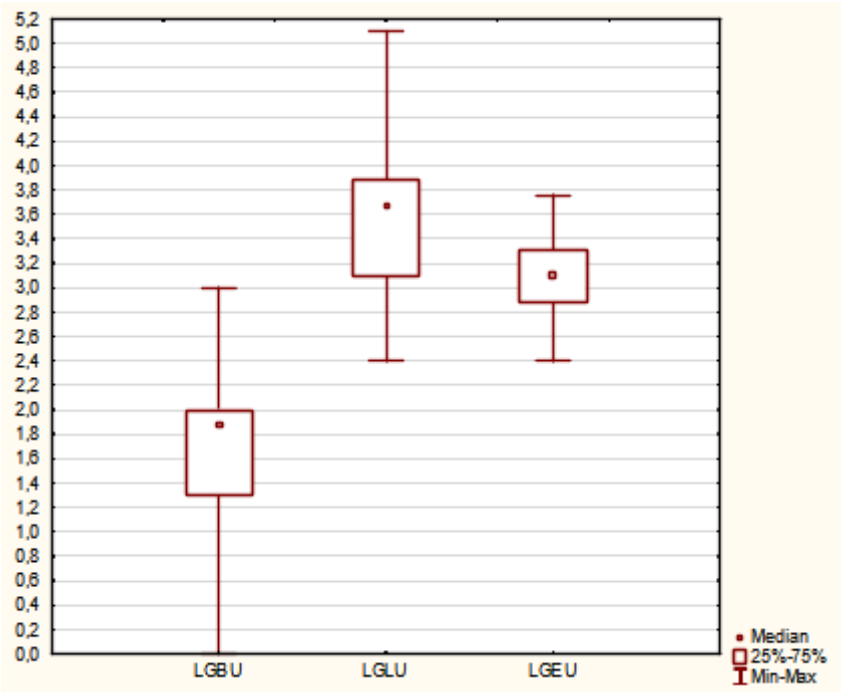


Fig. 2. Parameters of actual bacteriuria, leukocyturia and erythrocyturia (lg/mL) of the observed contingent

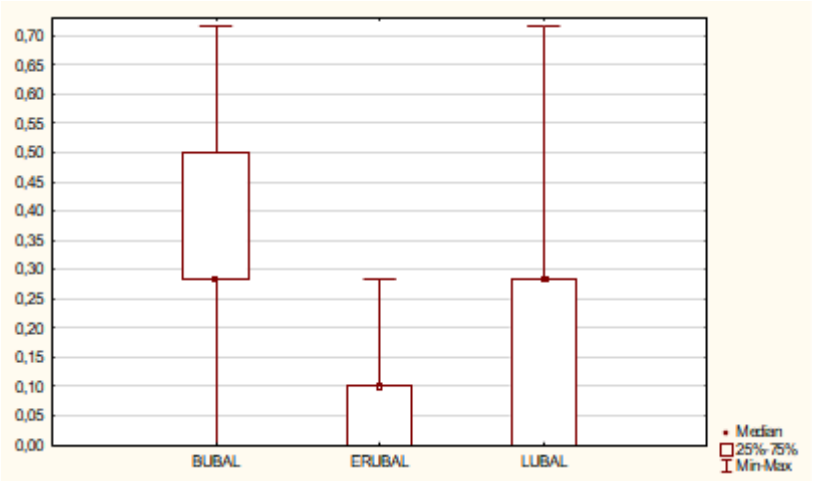


Fig. 3. Qualitative (in points) characteristics of bacteriuria, leukocyturia and erythrocyturia of the observed contingent

We recorded for 7 min electrocardiogram in II lead to assess the parameters of HRV [2,3,7] (software and hardware complex "CardioLab+HRV" production "KhAI-MEDICA", Kharkiv, Ukraine). For further analysis the following parameters heart rate variability (HRV) were selected. Temporal parameters (Time Domain Methods): heart rate (HR), 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 than 50 ms (pNN_{50}), triangular index (TNN). Spectral parameters (Frequency Domain Methods): power spectral (PS) 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 ultralow-frequency (ULF, range 0,015÷0,003 Hz). Calculated classical indexes: LF/HF, LFnu=100%•LF/(LF+HF), Centralization Index CI=(VLF+LF)/HF and Baevskiy's Activity Regulatory Systems Index (BARSI) [2] both in supine and orthostatic positions.

