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Tensioregulome as an accompaniment of quantitative-qualitative blood pressure clusters

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Abstract

Background. Earlier we studied the neural, endocrine, immune, microbiome and metabolome accompaniments of quantitative-qualitative blood pressure (BP) clusters of profile patients of Truskavets' spa. The obtained results give us grounds to put forward the concept of **tensioregulome** by analogy with the metabolome and the microbiome. The purpose of this study is detailing this concept. **Materials and methods.** Under an observations were 44 patients with chronic pyelonephritis and cholecystitis in the phase of remission. Testing was performed twice - on admission and after 7-10 days of standard balneotherapy. The main object of the study was BP. We determined parameters of EEG and HRV, plasma levels of adaptation hormones, electrolytes, lipids, and nitrogenous metabolites, components of humoral, cellular, and phagocytic links of immunity and markers of pyelonephritis. **Results**. The forward stepwise program identified 26 tensioregulome parameters as characteristic of quantitative-qualitative blood pressure clusters: 10 EEG, 6 metabolic, 6 immune, testosterone, cotrisol, sympathetic tone as well as sex. The accuracy of patient classification is 98,9%. Another 25 parameters were found to be characteristic, but were outside the discriminant model, including 11 EEG, 2 HRV, 5 metabolic, 4 immune, bacteriuria, body mass index, and age. Both linear and non-linear correlations between the BP and tensioregulome parameters were revealed. **Conclusion**. The quantitative-qualitative blood pressure clusters have a characteristic accompaniment named tensioregulome.
Keywords: blood pressure, EEG, HRV, immunity, metabolome, pyelonephritis.

INTRODUCTION

Earlier we showed that profile patients of Truskavets' spa are characterized by a wide range of blood pressure - from low norm to arterial hypertension III - that correspond to the hemodynamics parameters [10]. Than we clarified the neural, endocrine, metabolome, immune, and microbiome accompaniments of quantitative-qualitative blood pressure clusters in the same contingent [11-14]. The obtained results give us grounds to put forward the concept of **tensioregulome** by analogy with the metabolome and the microbiome. The purpose of this study is detailing this concept.

MATERIALS AND METHODS

Under an observations were 34 males and 10 females by age 24-76 years with chronic pyelonephritis and cholecystitis in the phase of remission. Testing was performed twice - on admission and after 7-10 days of standard balneotherapy (drinking of bioactive water Naftussya, applications of ozokerite, mineral pools).

The main object of the study was blood pressure (BP). Systolic and diastolic BP was measured (by tonometer "Omron M4-I", Netherlands) in a sitting position three times in a row.

Retrospectively, 5 quantitative-qualitative blood pressure clusters were created (Fig. 1) according to the existing gradation [3,18,21].

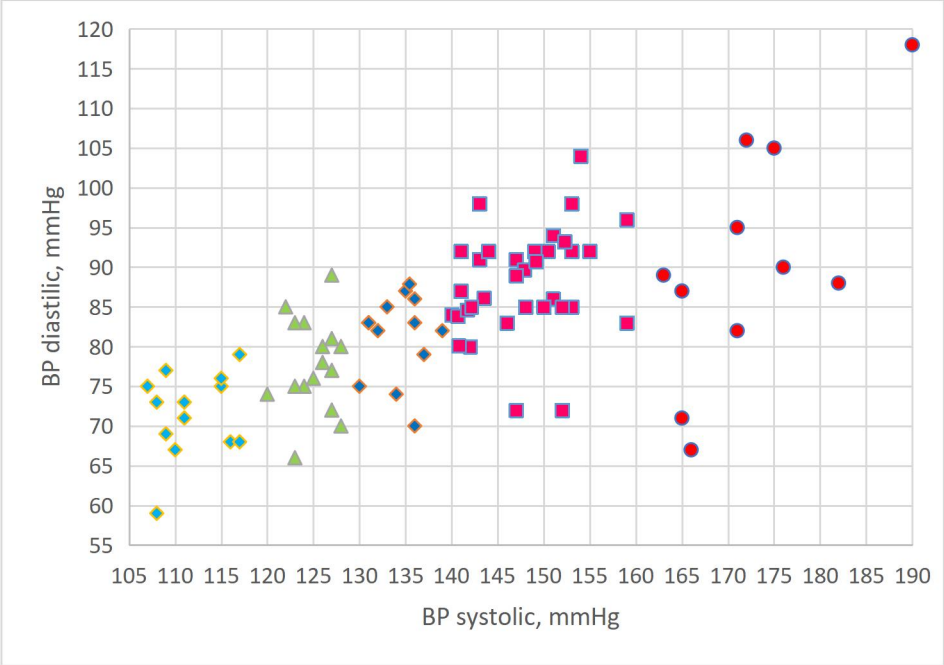


Fig. 1. Diagram of scattering of systolic and diastolic blood pressure of patients of Truskavets' spa

We determined parameters of EEG ("NeuroCom Standard", KhAI Medica) and HRV ("CardioLab+HRV", KhAI Medica), plasma levels of adaptation hormones Cortisol, Aldosterone, Testosterone, Triiodothyronine and Calcitonin (ELISA; "Tecan" and "RT-2100C"; "Алкор Био", XEMA Co Ltd, and DRG International Inc), electrolytes, lipids, and nitrogenous metabolites ("Reflotron" and "Pointe-180"), components of humoral, cellular, and phagocytic links of immunity and markers of pyelonephritis (please see the articles [7,11-14,17] for more details).

Reference values of variables are taken from the database of the Truskavetsian Scientific School of Balneology [5,22].

For statistical analysis used the software package "Statistica 6.4".

RESULTS

In order to identify among the registered parameters, those for which the blood pressure clusters differ from each other, a discriminant analysis was performed [8]. The forward stepwise program identified 26 tensioregulome parameters as characteristic: 10 EEG, 6 metabolic, 6 immune, testosterone, cotrisol, sympathetic tone as well as the sex (more precisely, the sex index) (Tables 1 and 2). Another 25 parameters were found to be characteristic, but were outside the discriminant model, including 11 EEG, 2 HRV, 5 metabolic, 4 immune, bacteriuria, body mass index as well as age (Table 3).

Obviously, this distribution is caused by duplication and/or redundancy of recognition information, the strongest evidence of which is the failure to include diastolic BP in the model.

Table 1. Discriminant Function Analysis Summary for Variables, their actual levels for Clusters of Blood Pressure as well as Reference levels and Coefficients of Variability

Step 27, N of vars in model: 27; Grouping: 5 grs; Wilks' Λ: 0,0023; approx. $F_{(108)}=7,7$; $p<10^{-6}$

