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RELATIONSHIPS BETWEEN PHOSPHATEMIA/PHOSPHATURIA AND EEG/HRV PARAMETERS IN PATIENTS WITH CHRONIC PYELONEPHRITIS

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Abstract

Background. As part of the project "Relationships between parameters of electrolytes exchange and EEG&HRV in people without kidney disease and patients with chronic pyelonephritis" we have previously shown that parameters of calcium exchange and EEG/HRV are closely related. In this study, we analyzed the relationships between parameters of phosphate exchange and EEG/HRV in the same cohort of patients. **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. Phosphate concentration was determined in blood plasma and daily urine. **Results**. It was stated normal or moderately reduced plasma phosphate levels in combination with a very wide range of phosphate urinary excretion. A very strong canonical correlation was found between phosphatemia and EEG/HRV parameters (R=0,982). The correlations with the parameters of the beta and theta rhythms of the EEG and the HRV are positive, while with the parameters of the delta rhythm of the EEG are negative. The canonical correlation between phosphaturia and EEG parameters is also very strong (R=0,879). **Conclusion**. Parameters of phosphate exchange and EEG/HRV are closely related, however the question of the causal nature of correlations remains open.

Key words: phosphatemia, phosphaturia, EEG, HRV, relationships, chronic pyelonephritis.

INTRODUCTION

As part of the project "Relationships between parameters of electrolytes exchange and EEG&HRV in people without kidney disease and patients with chronic pyelonephritis" we have previously shown that parameters of calcium exchange and EEG/HRV are closely

related [5]. In this study, we analyzed the relationships between parameters of phosphate exchange and EEG/HRV in the same cohort of patients.

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 for 7 min electrocardiogram in II lead to assess the parameters of HRV [2,3,6,11] (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 spectrum (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].

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 spectrum 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 [8]:

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 [10]:

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

Phosphates concentration was determined in blood plasma and daily urine (phosphate-molybdate method) as described in the handbook [4]. Use analyzer "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, as in the case of calcium, a wide range of phosphatemia and phosphaturia as well as a very weak relationship between them (r=-0,18) (Fig. 1).

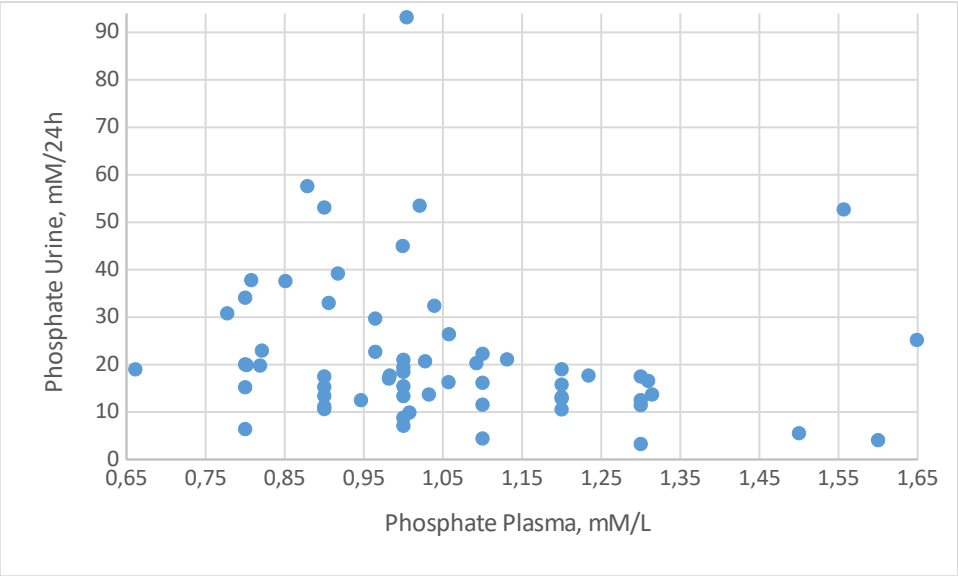


Fig. 1. Diagram of scattering of actual values of phosphatemia and phosphaturia

At the next stage, following the accepted algorithm, the actual parameters of phosphate exchange were normalized.