Simultaneosly we recorded EEG (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 the tassels of ears. The epoch for analysis was 25 sec. Among the options considered the average EEG amplitude (μV), average frequency (Hz), frequency deviation (Hz), index (%), coefficient of asymmetry (%) as well as absolute (μV^2/Hz) and relative (%) power spectral density (PSD) in the standard frequency bands: 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 [14]:

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

We calculated also for HRV and each locus EEG the Entropy (h) of normalized PSD using our formula based on CE Shannon's formula [19]:

$$hHRV = - [PSHF \bullet \log_2 PSHF + PSLF \bullet \log_2 PSLF + PSVLF \bullet \log_2 PSVLF + PSULF \bullet \log_2 PSULF] / \log_2 4;$$
$$hEEG = - [PSD\alpha \bullet \log_2 PSD\alpha + PSD\beta \bullet \log_2 PSD\beta + PSD\theta \bullet \log_2 PSD\theta + PSD\delta \bullet \log_2 PSD\delta] / \log_2 4$$

Calcium and creatinine concentration was determined in blood plasma and daily urine (by the reaction with arsenazo III and Popper's method respectively) as described in the handbook [5]. Use analyzers "Pointe-180" ("Scientific", USA) and "Reflotron" ("Boehringer Mannheim", BRD).

Results processed by methods of correlation and canonical analyses, using the software package "Statistica 64".

RESULTS AND DISCUSSION

Preliminary analysis revealed, firstly, a wide range of calciumemia and calciumuria, and secondly, a very weak relationship between them (r=-0,17) (Fig. 4).

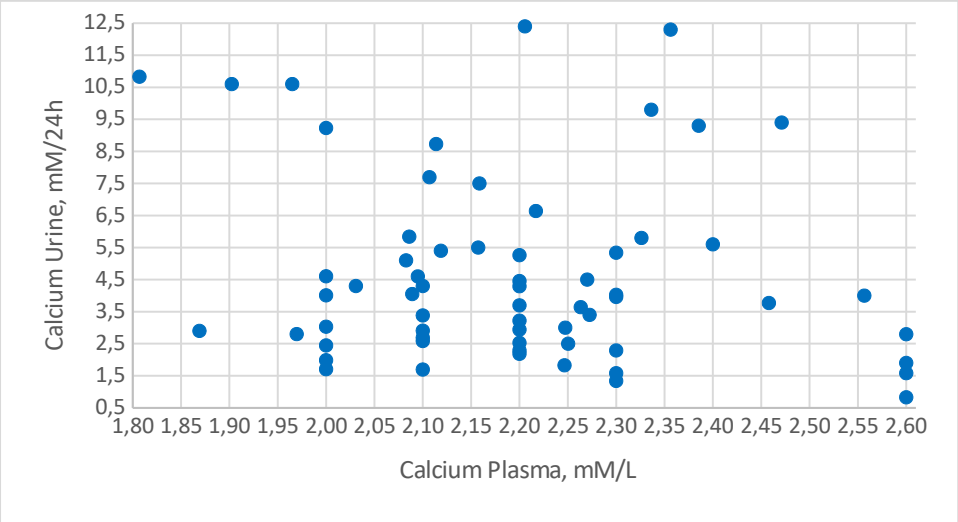


Fig. 4. Diagram of scattering of actual values of calciumemia and calciumuria

At the next stage, the actual parameters of calcium exchange were normalized by recalculation by the formula:

Z = (V/N - 1)/Cv, where

V is the actual value,

N is the normal (reference) value,

Cv is the coefficient of variation in the norm.

According to the database of our laboratory, for calciumemia N=2,30 mM/L, Cv=0,065; for calciumuria N=4,38 mM/24h, Cv=0,214. It was stated that the observed contingent is characterized by normal or moderately reduced plasma calcium levels in combination with a very wide range of calcium urinary excretion (Fig. 5). The latter is strongly related to the concentration of calcium in the daily urine (r=0,77).