Variables currently in the model	Clusters of Blood Pressure (n)					Parameters of Wilk's Statistics						
	AH II (11)	AH I (35)	High N (13)	No-rm (16)	Low N (13)	Wil-ks Λ	Par-tial Λ	F-re-move (4,57)	p-level	Tole-rancy	Refe-rence (88)	Cv
BP Systolic, mmHg	172 2,5	148 0,9	134 0,8	125 0,6	112 1,0	0,041	0,055	245	10^{-6}	0,511	124,5 1,6	,122
Sex Index (M=1;F=2)	1,36 0,15	1,11 0,05	1,00 0,00	1,25 0,11	1,62 0,14	0,004	0,622	8,64	10^{-4}	0,372	1,23 0,04	,343
Deviation-δ, Hz	0,64 0,07	0,70 0,04	0,55 0,04	0,66 0,08	0,85 0,10	0,003	0,802	3,52	0,012	0,727	0,67 0,03	,395
C3-δ PSD, %	30,4 6,8	27,9 2,7	37,5 7,5	28,8 3,3	43,5 7,4	0,003	0,866	2,21	0,080	0,200	28,0 1,8	,602
P3-δ PSD, %	25,2 6,0	27,7 2,8	26,0 5,6	24,8 3,5	36,7 7,1	0,003	0,906	1,47	0,222	0,232	25,6 1,9	,694
O1-θ PSD, %	8,5 1,6	8,2 0,8	8,2 1,4	7,0 0,9	10,3 1,7	0,003	0,815	3,24	0,018	0,492	8,2 0,5	,584
Index-α, %	49,5 8,5	48,4 5,7	47,3 8,7	62,6 6,0	53,4 6,6	0,003	0,773	4,19	0,005	0,185	50,7 3,0	,560
Deviation-α, Hz	0,86 0,10	1,11 0,12	0,91 0,10	0,81 0,10	1,23 0,15	0,003	0,878	1,97	0,111	0,738	1,02 0,06	,527
Fp2-α PSD, %	27,9 4,2	31,3 2,4	27,2 4,1	34,3 4,7	31,9 5,1	0,003	0,893	1,70	0,163	0,218	32,9 1,6	,448
F7-α PSD, %	28,9 6,1	27,1 2,5	21,1 3,9	18,4 3,4	26,6 3,7	0,003	0,731	5,24	0,001	0,231	27,6 1,5	,522
F8-β PSD, %	26,3 4,6	33,4 3,9	31,7 5,9	18,9 4,0	26,8 4,1	0,003	0,835	2,81	0,034	0,435	29,4 1,8	,567
T3-β PSD, %	28,6 3,7	28,5 2,1	38,5 6,1	19,5 3,3	28,55 5,1	0,003	0,785	3,91	0,007	0,335	30,7 1,5	,462
LF PSD nu, %	74,9 3,9	71,1 2,5	68,6 5,1	79,4 3,6	58,7 5,7	0,003	0,720	5,53	0,001	0,584	64,2 1,4	,201
Cortisol, nM/L	469 49	374 26	446 56	386 47	391 44	0,002	0,909	1,43	0,237	0,689	370 12	,303
Testostero-ne, Z	0,84 0,71	0,37 0,46	0,74 0,74	-0,35 0,34	-0,11 0,41	0,003	0,843	2,66	0,042	0,479	0	
Sodium P, mM/L	149	140	140,4	145	148,2	0,004	0,609	9,15	10^{-5}	0,505	145	,034

	2,8	1,5	2,1	2,0	1,2						0,5	
Potassium P, mM/L	4,49 0,14	4,22 0,09	4,35 0,15	4,22 0,14	4,72 0,16	0,003	0,781	3,99	0,006	0,359	4,55 0,05	,104
Magnesium P, mM/L	0,85 0,02	0,83 0,01	0,84 0,01	0,84 0,01	0,82 0,01	0,002	0,918	1,27	0,291	0,421	0,90 0,01	,056
Phosphate P, mM/L	1,08 0,07	1,02 0,03	1,09 0,07	1,00 0,04	0,90 0,05	0,003	0,877	1,99	0,108	0,570	1,20 0,02	,167
Potassium Ex, mM/d	72 8	79 7	71 13	66 5	63 9	0,003	0,895	1,67	0,171	0,385	65 2	,269
Calcium Ex, mM/d	3,74 0,72	6,17 0,60	4,88 0,86	3,92 0,44	4,82 0,79	0,003	0,816	3,21	0,019	0,408	4,38 0,10	,214
$CD4^+CD25^+$ T-regs, %	18,8 1,1	21,1 0,6	19,1 1,1	20,8 1,2	17,6 1,3	0,003	0,843	2,65	0,042	0,311	16,4 0,3	,153
$CD4^+$ T-helper Lym, %	33,7 1,9	27,4 1,0	33,1 1,9	30,5 2,2	35,9 2,6	0,003	0,850	2,51	0,052	0,239	39,5 0,7	,164
CIC, units	42 6	34 2	30 3	34 4	43 5	0,003	0,777	4,08	0,006	0,575	45 2	,389
IgA Serum, g/L	2,03 0,05	1,58 0,09	1,91 0,14	1,78 0,11	1,92 0,12	0,003	0,803	3,49	0,013	0,434	1,875 0,03	,167
Phag Ind vs St. aur., %	98,5 0,34	98,6 0,24	99,3 0,21	99,2 0,19	98,9 0,32	0,003	0,727	5,34	0,001	0,288	98,3 0,19	,018
Mic Cou St. aur., B/Ph	59,7 1,9	61,3 1,6	63,2 1,9	64,1 1,9	63,9 1,9	0,003	0,904	1,52	0,209	0,391	61,6 1,1	,160

Table 2. Summary of Stepwise Analysis for Variables, ranked by criterion Lambda

Variables currently in the model	F to enter	p-level	**Λ**	F-value	p-value
BP Systolic, mmHg	298	10^{-6}	0,065	298	10^{-6}
Sex Index (M=1;F=2)	4,95	0,001	0,052	68,99	10^{-6}
Sodium P, mM/L	4,29	0,003	0,043	40,71	10^{-6}
T3-β PSD, %	3,77	0,007	0,036	29,97	10^{-6}
IgA Serum, g/L	3,48	0,011	0,031	24,33	10^{-6}
Phagocytosis Index vs Staph. aur., %	2,86	0,029	0,027	20,68	10^{-6}
Potassium Plasma, mM/L	3,39	0,013	0,023	18,42	10^{-6}
Deviation-δ, Hz	3,07	0,021	0,020	16,72	10^{-6}
P3-δ PSD, %	2,70	0,037	0,017	15,35	10^{-6}
F7-α PSD, %	2,83	0,030	0,015	14,32	10^{-6}
LF PSD nu, %	3,36	0,014	0,013	13,64	10^{-6}
$CD4^+$ T-helper Lymphocytes, %	2,39	0,059	0,011	12,87	10^{-6}
Potassium Excretion, mM/d	2,25	0,073	0,010	12,21	10^{-6}
Calcium Excretion, mM/d	2,28	0,069	0,009	11,66	10^{-6}
Circulating Immune Complex, units	2,11	0,088	0,008	11,16	10^{-6}
Testosterone, Z	1,82	0,135	0,007	10,67	10^{-6}
$CD4^+CD25^+$ T-regulatory Lymphoc, %	1,78	0,143	0,006	10,24	10^{-6}
Deviation-α, Hz	1,67	0,167	0,006	9,842	10^{-6}
Cortisol, nM/L	1,58	0,191	0,005	9,472	10^{-6}
O1-θ PSD, %	1,38	0,250	0,005	9,107	10^{-6}
Index-α, %	2,42	0,057	0,004	8,956	10^{-6}
C3-δ PSD, %	1,87	0,127	0,004	8,735	10^{-6}
F8-β PSD, %	2,44	0,056	0,003	8,632	10^{-6}
Fp2-α PSD, %	1,53	0,206	0,003	8,396	10^{-6}
Microbial Count Staph. aur., Bac/Ph	1,41	0,242	0,003	8,162	10^{-6}
Phosphate Plasma, mM/L	1,25	0,301	0,002	7,921	10^{-6}
Magnesium Plasma, mM/L	1,27	0,291	0,002	7,704	10^{-6}