According to the database of our laboratory, for phosphatemia N=1,20 mM/L, Cv=0,167; for phosphaturia N=25,2 mM/24h, Cv=0,294. It was stated that the observed contingent is characterized by normal or moderately reduced plasma phosphate levels in combination with a very wide range of phosphate urinary excretion (Fig. 2). The latter is strongly related to the concentration of phosphates in the daily urine (r=0,71).

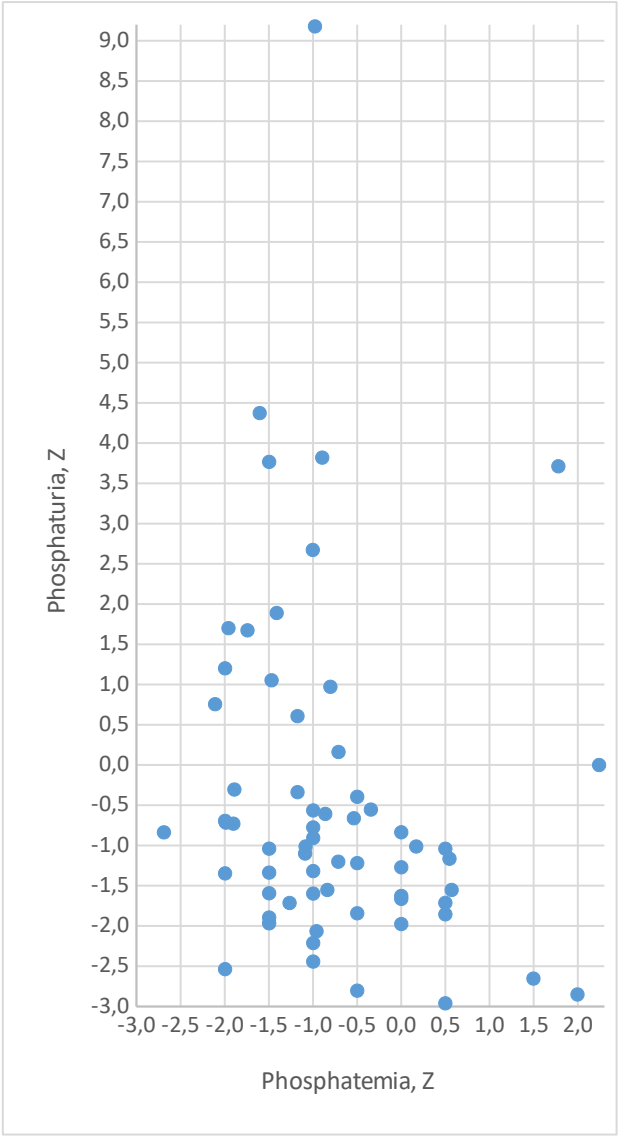


Fig. 2. Scattering diagram of normalized values of phosphatemia and phosphaturia

No significant association was found between plasma phosphate and calcium levels (Fig. 3), but their urinary excretion is significantly associated (Fig. 4).