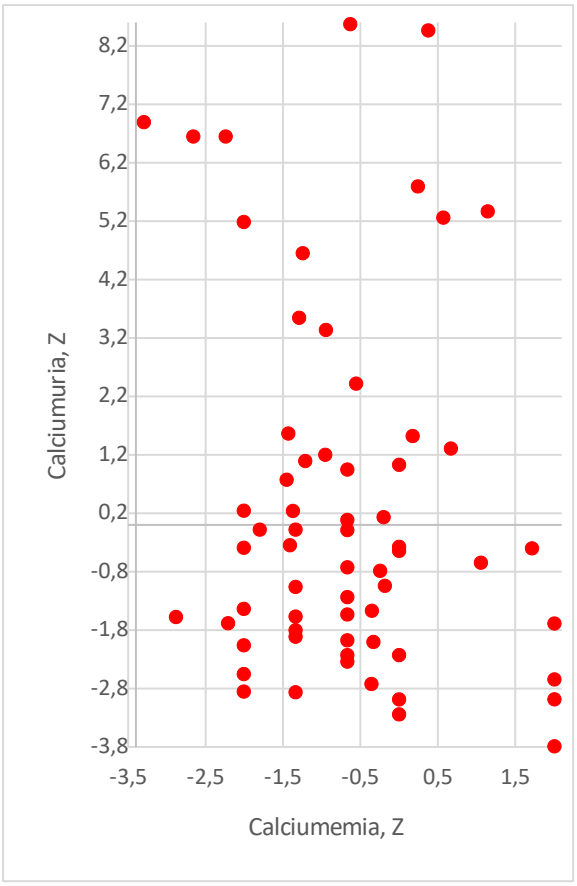


Fig. 5. Scattering diagram of normalized values of calciumemia and calciumuria

Next, the correlations between calciumemia and EEG&HRV parameters were screened, followed by the construction of a regression model by stepwise exclusion until the maximum value of Adjusted R^2 was reached (Table 1).

We hypothesized that EEG&HRV parameters, which reflect neurogenic regulatory effects on plasma calcium levels, both direct (?) and mediated by calcitonin, parathyroid, and other hormones [12], are a factor. However, there is a right to the existence of a provision on the effect of calciumemia on the parameters of EEG & HRV.

Table 1. Regression Summary for Calciumemia
R=0,910; R^2=0,828; Adjusted R^2=0,705; $F_{(26)}$=6,7; $p<10^{-5}$

N=63		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(55)}$	p-level
Variables	r		Intercpt	1,487	0,195	7,61	10^{-6}
Fp1-β PSD, %	**0,43**	0,669	0,177	0,0083	0,0022	3,77	10^{-3}
O1-β PSD, %	**0,37**	0,369	0,213	0,0047	0,0027	1,73	0,092
VLF HRV PS, %	**0,37**	0,385	0,086	0,0039	0,0009	4,48	10^{-4}
θ-Laterality Index, %	**0,36**	0,957	0,191	0,0049	0,0010	4,99	10^{-4}
P3-β PSD, %	**0,36**	-0,226	0,176	-0,0043	0,0033	-1,29	0,207
C3-β PSD, %	**0,32**	0,430	0,230	0,0067	0,0036	1,86	0,070
F7-β PSD, %	**0,31**	0,306	0,163	0,0032	0,0017	1,87	0,069
O2-β PSD, %	**0,28**	-0,547	0,199	-0,0076	0,0028	-2,74	0,009
P3 Entropy	**0,28**	0,383	0,124	0,5899	0,1907	3,09	0,004
ULF HRV PS, msec^2	**0,28**	0,569	0,124	0,0007	0,0002	4,60	10^{-4}
P4-β PSD, %	**0,26**	-0,679	0,204	-0,0103	0,0031	-3,32	0,002
C4-β PSD, %	**0,24**	0,800	0,281	0,0125	0,0044	2,85	0,007
T5-β PSD, %	**0,23**	-0,615	0,210	-0,0074	0,0025	-2,93	0,006
F4-β PSD, %	**0,22**	-0,719	0,290	-0,0097	0,0039	-2,48	0,018
δ-Laterality Index, %	**0,23**	-0,708	0,235	-0,0035	0,0012	-3,01	0,005
θ-Asymmetry, %	**0,21**	0,327	0,111	0,0028	0,0009	2,94	0,006
α-Index, %	**-0,32**	-0,538	0,240	-0,0036	0,0016	-2,24	0,031
C3-α PSD, %	**-0,31**	0,438	0,266	0,0052	0,0031	1,65	0,109
F8-α PSD, %	**-0,28**	0,421	0,177	0,0053	0,0022	2,38	0,023
C4-α PSD, %	**-0,26**	-0,504	0,332	-0,0064	0,0042	-1,52	0,137
T3-α PSD, %	**-0,26**	-0,475	0,224	-0,0063	0,0030	-2,12	0,041
O2-α PSD, %	**-0,26**	-0,616	0,250	-0,0060	0,0024	-2,47	0,019
Fp1-α PSD, %	**-0,25**	-0,604	0,257	-0,0069	0,0029	-2,35	0,024
T6-α PSD, %	**-0,23**	0,211	0,163	0,0026	0,0020	1,30	0,203
F3-α PSD, %	**-0,22**	1,256	0,366	0,0146	0,0042	3,43	0,002
α-Amplitude, μV	**-0,21**	0,574	0,150	0,0094	0,0025	3,83	10^{-3}