Table 3. Variables currently not in model

Variables	AH II (11)	AH I (35)	High N (13)	No-rm (16)	Low N (13)	Wilks' Λ	Par-tial Λ	F to enter	p-level	Tole-rancy	Refe-rence (88)	Cv SD
BP Diasto-lic, mmHg	90,7 4,5	87,6 1,2	81,3 1,5	77,8 1,5	71,5 1,5	0,002	0,969	0,45	0,772	0,530	79,0 0,7	,083
Age, years	61,3 2,5	49,2 2,6	50,9 2,5	47,3 2,6	43,1 2,1	0,002	0,988	0,18	0,949	0,442	49,7 1,4	,257
Fp1-θ PSD, %	9,4 1,6	13,4 1,6	6,65 0,8	7,7 0,9	10,8 2,1	0,002	0,946	0,80	0,532	0,532	10,4 0,7	,588
C4-θ PSD, %	9,4 1,1	13,9 1,1	9,5 1,4	9,8 1,1	11,9 1,3	0,002	0,958	0,61	0,656	0,287	11,1 0,5	,442
O2-θ PSD, %	6,8 1,3	7,5 0,8	7,3 1,4	6,1 0,9	7,45 1,4	0,003	0,837	0,91	0,197	0,089	7,1 0,4	,554
F3-α PSD, %	31,6 5,8	29,5 2,2	30,1 6,1	30,9 4,3	26,9 5,7	0,015	0,978	0,37	0,831	0,432	33,2 1,7	,479
F4-α PSD, %	27,2 5,7	28,7 2,0	27,5 6,5	31,1 4,0	28,1 5,6	0,002	0,961	0,43	0,789	0,307	31,1 1,6	,485
T4-α PSD, %	31,6 5,9	29,3 2,5	22,0 4,4	26,7 3,1	24,5 4,7	0,002	0,940	0,89	0,476	0,412	29,0 1,6	,500
F3-β PSD, %	25,5 3,6	27,0 2,4	27,8 3,5	15,6 2,6	17,1 2,7	0,002	0,946	0,80	0,532	0,250	26,7 1,3	,463
C3-β PSD, %	27,1 3,6	26,3 2,0	26,7 3,8	21,6 2,8	16,6 2,4	0,002	0,971	0,41	0,799	0,192	25,45 1,1	,420
T5-β PSD, %	26,4 4,9	31,2 3,2	35,4 5,9	19,9 2,5	24,9 5,3	0,002	0,971	0,41	0,799	0,192	29,0 1,7	,536
O1-β PSD, %	31,6 4,8	28,0 3,2	26,1 4,4	16,4 3,1	18,4 2,7	0,002	0,958	0,61	0,656	0,287	26,3 1,5	,542
Entropy PSD O2	0,76 0,06	0,81 0,02	0,78 0,04	0,67 0,05	0,75 0,03	0,002	0,940	0,89	0,476	0,412	0,776 0,015	,178
Baevskiy's Stress Ind	243 71	177 26	125 11	214 59	95 14	0,002	0,961	0,43	0,789	0,307	136 6	,417
Triangular Index, un.	8,5 0,9	11,1 0,7	10,8 0,7	10,2 1,1	13,7 1,0	0,002	0,946	0,80	0,532	0,250	11,2 0,26	,217
Body Mass Index,kg/m^2	27,5 1,3	27,2 0,7	27,4 0,8	27,9 0,9	25,5 0,6	0,003	0,893	0,929	0,290	0,288	24,2 0,3	,133
Cholesterol, mM/L	5,93 0,24	5,43 0,15	5,55 0,35	4,88 0,27	5,36 0,20	0,002	0,979	0,29	0,881	0,644	5,37 0,11	,192
Uric acid Ex, mM/d	4,01 0,56	4,25 0,25	3,71 0,45	3,44 0,30	3,29 0,38	0,002	0,940	0,89	0,476	0,412	3,00 0,08	,250
Sodium Ex, mM/d	238 37	221 14	189 21	217 24	194 22	0,002	0,953	0,69	0,601	0,323	154 3	,211
Chloride Ex, mM/d	206 26	235 19	186 20	187 20	190 22	0,002	0,930	0,79	0,539	0,160	167,5 3	,172
Chloride P, mM/L	106 2,2	99,3 1,2	99,8 1,7	104 1,6	106,0 1,0	0,004	0,978	0,37	0,832	0,468	101,5 0,4	,032
C-Reactive Prot., µg/L	2,92 0,18	2,54 0,11	2,64 0,26	2,14 0,20	2,50 0,15	0,002	0,981	0,28	0,893	0,644	2,18 0,08	,324
TNF-α, ng/L	6,94 0,42	6,06 0,25	6,29 0,60	5,15 0,46	5,97 0,33	0,002	0,981	0,28	0,893	0,644	4,90 0,17	,326
Interleukin-1, ng/L	4,69 0,30	5,06 0,21	4,62 0,30	4,49 0,35	4,78 0,43	0,002	0,943	0,85	0,500	0,232	4,51 0,08	,172
Interleukin-6, ng/L	7,22 0,76	4,62 0,55	4,76 0,91	3,64 0,81	4,61 0,88	0,002	0,955	0,65	0,626	0,673	4,25 0,15	,324
Bacteriuria, lgCFU/mL	0,59 0,26	1,55 0,17	1,13 0,25	1,23 0,27	1,24 0,25	0,003	0,961	0,43	0,789	0,307	0	**,98**

The 27-dimensional space of discriminant variables transforms into 4-dimensional space of a canonical roots. For Root 1 r*=0,981 (Wilks' Λ=0,0023; $\chi^2_{(108)}$=432; $p<10^{-6}$), for Root 2 r*=0,855 (Wilks' Λ=0,0609; $\chi^2_{(78)}$=199; $p<10^{-6}$), for Root 3 r*=0,776 (Wilks' Λ=0,227;

$\chi^2_{(50)}$=105; p<10^{-5}), and for Root 4 r*=0,655 (Wilks' Λ=0,571; $\chi^2_{(24)}$=40; p=0,022). The first root contains 83,8% of discriminative opportunities, the II 8,9%, the III 5,0%, the last 2,3%.

Table 4 presents raw and standardized coefficients for discriminant variables, which are used for the calculation of the discriminant root values for each person, which enables the visualization of each patient in the information space of the roots (Fig. 2).

Table 4. Standardized and Raw Coefficients and Constants for Variables

Coefficients	Standardized			Raw		
Variables currently in the model	Root 1	Root 2	Root 3	Root 1	Root 2	Root 3
BP Systolic, mmHg	-1,382	-0,101	0,060	-0,285	-0,021	0,012
Sex Index (Male=1;Female=2)	0,030	-0,784	0,906	0,079	-2,047	2,366
Sodium P, mM/L	0,248	-0,917	0,255	0,031	-0,115	0,032
T3-β PSD, %	-0,036	-0,188	-1,001	-0,0025	-0,0132	-0,070
IgA Serum, g/L	0,178	-0,156	-0,724	0,387	-0,339	-1,574
Phagocytosis Index vs Staph. aur., %	0,009	1,053	-0,348	0,008	0,909	-0,301
Potassium Plasma, mM/L	0,361	-0,764	0,307	0,677	-1,432	0,574
Deviation-δ, Hz	0,251	-0,419	0,261	1,000	-1,671	1,040
P3-δ PSD, %	0,368	-0,361	-0,453	0,021	-0,021	-0,026
F7-α PSD, %	0,680	-0,406	-0,985	0,049	-0,029	-0,071
LF PSD nu, %	0,108	0,275	0,821	0,007	0,017	0,052
CD4⁺ T-helper Lymphocytes, %	-0,329	0,137	-0,564	-0,046	0,019	-0,079
Potassium Excretion, mM/d	0,020	-0,597	-0,049	0,0006	-0,016	-0,0014
Calcium Excretion, mM/d	0,047	0,558	-0,598	0,016	0,186	-0,199
Circulating Immune Complex, units	0,066	-0,603	0,390	0,0043	-0,039	0,025
Testosterone, Z	-0,278	0,057	-0,646	-0,169	0,035	-0,393
CD4⁺CD25⁺ T-regulatory Lymphoc, %	-0,248	0,576	-0,523	-0,061	0,142	-0,129
Deviation-α, Hz	0,001	0,241	-0,209	0,0029	0,501	-0,433
Cortisol, nM/L	0,011	-0,207	0,076	0,0001	-0,0012	0,0004
O1-θ PSD, %	-0,576	-0,041	-0,285	-0,129	-0,009	-0,064
Index-α, %	-0,692	-0,003	-1,056	-0,026	-0,0001	-0,040
C3-δ PSD, %	-0,442	-0,011	-0,891	-0,024	-0,0006	-0,048
F8-β PSD, %	-0,232	-0,234	-0,679	-0,013	-0,013	-0,039
Fp2-α PSD, %	-0,250	0,508	0,603	-0,017	0,034	0,041
Microbial Count Staph. aur., Bac/Ph	-0,179	-0,371	0,399	-0,022	-0,045	0,049
Phosphate Plasma, mM/L	-0,004	0,452	-0,132	-0,022	2,282	-0,668
Magnesium Plasma, mM/L	0,088	0,343	-0,122	2,267	8,847	-3,150
	Constants			33,79	-68,69	30,55
	Eigenvalues			25,85	2,727	1,514
	Cumulative proportions			0,838	0,927	0,976

Table 5 shows the correlation coefficients of BP and tensioregulome with canonical discriminant roots; the cluster centroids of roots; and Z-scores of the variables. In addition, in view of the previously stated remark, extra-model variables are also included in the table.