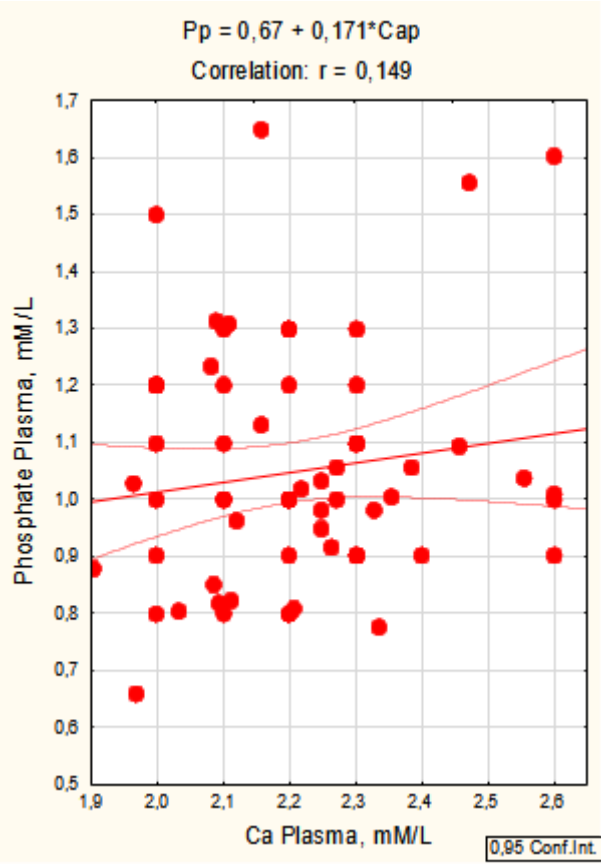


Fig. 3. Scatterplot of correlation between Calciumemia (X-line) and Phosphatemia (Y-line)

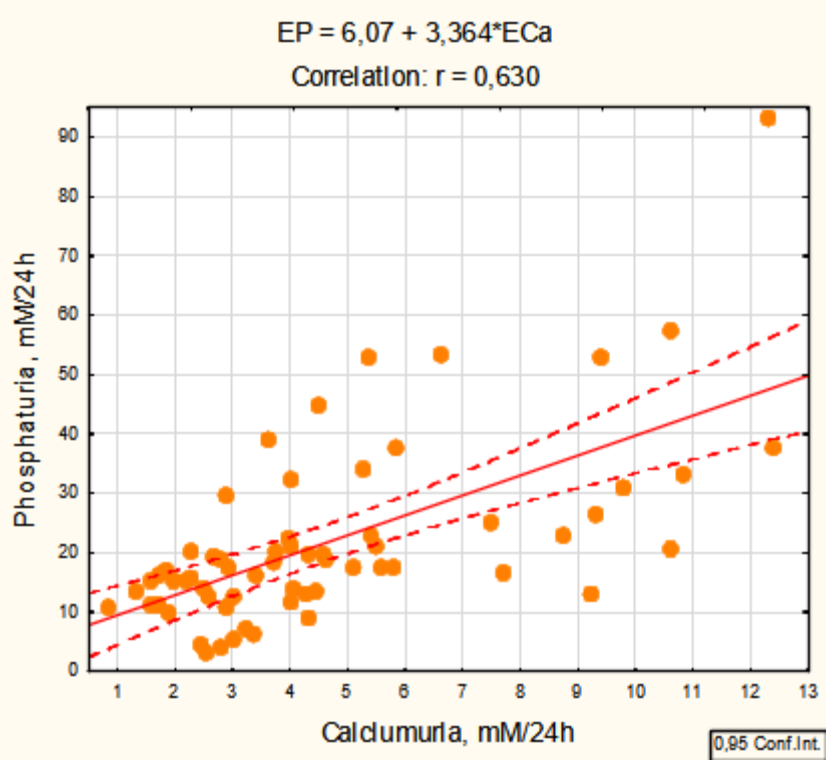


Fig. 4. Scatterplot of correlation between Calciumuria (X-line) and Phosphaturia (Y-line)

Next, the correlations between phosphatemia 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).

The pseudo-staining we use visualizes that the most numerous EEG-parameters included in the model are relative and absolute PSD of **β-rhythm** as well as **θ-rhythm**, which correlate positively with phosphatemia. In contrast, the frequency and lateralization of **β-** and **θ-rhythms** as well as the four parameters of **δ-rhythm** correlate negatively with phosphatemia.

Table 1. Regression Summary for Phosphatemia
R=0,982; R^2=0,964; Adjusted R^2=0,904; $F_{(39)}$=15,9; $p<10^{-6}$