The pseudo-staining we use visualizes that the most numerous parameters included in the model are relative PSD of **β-rhythm**, which correlate positively with calciumemia, and relative PSD of **α-rhythm**, which are negatively related to it. For example, we give a pair with the maximum correlation coefficient for the sample (Fig. 6).

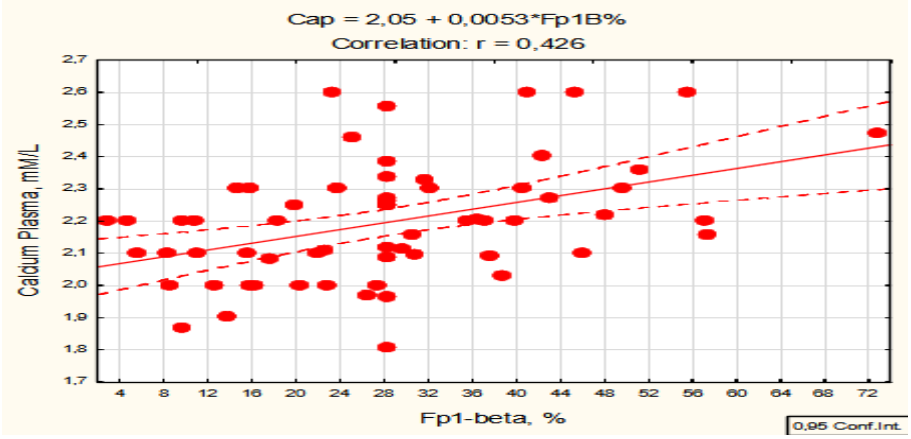


Fig. 6. Scatterplot of correlation between relative PSD of β-rhythm in locus Fp1 (X-line) and Calciumemia (Y-line)

An additional upregulating factors are right-sided Lateralization of **θ**-and **δ**-rhythms, the **Entropy** of EEG in locus P3 as well as PS of **VLF and ULF** bands of HRV.

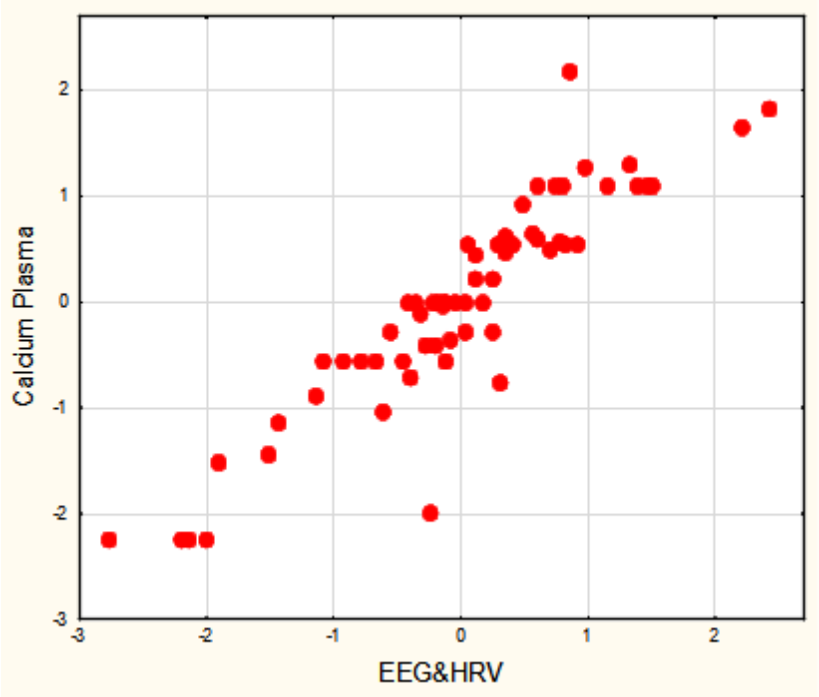
ULF band, in turn, is subject to upregulation by nerve structures that generate **β-rhythm**, while downregulation by generating **δ-rhythm** nuclei (Table 2). No significant links have been identified for the **VLF** band, contrary to expectations from previous research [16,17].