Table 5. Correlations Variables-Canonical Roots, Means of Roots and Z-scores of Blood Pressure and Neuro-Endocrine, Immune and Metabolic (Tensioregulome) Variables

Variables currently in the model	Correlations Variables-Roots			AH II (11)	AH I (35)	High N (13)	Norm (16)	Low N (13)
Root 1 (83,8%)	**R 1**	**R 2**	**R 3**	**-8,8**	-2,4	+1,1	**+3,8**	**+8,1**
BP systolic	**-0,744**	-0,111	0,015	**+3,15**	+1,54	+0,64	+0,04	**-0,84**
BP diastolic				**+1,79**	+1,31	+0,35	-0,19	**-1,14**
Sodium Excretion				**+2,58**	+2,07	+1,07	+1,95	+1,23

Chloride Excretion				+2,74	+2,37	+1,45	+2,29	+1,36
Age				+0,92	-0,04	+0,10	-0,18	-0,52
Testosterone	-0,036	-0,025	-0,059	+0,84	+0,37	+0,74	-0,35	-0,11
Cortisol	-0,015	-0,039	-0,045	+0,89	+0,04	+0,68	+0,15	+0,19
C3-β PSD				+0,16	+0,08	+0,11	-0,36	-0,83
T4-α PSD				+0,18	+0,02	-0,48	-0,15	-0,31
F3-α PSD				-0,10	-0,24	-0,20	-0,14	-0,39
Phosphate Plasma	-0,044	0,075	-0,043	-0,58	-0,89	-0,57	-0,98	-1,49
Magnesium Plasma	-0,017	0,014	0,075	-1,02	-1,49	-1,21	-1,15	-1,56
C3-δ PSD	0,035	-0,108	-0,088	+0,14	-0,01	+0,33	0,04	+0,92
P3-δ PSD	0,026	-0,084	-0,061	-0,02	+0,12	+0,03	-0,04	+0,63
Deviation-δ	0,033	-0,124	0,023	-0,13	+0,10	-0,47	-0,05	+0,67
Triangular Index HRV				-1,13	-0,04	-0,15	-0,40	+1,03
Phagocytose Index vs St. aur.	0,035	0,069	-0,009	+0,14	+0,18	+0,59	+0,53	+0,35
Microbial Count for St. aur.	0,036	0,025	0,114	-0,19	-0,03	+0,16	+0,26	+0,23
Root 2 (8,9%)	R 1	R 2	R 3	-2,4	+0,6	+1,5	+1,3	-2,7
Sex Index	0,043	-0,272	0,118	+0,32	-0,27	-0,54	+0,05	+0,94
Sodium Plasma	0,023	-0,222	0,167	+0,71	-1,05	-0,93	+0,07	+0,65
Chloride Plasma				+1,45	-0,67	-0,54	+0,69	+1,38
Potassium Plasma	0,024	-0,182	-0,071	-0,12	-0,69	-0,43	-0,70	+0,35
CD4⁺ T-helper Lymphocytes	0,036	-0,180	-0,068	-0,89	-1,87	-0,99	-1,39	-0,55
Circulating Immune Compl	0,004	-0,168	0,053	-0,17	-0,62	-0,84	-0,60	-0,11
IgA Serum	0,009	-0,127	-0,025	+0,50	-0,94	+0,13	-0,31	+0,13
O1-θ PSD	0,012	-0,104	-0,092	+0,05	-0,01	-0,01	-0,26	+0,43
F7-α PSD	-0,026	-0,104	-0,068	+0,09	-0,03	-0,45	-0,63	-0,07
Root 3 (5,0%)	R 1	R 2	R 3	+0,6	-0,2	-2,0	+2,0	-0,5
T3-β PSD	-0,014	-0,008	-0,286	-0,15	-0,15	+0,55	-0,79	-0,15
F8-β PSD	-0,020	0,010	-0,181	-0,19	+0,24	+0,14	-0,63	-0,15
F3-β PSD				-0,10	+0,02	+0,09	-0,90	-0,78
T5-β PSD				-0,16	+0,15	+0,42	-0,58	-0,26
O1-β PSD				+0,37	+0,12	-0,01	-0,70	-0,56
Deviation-α	0,018	-0,074	-0,115	-0,29	+0,17	-0,21	-0,39	+0,39
Entropy PSD O2				-0,15	+0,24	+0,04	-0,78	-0,18
O2-θ PSD				-0,08	+0,11	+0,05	-0,24	+0,10
Cholesterol				+0,27	+0,12	+0,13	-0,43	+0,05
Body Mass Index				+1,15	+1,02	+0,93	+0,41	+1,00
Interleukin-6				+2,16	+0,27	+0,37	-0,44	+0,26
Tumor Necrosis Factor-α				+1,28	+0,73	+0,87	+0,15	+0,67
C-Reactive Protein				+1,05	+0,57	+0,65	-0,05	+0,45
LF PSD nu	-0,035	0,125	0,220	+0,68	+0,51	+0,34	+1,28	-0,34
Baevskiy's Stress Index				+1,51	+0,75	-0,25	+1,26	-0,62
Index-α	0,021	0,018	0,131	-0,04	-0,08	-0,12	+0,42	+0,09
Fp2-α PSD	0,017	0,017	0,088	-0,34	-0,11	-0,39	+0,09	-0,07
F4-α PSD				-0,26	-0,16	-0,24	+0,00	-0,20
Root 4 (2,3%)	R 1	R 2	R 4	-0,9	+0,9	-1,2	-0,5	+0,3
Calcium Excretion	-0,010	0,062	0,320	-0,68	+1,92	+0,54	-0,48	+0,47
Potassium Excretion	-0,025	0,038	0,107	+0,43	+0,80	+0,36	+0,05	-0,11
Uric acid Excretion				+1,35	+1,67	+0,95	+0,58	+0,38
CD4⁺CD25⁺ T-regulatory Ly	-0,014	0,109	0,117	+0,95	+1,85	+1,07	+1,74	+0,47
Interleukin-1				+0,17	+0,65	+0,09	-0,07	+0,29
C4-θ PSD				-0,36	+0,59	-0,34	-0,29	+0,16
Fp1-θ PSD				-0,16	+0,50	-0,61	-0,44	+0,06
Bacteriuria				+0,60	+1,58	+1,15	+1,25	+1,26