N=63		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(23)}$	p-level
Variables	r		Intercpt	0,822	0,242	3,40	0,002
ULF HRV PS, msec²	**0,47**	0,578	0,066	0,0009	0,0001	8,73	10^{-6}
C3-β PSD, %	**0,42**	0,535	0,229	0,0096	0,0041	2,34	0,028
C3-β PSD, μV²/Hz	**0,39**	1,264	0,337	0,0041	0,0011	3,75	0,001
T3-θ PSD, %	**0,41**	1,581	0,195	0,0660	0,0081	8,12	10^{-6}
P3-θ PSD, %	**0,35**	-0,412	0,150	-0,0207	0,0075	-2,75	0,011
P4-β PSD, %	**0,33**	-0,571	0,169	-0,0099	0,0029	-3,37	0,003
C4-β PSD, %	**0,31**	0,445	0,186	0,0080	0,0033	2,40	0,025
C4-β PSD, μV²/Hz	**0,29**	-1,447	0,303	-0,0052	0,0011	-4,77	10^{-4}
P3 Entropy	**0,30**	-0,545	0,181	-0,9660	0,3209	-3,01	0,006
P3-β PSD, %	**0,29**	0,612	0,148	0,0132	0,0032	4,13	10^{-4}
LF/HF	**0,28**	0,217	0,095	0,0088	0,0039	2,28	0,032
O2-β PSD, %	**0,27**	0,716	0,204	0,0114	0,0033	3,50	0,002
T4-θ PSD, %	**0,27**	-1,177	0,249	-0,0465	0,0098	-4,73	10^{-4}
θ-Amplitude, μV	**0,24**	0,497	0,234	0,027	0,013	2,12	0,045
O2-θ PSD, μV²/Hz	**0,24**	-0,876	0,187	-0,0033	0,0007	-4,67	10^{-4}
F7-θ PSD, %	**0,23**	0,462	0,099	0,0225	0,0048	4,64	10^{-4}
F4-β PSD, %	**0,23**	-0,492	0,203	-0,0076	0,0031	-2,42	0,024
(VLF+LF)/HF	**0,22**	0,401	0,125	0,0056	0,0018	3,22	0,004
T6-β PSD, %	**0,22**	-1,023	0,214	-0,0133	0,0028	-4,77	10^{-4}
O1-β PSD, μV²/Hz	**0,22**	0,569	0,126	0,0020	0,0004	4,53	10^{-4}
F3-β PSD, %	**0,22**	-0,385	0,173	-0,0067	0,0030	-2,23	0,036
F3-β PSD, μV²/Hz	**0,21**	-1,060	0,274	-0,0041	0,0011	-3,87	0,001
Fp1-β PSD, μV²/Hz	**0,21**	1,175	0,226	0,0060	0,0012	5,20	10^{-4}
P4-β PSD, μV²/Hz	**0,20**	0,753	0,181	0,0027	0,0006	4,17	10^{-4}
C3-θ PSD, %	**0,21**	-1,076	0,180	-0,0518	0,0087	-5,99	10^{-5}
F4-θ PSD, %	**0,21**	1,392	0,204	0,0432	0,0063	6,84	10^{-6}
F4-θ PSD, μV²/Hz	**0,21**	-1,040	0,217	-0,0031	0,0006	-4,79	10^{-4}
F7-θ PSD, μV²/Hz	**0,20**	-0,908	0,232	-0,0048	0,0012	-3,91	0,001
T4-θ PSD, μV²/Hz	**0,20**	1,063	0,228	0,0052	0,0011	4,65	10^{-4}
C3 Entropy	**0,19**	0,457	0,147	0,7575	0,2437	3,11	0,005
α-Asymmetry, %	**0,19**	0,638	0,108	0,011	0,002	5,90	10^{-5}
β-Frequency, Hz	**-0,32**	-0,596	0,110	-0,031	0,006	-5,44	10^{-4}
β-Laterality, %	**-0,27**	0,188	0,115	0,0015	0,0009	1,63	0,117
θ-Laterality Index, %	**-0,22**	0,856	0,172	0,0050	0,0010	4,96	10^{-4}
δ-Index, %	**-0,22**	0,417	0,090	0,0022	0,0005	4,63	10^{-4}
C4-α PSD, %	**-0,23**	-0,201	0,144	-0,0029	0,0021	-1,40	0,176
T5-δ, %	**-0,21**	-0,730	0,159	-0,0075	0,0016	-4,59	10^{-4}
O2-δ, %	**-0,20**	1,304	0,211	0,0153	0,0025	6,17	10^{-5}
O1-δ, %	**-0,19**	-0,621	0,137	-0,0069	0,0015	-4,54	10^{-4}

For example, we give a pair with the maximum correlation coefficient for the sample (Fig. 5).