Table 2. Regression Summary for PS ULF band, ms^2
R=0,578; R^2=0,334; Adjusted R^2=0,225; $F_{(7,4)}$=3,1; p=0,010

N=63		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(55)}$	p-level
Variables	r		Intercpt	-141,2	97,6	-1,45	0,145
O2-β PSD, %	**0,45**	0,502	0,197	5,347	2,101	2,54	0,015
T5-β PSD, %	**0,40**	0,338	0,239	3,055	2,161	1,41	0,165
T4-β PSD, %	**0,40**	0,326	0,245	2,978	2,242	1,33	0,191
C3-β PSD, %	**0,36**	-0,279	0,257	-3,346	3,080	-1,09	0,283
F4-β PSD, %	**0,33**	0,429	0,272	4,358	2,767	1,57	0,123
T6-β PSD, %	**0,31**	-0,541	0,268	-4,583	2,271	-2,02	0,050
T4-δ PSD, %	**-0,23**	0,298	0,232	2,041	1,591	1,28	0,206

Because our device does not have the option "Tomography" we can only assume that loci C3 and C4 projected hippocampus, and loci T3 and T4 reflect the activity of the amygdala [18]. It is more likely that the frontal loci record the activity of anterior cingulate [4] as well as orbito-frontal cortex. It is shown that the cortical thickness of an area within these regions is positively correlated with two HRV markers of parasympathetic activity both HF [13,19] and RMSSD [20].

Taken together, the structures of the central and autonomic nervous systems determine the level of calciumemia by 82,8% (Fig. 7).



R=0,910; R^2=0,828; $\chi^2_{(26)}$=85; p<10^{-6}; Λ Prime=0,172
Fig. 7. Scatterplot of canonical correlation between EEG&HRV parameters (X-line) and Calcium Plasma (Y-line)

At the same time, urinary calcium excretion is much less subject to neurogenic regulation. Interestingly, upregulation is also performed by structures that generate **β-rhythm**, but are projected onto other, exclusively left-handed EEG loci, whereas downregulation is associated with left-handed structures that generate **δ-rhythm**, as well as **VLF and LF** bands of HRV (Fig. 8 and Table 3).

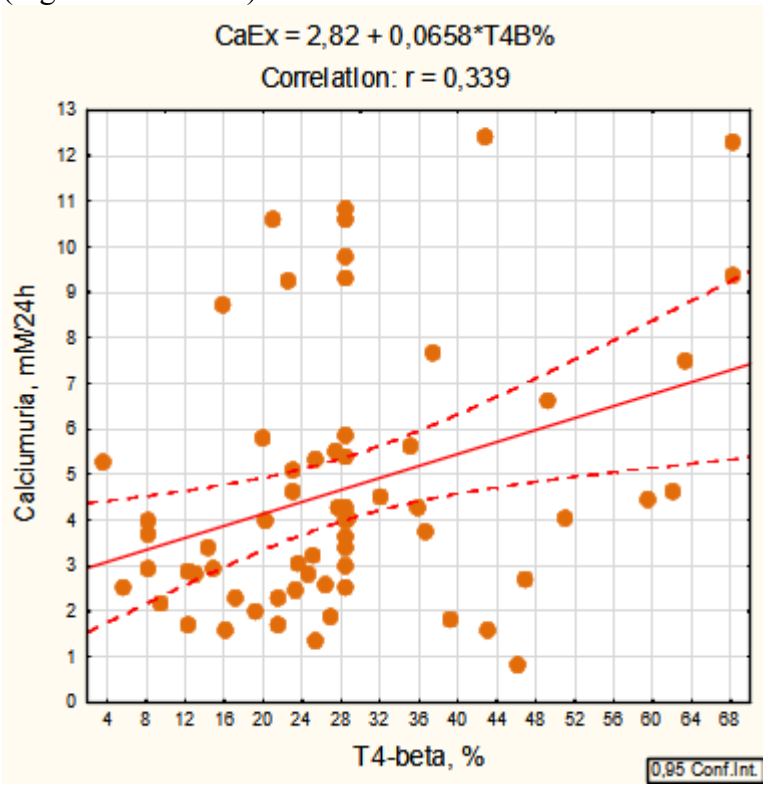


Fig. 8. Scatterplot of correlation between relative PSD of β-rhythm in locus T4 (X-line) and Calciumuria (Y-line)