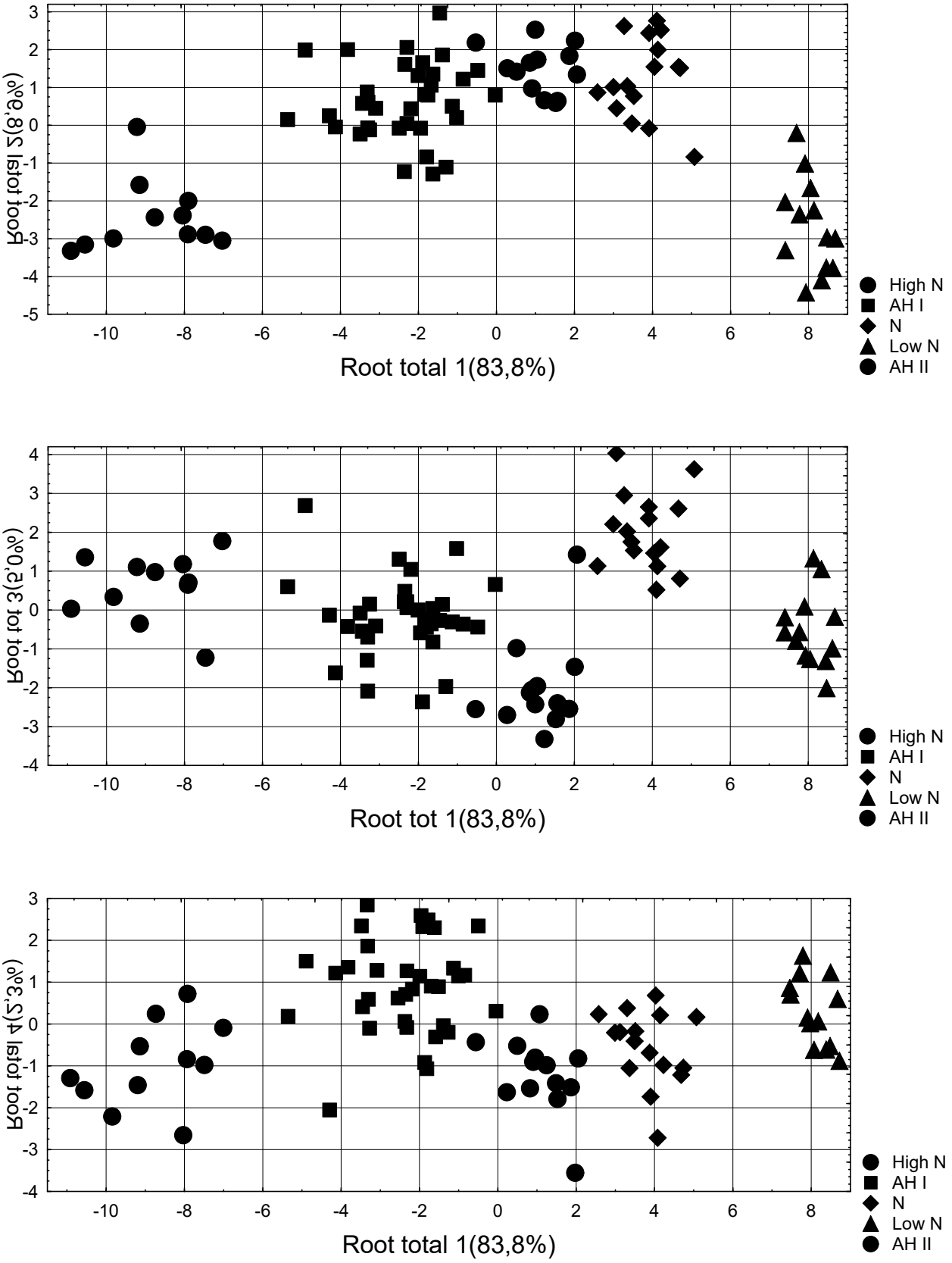


Fig. 2. Scattering of individual values of the discriminant roots of patients of different blood pressure clusters

The localization along the major root axis of the patients with **AH II** (Fig. 2) in the extreme left (negative) zone reflects combination of maximum for sampling BP levels with **maximally increased** sodium and chloride excretion, plasma testosterone and cortisol levels, normal, but maximum for the sample levels of PSD of beta-rhythm in C3 locus and alpha-rhythm in T4 and F3 loci, as well as minimally decreased plasma phosphate and magnesium levels. In addition, such patients are the oldest in the sample. On the other hand, **AH II** is accompanied by a **decreased** vagal tone (triangular index as marker), normal, but minimum for the sample levels of deviation of delta-rhythm and its PSD in C3 and P3 loci as well as activity and intensity of phagocytosis of Staph. aureus. At the opposite pole of the axis of the first root, there are patients with **Low Norm** BP, whose minimum BP is accompanied by, as a rule, **minimum** for the sample levels of the listed variables correlated with root inversely while **maximally** levels of variables correlated with root direct. In addition, such patients are the youngest in the sample. Clusters of patients with intermediate BP levels are also characterized by intermediate levels of the listed variables. Therefore, all 5 clusters are quite clearly demarcated already in the space of the major root.

Additional demarcation of patients with **AH II** and **Low Norm** BP occurs along the axis of the second root, the bottommost position of which reflects the **maximal** for the sample the PSD of alpha-rhythm in F7 locus and theta-rhythm in O1 locus, plasma levels of sodium, chloride and potassium, serum levels of IgA and CIC as well as minimal decreased blood level of T-helper lymphocytes. In addition, among the patients of both clusters, the share of women is the maximum for the sample (positive sex index).

Patients with **Norm** BP, in turn, are additionally distinguished from others along the axis of the third root due to a **maximally suppressed** deviation of alpha-rhythm, PSD of beta-rhythm in 5 loci and theta-rhythm in O2 locus, entropy of PSD in O2 locus, plasma cholesterol and IL-6 levels as well as minimum for the sample levels of TNF-alpha and C-RP, and body mass index. On the other hand, a normal BP level is accompanied by normal, but maximum for the sample the index and PSD of alpha-rhythm in Fp2 and F4 loci, as well as maximally increased sympathetic tone, which is quite surprising, but the fact. This will be the subject of a special discussion in the next article, and now we will limit ourselves to indicating the leading role in this situation the enhancing of beta-adrenergic vasodilatory outflows, reduction of ACE2 in the brain [6] and decrease in production of pro-inflammatory cytokines, however increasing anti-inflammatory cytokines such as IL-10 [26] while alpha-adrenergic receptors have predominantly pro-inflammatory and vasoconstrictory actions [26].

Finally, along the axis of the fourth root, the top positions are occupied by clusters of patients with **AH I**, which reflects their **maximum increased** levels of calcium, potassium and uric acid excretion, PSD of theta-rhythm in C4 and Fp1 loci, blood content of T-regulatory lymphocytes and IL-1 as well as bacteriuria as marker of pyelonephritis.

In general, all clusters on the planes of four roots are clearly delineated, which is documented by calculating the Mahalanobis distances (Table 6).

Table 6. Squared Mahalanobis Distances between Blood Pressure Clusters and F-values (df=27,6; for High N-N $p=10^{-6}$; for other pairs $p<10^{-6}$)

Blood Pressure Clusters	High Norm	AH I	Norm	Low Norm	AH II
High Norm	0	**20,6**	**24,0**	**70,4**	**120**
AH I	**4,96**	0	**45,8**	**121**	**54,2**
Norm	**4,38**	**12,8**	0	**40,7**	**175**
Low Norm	**11,6**	**29,1**	**7,43**	0	**287**
AH II	**18,2**	**11,6**	**29,0**	**43,5**	0

The same discriminant parameters can be used to identify the belonging of one or another person to one or another blood pressure cluster (Table 7).

In this case, we can retrospectively recognize patients with one mistake only. Overall classification accuracy is 98,9% (Table 8).