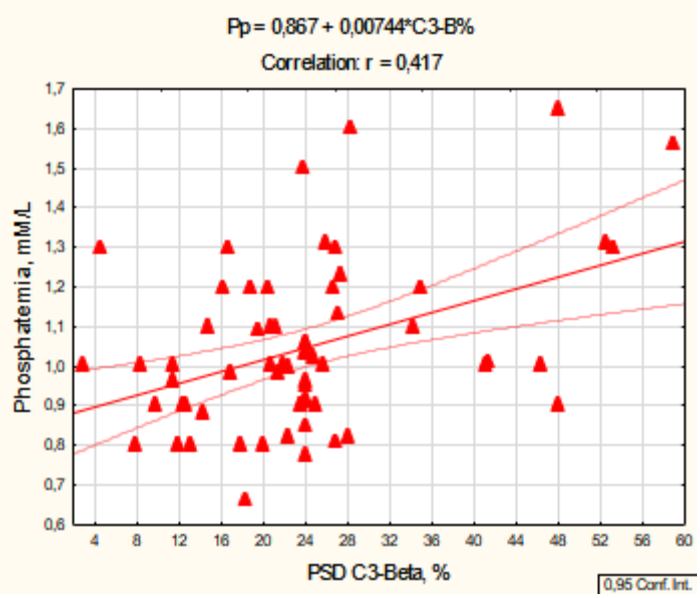


Fig. 5. Scatterplot of correlation between PSD of the beta rhythm in locus C3 (X-line) and Phosphatemia (Y-line)

Among the parameters of HRV, most closely related to phosphatemia PS of ULF band (Fig. 6), to a lesser extent - indices of sympatho-vagal balance and centralization of autonomic regulation.

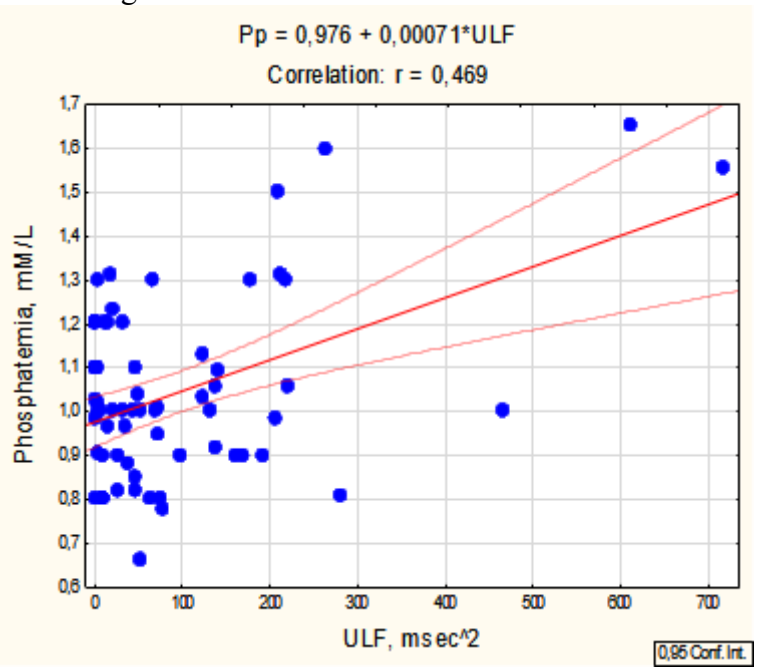
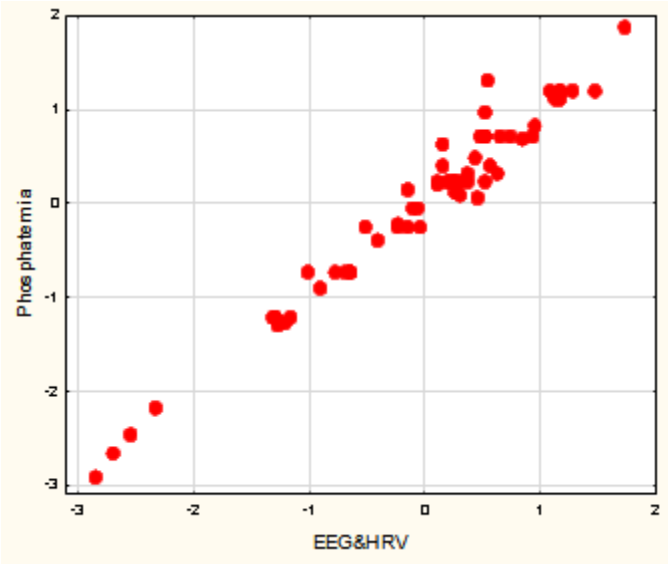