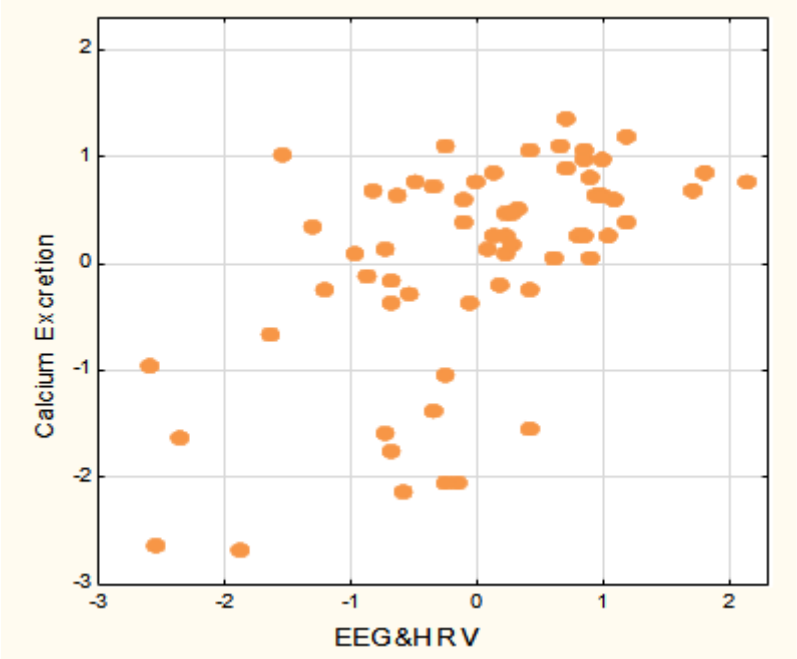
Table 3. Regression Summary for Calciumuria
R=0,571; R^2=0,326; Adjusted R^2=0,226; $F_{(8,5)}$=3,3; p=0,004

N=63		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(55)}$	p-level
Variables	r		Intercpt	10,05	2,42	4,14	10^{-4}
T4-β PSD, %	**0,34**	0,880	0,353	0,1715	0,0686	2,49	0,016
T6-β PSD, %	**0,29**	-0,164	0,113	-0,0264	0,0182	-1,45	0,152
F8-β PSD, %	**0,25**	-0,183	0,181	-0,0327	0,0323	-1,01	0,316
C4-β PSD, %	**0,20**	-1,013	0,355	-0,2527	0,0885	-2,85	0,006
T4-δ-PSD, %	**-0,27**	0,317	0,306	0,0466	0,0449	1,04	0,305
LFnu HRV, %	**-0,25**	-0,212	0,114	-0,0393	0,0211	-1,86	0,068
C4-δ-PSD, %	**-0,21**	-0,676	0,302	-0,1019	0,0455	-2,24	0,029
VLF HRV PS, %	**-0,20**	-0,164	0,113	-0,0264	0,0182	-1,45	0,152

It should be noted that outside the regression model, it is unclear why the HRVs-markers of Vagal tone appeared: HF% (r=0,26), pNN_{50} (r=0,24), HF (r=0,22) and RMSSD (r=0,23).

This suggested hypothesis that downregulation of calciumuria is realized by Sympathetic nucleus of Brain Stem (probably caudal and rostral ventro-lateral medulla). On the other hand, Parasympathetic nucleus of Brain Stem (probably nucleus ambiguous) upregulate it.

Taken together, listed structures of the central and autonomic nervous systems determine the level of calciumuria by 32,6% (Fig. 9).



R=0,571; R^2=0,326; $\chi^2_{(8)}$=22; p=0,004; Λ Prime=0,674

Fig. 9. Scatterplot of canonical correlation between EEG&HRV parameters (X-line) and Calcium Urinary Excretion (Y-line)

An unambiguous physiological interpretation of VLF and ULF components of HRV is still lacking, so the vast majority of researchers carefully **avoid** analyzing them, despite the fact that they are recorded **inseparably** with HF and LF bands.