Table 7. Coefficients and Constants for Classification Functions for Blood Pressure Clusters

Blood Pressure Clusters	High N	AH I	Norm	Low N	AH II
Variables currently in the model	p=,148	p=,398	p=,182	p=,148	p=,125
BP Systolic, mmHg	7,735	8,793	7,024	5,874	10,67
Sex Index (M=1;F=2)	-186,1	-178,1	-175,2	-171,9	-172,5
Sodium P, mM/L	-8,579	-8,630	-8,371	-7,905	-8,365
T3-β PSD, %	1,660	1,530	1,366	1,576	1,552
IgA Serum, g/L	-12,20	-18,19	-18,07	-11,94	-19,04
Phagocytosis Index vs Staph. aur., %	210,8	210,1	209,6	207,1	206,5
Potassium Plasma, mM/L	-85,29	-85,34	-80,81	-73,72	-84,89
Deviation-δ, Hz	-65,16	-62,72	-57,05	-47,79	-65,50
P3-δ PSD, %	-0,394	-0,453	-0,422	-0,167	-0,584
F7-α PSD, %	2,420	2,173	2,284	2,797	1,870
LF PSD nu, %	0,650	0,721	0,877	0,713	0,651
$CD4^+$ T-helper Lymphocytes, %	-2,295	-2,545	-2,820	-2,993	-2,151
Potassium Excretion, mM/d	-0,322	-0,304	-0,320	-0,245	-0,266
Calcium Excretion, mM/d	17,17	16,67	16,39	16,26	15,78
Circulating Immune Complex, units	-3,349	-3,252	-3,217	-3,097	-3,170
Testosterone, Z	22,10	21,92	20,05	20,17	22,62
$CD4^+CD25^+$ T-regulatory Lymphoc, %	19,64	19,35	18,88	18,33	19,34
Deviation-α, Hz	50,34	51,18	49,16	49,12	47,49
Cortisol, nM/L	-0,153	-0,157	-0,153	-0,151	-0,148
O1-θ PSD, %	0,605	1,009	0,020	-0,307	1,760
Index-α, %	2,931	2,988	2,712	2,717	3,091
C3-δ PSD, %	3,954	3,963	3,703	3,730	4,069
F8-β PSD, %	1,167	1,172	0,984	1,085	1,252
Fp2-α PSD, %	-0,715	-0,643	-0,615	-0,938	-0,580
Microbial Count Staph. aur., Bac/Ph	-16,01	-15,86	-15,88	-15,94	-15,49
Phosphate Plasma, mM/L	179,1	172,2	174,6	165,7	168,1
Magnesium Plasma, mM/L	-109,2	-155,5	-125,8	-153,2	-177,6
Constants	-9960	-9988	-9744	-9444	-9988

Table 8. Classification Matrix for Blood Pressure Clusters

	Rows: Observed classifications Columns: Predicted classifications					
Group	Percent Correct	High N p=,14773	AH I p=,39773	N p=,18182	Low N p=,14773	AH II p=,12500
High N	92,3	12	0	1	0	0
AH I	100,0	0	35	0	0	0
N	100,0	0	0	16	0	0
Low N	100,0	0	0	0	13	0
AH II	100,0	0	0	0	0	11
Total	98,9	12	35	17	13	11

At the next stage, an analysis of the correlations between the average Z-scores of systolic and diastolic BP, on the one hand, and the variables whose information is condensed in four discriminant roots, as well as not included in the model (see please Table 5), on the other hand, was performed.

A strong positive linear relationship between BP and the constellation of 3 EEG, 2 endocrine and 4 metabolic (more precisely, electrolyte) variables as well as age (Fig. 3), which obviously has an upregulating effect on the BP, was revealed.

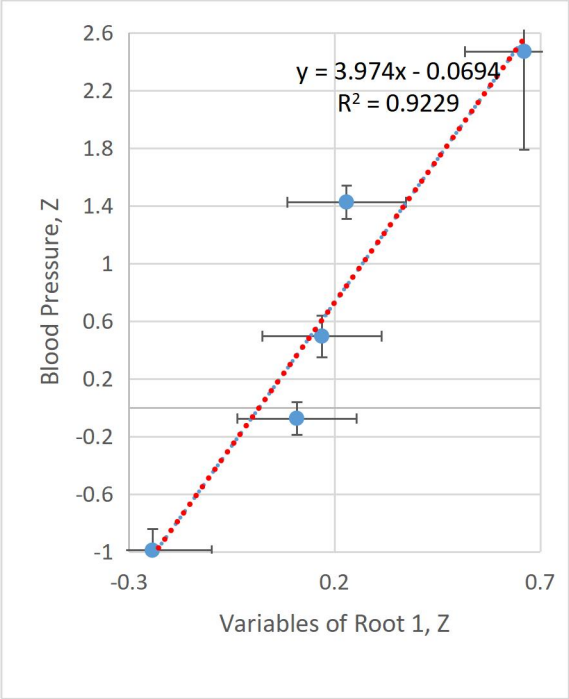


Fig. 3. Scatterplot of correlation between means of 10 variables of Root 1 (X-line) and means of systolic and diastolic blood pressure (Y-line)

Instead, the activity of delta-rhythm generating brain structures, vagal tone as well as the activity of microphages-neutrophils are negatively correlated with BP (Fig. 4).

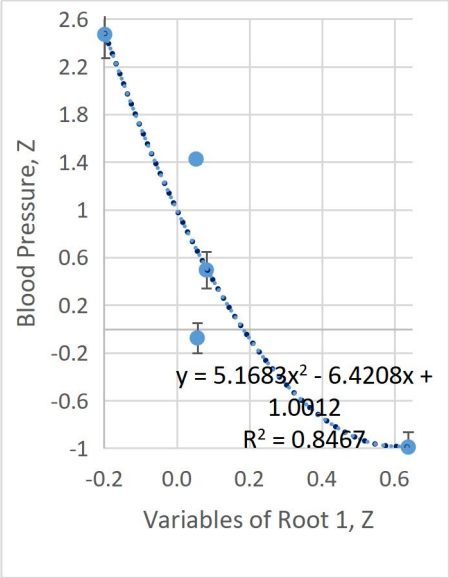


Fig. 4. Scatterplot of correlation between means of 6 variables of Root 1 (X-line) and means of systolic and diastolic blood pressure (Y-line)

If the downregulating vagal effect is quite expected and understandable, then the physiological basis of the negative relationship between phagocytosis and BP needs clarification and will be the subject of discussion.

In contrast to the described quazi-linear both direct and inverse relationships between BP and 16 variables, its relationship with 9 variables associated with the second root is non-linear, and satisfactorily approximated only by a third-order curve (Fig. 5). There is a paradoxical situation when the "extremes converge", that is, patients with extreme BP levels (AH II and Low Norm) are characterized by almost identical and maximal for the sample levels of variables. In particular, increased plasma levels of sodium and chloride, quasi-normal levels of potassium, IgA and CIC as well as PSD of O1-θ and F7-α rhythms, and reduced levels of T-helper lymphocytes. In addition, women predominate in both clusters. Instead, the intermediate values of the same variables decrease linearly from patients with AH I to Norm BP.

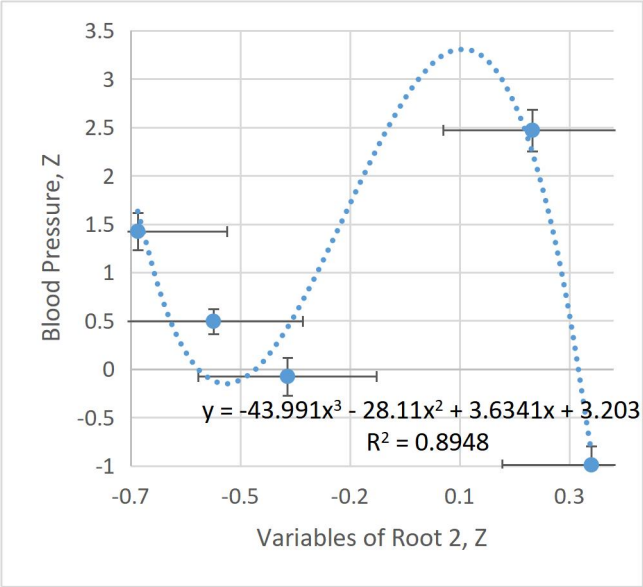


Fig. 5. Scatterplot of correlation between means of 9 variables of Root 2 (X-line) and means of systolic and diastolic blood pressure (Y-line)

Relationships of BP with variables related to the third root are approximated by curves of the second order (Figs. 6 and 7).