Fig. 6. Scatterplot of correlation between PS of ULF band HRV (X-line) and Phosphatemia (Y-line)

Despite moderate partial coefficients, the canonical correlation between EEG&HRV parameters and phosphatemia was drastically strong (Fig. 7).



R=0,982; R^2=0,964; $\chi^2_{(39)}$=138; p<10^{-6}; Λ Prime=0,036

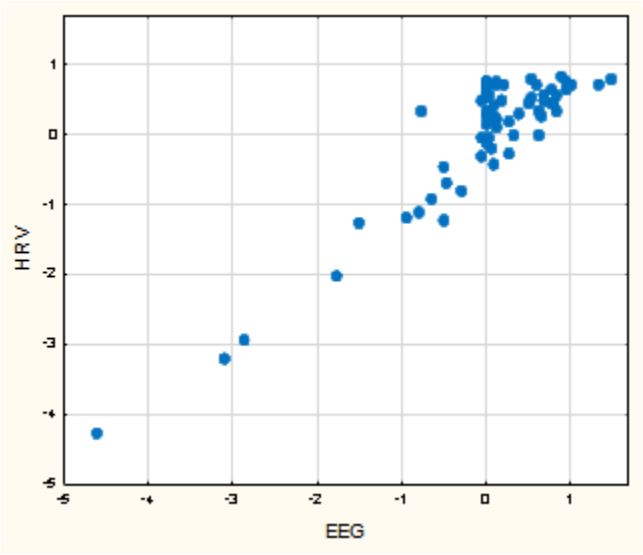
Fig. 7. Scatterplot of canonical correlation between EEG&HRV parameters (X-line) and Phosphate Plasma (Y-line)

The index of centralization of autonomic regulation **upregulated** by **θ-rhythm** generating nucleus projected onto locus P3 (r=0,247) and **β-rhythm** generating neural structures that are projected onto loci P3 (r=0,240), F3 (r=0,215) and T6 (r=0,185) while **downregulated** by **θ-rhythm** generating nucleus projected onto locus F4 (r=-0,187) and **δ-rhythm** generating nucleus projected onto locus O1 (r=-0,147). The same type, but weaker connections are found for index of sympatho-vagal balance. **ULF** band, in turn, is subject to **upregulation** by **β-rhythm** generating neural structures that are projected onto loci F3 (r=0,321) and O2 (r=0,430) as well as **θ-rhythm** generating nucleus that are projected onto locus T3 (r=0,289). The factor structure of EEG and HRV canonical roots is shown in table. 2.

Table 2. Factor load on canonical roots of EEG and HRV parameters

Left site	R
P3-θ PSD, %	-0,292
P3-β PSD, %	-0,269
F3-β PSD, %	-0,260
P3 Entropy	-0,256
T6-β PSD, %	-0,212
α-Asymmetry, %	-0,118
F4-θ PSD, μV^2/Hz	0,197
O1-δ, %	0,158
β-Laterality, %	0,261
δ-Index, %	0,189
θ-Amplitude, μV	0,153
F3-β PSD, μV^2/Hz	0,183
O2-β PSD, %	0,030
T3-θ PSD, %	0,082
Right site	**R**
(VLF+LF)/HF	-0,995
LF/HF	-0,695
ULF HRV PS, $msec^2$	0,114

Relationships between of EEG parameters and HRV parameters is very strong (Fig. 8).



R=0,913; R^2=0,834; $\chi^2_{(111)}$=159; p=0,002; Λ Prime=0,022
Fig.8. Scatterplot of canonical correlation between EEG (X-line) and HRV (Y-line) parameters

Phosphaturia has been shown to be most closely associated with PSD of **β-rhythm** in locus T6 (Fig. 9). By the way, the figure shows the error, in our opinion, the conception of the "jumping" variables: abnormally high value of PSD corresponds to abnormal phosphaturia.