It is speculated that PS 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 [cited by: 3,11], cerebral ergotropic and metabolotropic outflows [cited by: 2], activation of cerebral sympatho-adrenal system [cyted by: 8], sympathetic activity [cited by: 10]; and 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) [cited by: 11].

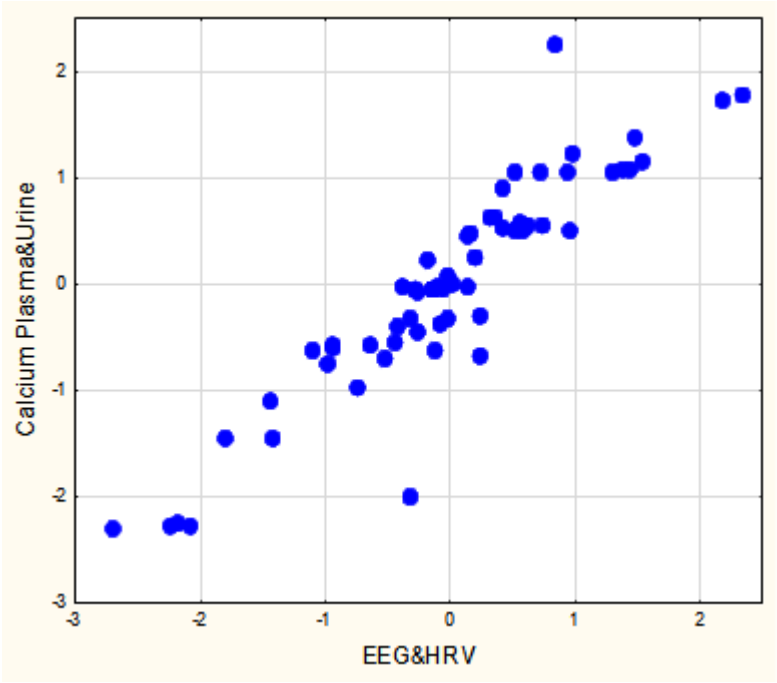
At the final stage, the analysis of the canonical correlation between the parameters of EEG&HRV, on the one hand, and the parameters of calcium exchange - on the other. Judging by the factor loads, the effective canonical root represents mainly calciumemia, while calciumuria gives a meager and opposite in sign load (Table 4).

This suggested hypothesis that upregulation of calciumemia is realized by Sympathetic nerves as well as by circulating Norepinephrine and Cortisol. Instead, calcium excretion is subject to sympathetic inhibition.

Table 4. Factor load on canonical roots of EEG&HRV and Ca Plasma&Urine parameters

Left set	R
Fp1-β PSD, %	-0,447
VLF HRV PS, %	-0,413
θ-Laterality Index, %	-0,391
O1-β PSD, %	-0,390
P3-β PSD, %	-0,384
T6-β PSD, %	-0,370
C3-β PSD, %	-0,335
F7-β PSD, %	-0,322
P3 Entropy	-0,307
O2-β PSD, %	-0,291
ULF HRV PS, msec^2	-0,290
P4-β PSD, %	-0,271
δ-Laterality Index, %	-0,255
C4-β PSD, %	-0,249
θ-Asymmetry, %	-0,236
T5-β PSD, %	-0,234
F4-β PSD, %	-0,227
F8-β PSD, %	-0,222
T4-β PSD, %	-0,191
T4-δ-PSD, %	-0,095
C4-δ-PSD, %	-0,061
α-Index, %	0,343
C3-α PSD, %	0,337
F8-α PSD, %	0,307
C4-α PSD, %	0,284
T3-α PSD, %	0,281
Fp1-α PSD, %	0,274
O2-α PSD, %	0,270
T6-α PSD, %	0,249
F3-α PSD, %	0,234
α-Amplitude, μV	0,220
LFnu HRV, %	0,033
Right set	R
Calciumemia, mM/L	-0,999
Calciumuria, mM/24h	0,211

Taken together, the structures of the central and autonomic nervous systems determine the exchange of calcium by 84,4% (Fig. 10).



$R=0,919$; $R^2=0,844$; $\chi^2_{(64)}=121$; $p<10^{-4}$; Λ Prime=0,066
Fig. 10. Scatterplot of canonical correlation between EEG&HRV parameters (X-line) and Calcium Plasma&Urine (Y-line)

CONCLUSION

Parameters of calcium exchange and EEG/HRV are closely related, however the question of the causal nature of correlations remains open.

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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