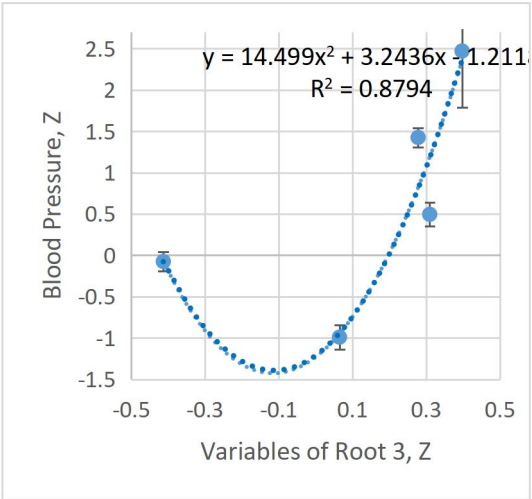


Fig. 6. Scatterplot of correlation between means of 13 variables of Root 3 (X-line) and means of systolic and diastolic blood pressure (Y-line)

Figure 6 illustrates that patients with normal BP are characterized by reduced levels of PSD of beta-rhythm in 5 loci and entropy in O2 locus, as well as normal, but minimal for the sample PSD of theta-rhythm in O2 locus and deviation of alpha-rhythm. This is combined with normal, but minimal for the sample, levels of body mass index, cholesterol and pro-inflammatory factors. It is interesting that these same parameters increase not only as BP increases, but also when it decreases.

An almost mirror-image figure 7 illustrates the presence in normotensive patients of increased sympathetic tone and normal, but maximal for the sample of three parameters of the alpha-rhythm, while these parameters are lower in both hypotensive and hypertensive patients.

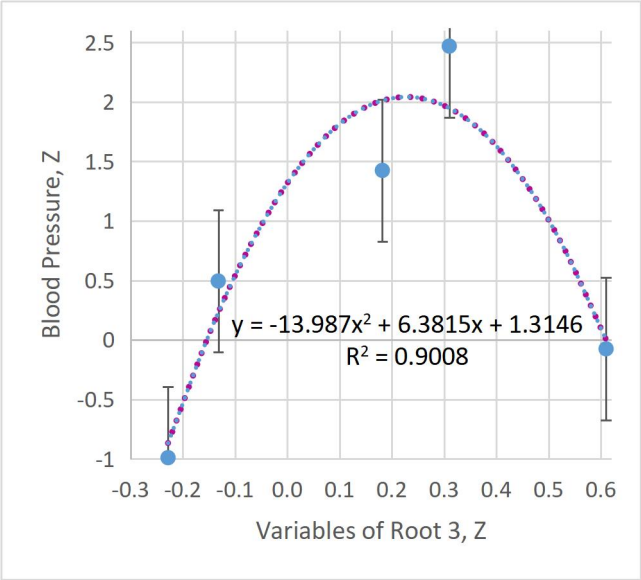


Fig. 7. Scatterplot of correlation between means of 5 variables of Root 3 (X-line) and means of systolic and diastolic blood pressure (Y-line)

The U-shaped form of the graph shown in fig. 8, illustrates situations in which 2 EEGs, 3 metabolic, and 2 immune variables, as well as bacteriuria are equally minimal in patients with both AH II and Norm BP, slightly higher and also the same in both High Norm and Low Norm BP , instead, are maximally increased in patients with AH I.

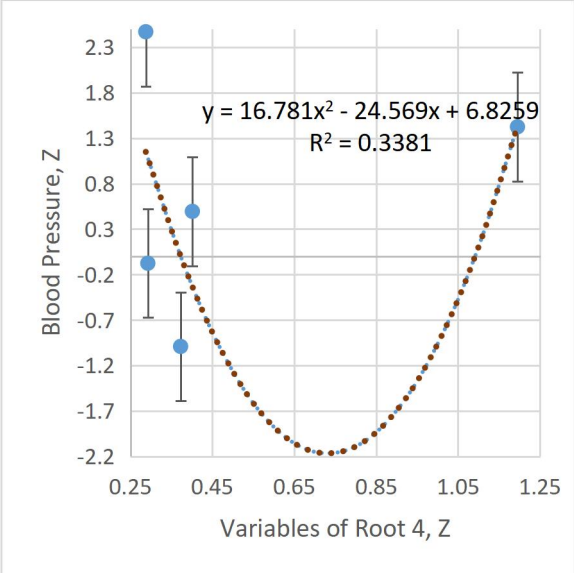


Fig. 8. Scatterplot of correlation between means of 8 variables of Root 4 (X-line) and means of systolic and diastolic blood pressure (Y-line)

Allow us to transfer the interpretation of nonlinear relationships to the next article, and now focus on the construction of regression models based on the correlation matrix (Table 9).

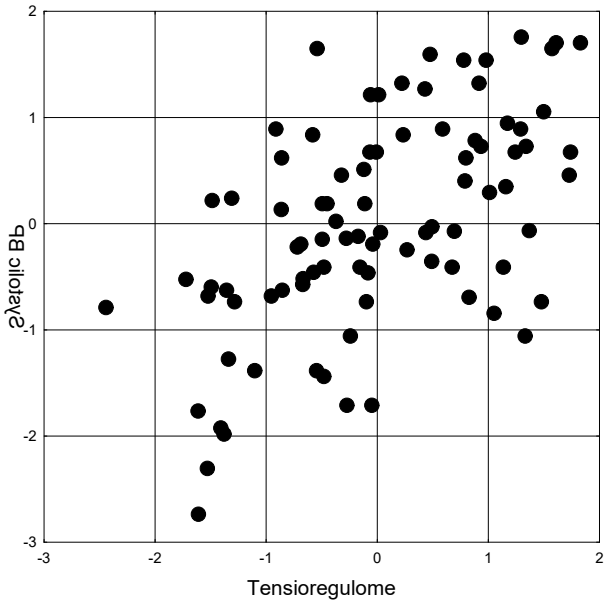
Table 9. Matrix of correlations between BP and tensioregulome parameters

variable	Correlations PS	PD
IL-6	0,235	0,109
Sex	-0,195	-0,436
Age	0,368	0,175
LFnu	0,185	0,251
Dev Alpha	-0,062	-0,178
Index Alpha	-0,153	-0,266
F3-B%	0,304	0,330
C3-B%	0,298	0,226
O1-B%	0,330	0,271
EUA	0,251	0,379
ECl	0,100	0,252
ENa	0,117	0,243

After step-by-step elimination until the maximum value of Adjusted R^2 was reached, only 4 upregulating variables remained in the regression model for systolic BP, which, taken together, determine its level by 31,7% (Table 10 and Fig. 9).