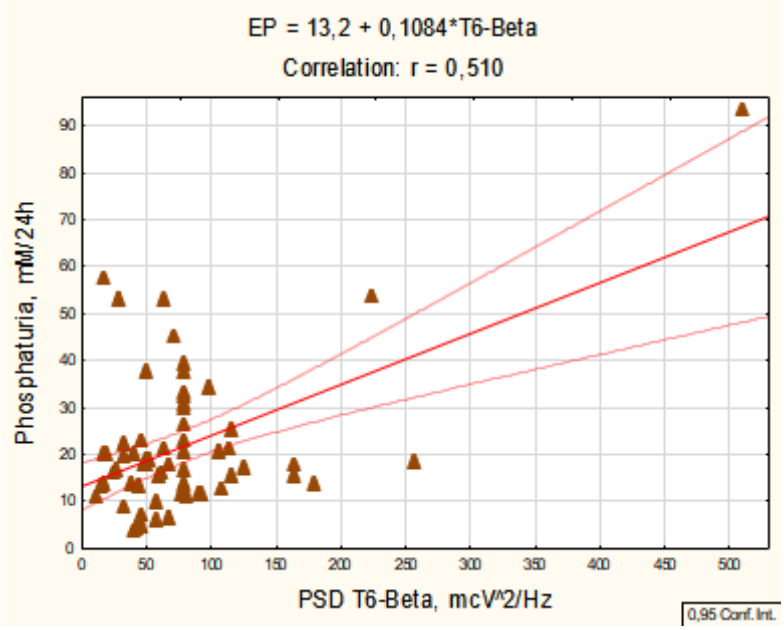


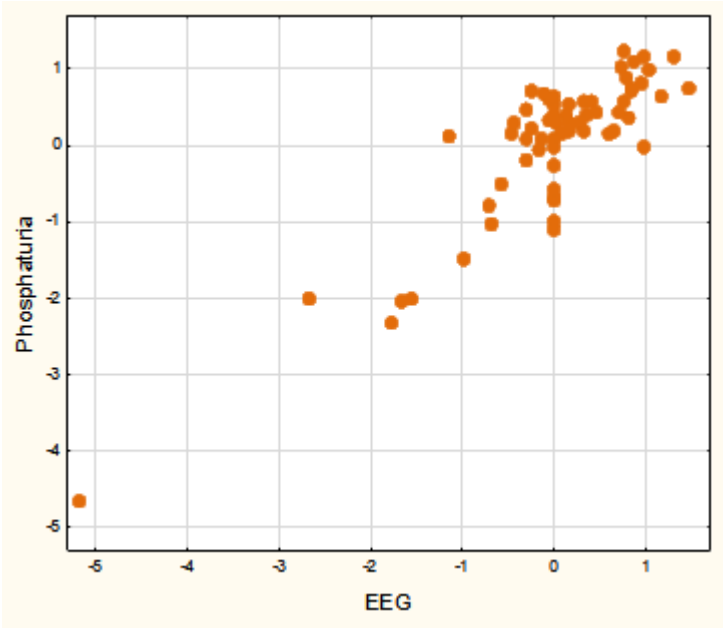
Fig. 9. Scatterplot of correlation between PSD of the beta rhythm in locus T6 (X-line) and Phosphaturia (Y-line)

Like phosphatemia, phosphaturia also correlates positively with **β-rhythm** parameters and negatively with **δ-rhythm** parameters, while phosphaturia correlates negatively with **θ-rhythm** parameters (Table 3). Another difference from phosphatemia is the lack of HRV parameters in the regression model.