Table 10. Regression Summary for Blood Pressure Systolic
R=0,563; R^2=0,317; Adjusted R^2=0,284; $F_{(4,8)}$=9,6; $p<10^{-5}$; SD: 15,7 mmHg

		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(83)}$	p-level
Variables	r		Intercpt	88,6	9,0	9,84	10^{-6}
Age, years	**0,37**	0,348	0,104	0,511	0,153	3,33	0,001
O1-β PSD, %	**0,33**	0,268	0,092	0,338	0,116	2,90	0,005
Uric acid Excretion, mM/d	**0,25**	0,300	0,093	3,689	1,147	3,22	0,002
Interleukin-6, ng/L	**0,24**	0,108	0,102	0,773	0,727	1,06	0,291

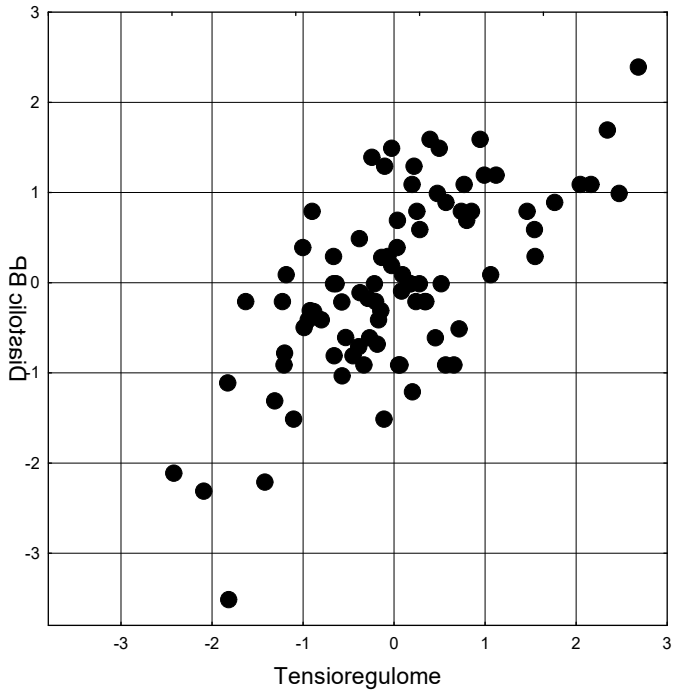


R=0,563; R^2=0,317; $\chi^2_{(4)}$=32,0; $p<10^{-5}$; Λ Prime=0,682
Fig. 9. Scatterplot of canonical correlation between Tensioregulome (X-line) and Systolic Blood Pressure (Y-line)

The tensioregulome of diastolic BP is more numerous and includes both upregulating and downregulating factors, the constellation of which determines its level by 45.9% (Table 11 and Fig. 10).

Table 11. Regression Summary for Blood Pressure Diastolic
R=0,677; R^2=0,459; Adjusted R^2=0,396; $F_{(9,8)}$=7,3; $p<10^{-5}$; SE: 7,8 mmHg

		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(78)}$	p-level
Variables	r		Intercpt	74,8	7,5	9,92	10^{-6}
Uric acid Excretion, mM/d	**0,38**	0,282	0,093	1,881	0,622	3,02	0,003
F3-β PSD, %	**0,33**	0,294	0,140	0,249	0,119	2,10	0,039
LF PSD nu, %	**0,25**	0,159	0,087	0,096	0,052	1,83	0,071
NaCl Excretion, mM/d	**0,25**	0,105	0,093	0,011	0,009	1,13	0,263
C3-β PSD, %	**0,23**	-0,235	0,139	-0,217	0,128	-1,69	0,095
Age, years	**0,18**	0,171	0,093	0,136	0,074	1,84	0,069
Sex Index	**-0,44**	-0,294	0,092	-7,013	2,198	-3,19	0,002
Index-α, %	**-0,27**	-0,241	0,097	-0,092	0,037	-2,48	0,015
Deviation-α, Hz	**-0,18**	-0,106	0,091	-2,177	1,861	-1,17	0,246



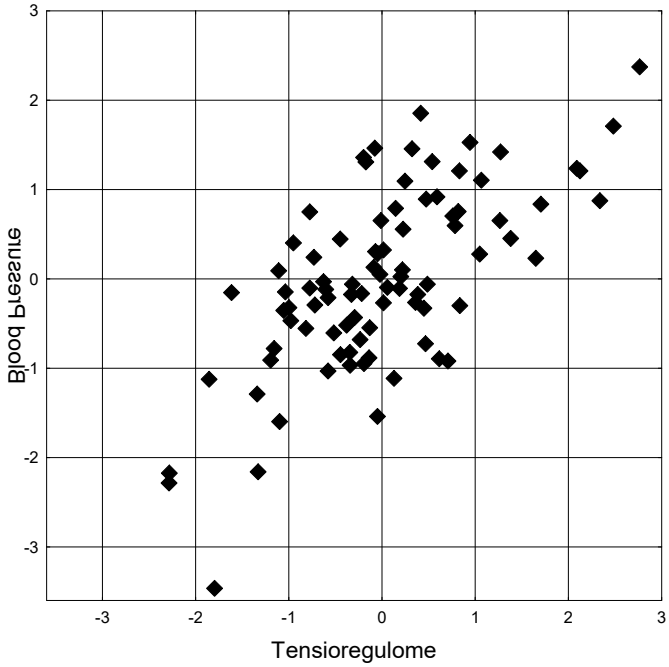
R=0,677; R^2=0,459; $\chi^2_{(9)}$=50; $p<10^{-6}$; Λ Prime=0,541
Fig. 10. Scatterplot of canonical correlation between Tensioregulome (X-line) and Diastolic Blood Pressure (Y-line)

In conclusion, we will analyze the canonical correlation between both BP parameters and the constellation of Tensioregulome.

As we can see, the degree of determination of BP by the factors involved in its regulation does not increase significantly (Table 12 and Fig. 12).

Table 12. Factor loads on canonical Roots of Tensioregulome (left set) and Blood Pressure (right set)

Left set	R
Uric acid Excretion, mM/d	-0,555
F3-β PSD, %	-0,469
Chloride Excretion, mM/d	-0,380
O1-β PSD, %	-0,373
LF PSD nu, %	-0,365
Sodium Excretion, mM/d	-0,363
C3-β PSD, %	-0,308
Age, years	-0,217
Interleukin-6, ng/L	-0,134
Sex Index	0,654
Index-α, %	0,393
Deviation-α, Hz	0,270
Right set	R
Systolic Blood Pressure	-0,997
Diastolic Blood Pressure	-0,606



$R=0,681$; $R^2=0,464$; $\chi^2_{(24)}=75$; $p<10^{-6}$; Λ Prime=0,391

Fig. 12. Scatterplot of canonical correlation between Tensioregulome (X-line) and Systolic&Diastolic Blood Pressure(Y-line)

CONCLUSION

So, the qualitative-quantitative clusters of blood pressure are very clearly different from each other by age, sex and the constellation of neuro-endocrine, immune and metabolic variables, which we called the tensioregulome.

Our data, first of all, are consistent with the classical notions of downregulation of BP by vagal tone and factors linked to female sex, instead of upregulation by factors linked to male sex and age, as well as by sympathetic tone, NaCl and uric acid [6].

Recent laboratory evidence has defined a link between inflammation and the immune system in initiation and progression of hypertension. Moreover, cross-talk among natural

killer cells, adaptive immune cells (T cells and B cells), and innate immune cells (i.e. monocytes, macrophages, neutrophils, and dendritic cells) contributes to end-cardiovasculature damage and dysfunction in hypertension [24,25,27]. Cells in innate immune system produce ROS, such as superoxide and hydrogen peroxide, which aimed at killing pathogens. Long-term inflammation process increases ROS production, causing oxidative stress which leads to endothelial dysfunction. Endothelial function is to regulate blood vessel tone and structure. When inflammation lasts, NO bioavailability decreases, disrupting its main function as vasodilator, so that blood vessels relaxation and vasodilatation are absent [2]. It is important that the role of adaptive immunity is sex-specific with much more pronounced mechanisms in males than that in females [20]. It is known that both CR-mediated and FcγR-mediated phagocytosis increases levels of pro-inflammatory factors such as IL-6, TNF-α, IL-1β, and MMP-9 [1]. Cytokines released from immune cells, promote both renal and vascular dysfunction and damage, leading to enhanced sodium retention and increased systemic vascular resistance. Recent experiments have defined a link between oxidative stress and immune activation in hypertension [19]. In our study, it was shown that the levels of IL-6, TNF-α, and C-RP are normal in patients with normal BP, instead, they increase both when it increases and when it decreases. However, our data disagree with the concept that the hypertensive responses can be inhibited by T regulatory lymphocytes and their anti-inflammatory IL-10 [20,25].

In our humble opinion, what is new is the discovery of relationships between BP and EEG parameters, which, in turn, are related to immunity parameters [15,16,23].

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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 parent of 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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