Table 3. Regression Summary for Phosphaturia
R=0,878; R^2=0,772; Adjusted R^2=0,656; $F_{(21)}$=6,6; $p<10^{-6}$

N=63		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(41)}$	p-level
Variables	r		Intercpt	15,1	13,7	1,10	0,276
T6-β PSD, μV²/Hz	**0,51**	0,937	0,164	0,199	0,035	5,71	10^{-6}
T6-β PSD, %	**0,41**	-0,420	0,261	-0,405	0,252	-1,61	0,116
F8-β PSD, %	**0,39**	0,600	0,230	0,573	0,220	2,60	0,013
Fp2-β PSD, %	**0,32**	0,722	0,207	0,741	0,213	3,49	0,001
F7-β PSD, %	**0,30**	0,523	0,146	0,460	0,128	3,58	0,001
P4-β PSD, %	**0,26**	0,397	0,212	0,513	0,274	1,87	0,069
F3-β PSD, %	**0,23**	-0,271	0,172	-0,348	0,222	-1,57	0,124
T3-β PSD, %	**0,22**	-0,612	0,138	-0,614	0,138	-4,45	10^{-4}
T3-β PSD, μV²/Hz	**0,20**	0,408	0,185	0,095	0,043	2,20	0,033
β-Amplitude, μV	**0,22**	-0,785	0,170	-3,813	0,825	-4,62	10^{-4}
F4-β PSD, %	**0,19**	-0,534	0,261	-0,612	0,300	-2,04	0,048
θ-Frequency, Hz	**0,21**	0,402	0,116	5,021	1,444	3,48	0,001
T6-θ PSD, %	**-0,33**	0,343	0,177	1,194	0,614	1,94	0,059
F8-θ PSD, %	**-0,24**	-0,592	0,171	-1,689	0,489	-3,46	0,001
T4-δ, %	**-0,25**	-0,520	0,161	-0,408	0,127	-3,22	0,003
Fp1-δ, %	**-0,23**	-0,706	0,164	-0,541	0,126	-4,29	10^{-4}
Fp2-δ, %	**-0,19**	0,606	0,189	0,525	0,163	3,21	0,003
F8-δ, %	**-0,19**	0,613	0,201	0,412	0,135	3,05	0,004
δ-Index, %	**-0,20**	-0,191	0,111	-0,075	0,044	-1,72	0,094

The canonical correlation is somewhat weaker, but also very strong (Fig. 10).



R=0,879; R^2=0,772; $\chi^2_{(21)}$=75; $p<10^{-6}$; Λ Prime=0,228
Fig. 10. Scatterplot of canonical correlation between EEG parameters (X-line) and Phosphaturia (Y-line)

The electroencephalograph used in this study, unfortunately, allows only approximately to identify neural structures whose activity is associated with phosphate exchange parameters. It

is traditionally believed that loci C3/C4 projected hippocampus, and loci T3/T4 reflect the activity of the amygdala [9]. In practice, transcranial magnetic and direct current stimulation of the T3/T4 scalp position is used to reach the insular cortex, and F3/F4 loci - to activate the dorsolateral prefrontal cortex nuclei [review: 1,7]. The figures presented by Winkelmann T et al [12] and Yoo HJ et al [13] give us reason to assume that the loci C3/C4 projected precentral gyrus, T3/T4 – inferior temporal gyrus, F3/F4 - caudal anterior cingulate cortex or rostral middle frontal gyrus or superior frontal gyrus, P3/P4 – supramarginal gyrus, T5/T6 – caudal anterior cingulate cortex. These cortical structures affect the activity of the vagus and sympathetic nuclei.

Judging by the correlation coefficients, the level of phosphatemia is subject to **upregulation** by: **β-rhythm**-generating nuclei of the left (mostly) and right (less) **hippocampus** and/or cortex of the right **precentral gyrus** as well as right and left **supramarginal gyrus**; **θ-rhythm**-generating nuclei of the left **amygdala** and **supramarginal gyrus** cortex**.** Instead **α-rhythm**-generating nuclei of the right **hippocampus** and/or of the **precentral gyrus** cortex as well as **δ-rhythm**-generating nuclei of the left **caudal anterior cingulate** cortex causes an **downregulation**. Phosphaturia is subject to **upregulation** by **β-rhythm**-generating nuclei instead **downregulation** by **θ-rhythm**-generating nuclei of the right **caudal anterior cingulate** cortex.

Surprisingly, we have not been able to find any sources on the subject of the study on PubMed & PMC resources, so the discussion is unproductive.

CONCLUSION

Parameters of phosphate 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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