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RELATIONSHIPS BETWEEN PARAMETERS OF NITROGENOUS METABOLITES AND HRV IN HUMANS EXPOSED TO THE FACTORS OF THE ACCIDENT AT THE CHORNOBYL NUCLEAR POWER PLANT

Igor L. Kuchma[1], Anatoliy I. Gozhenko[1], Volodymyra R. Bilas[5], Bohdan Y. Huchko[5], Ruslan B. Ponomarenko[2], Yaryna V. Nahurna[3], Walery Zukow[4], Igor L. Popovych[1,5]

[1]Ukrainian Scientific Research Institute for Medicine of Transport, Odesa, Ukraine igorkuchma@ukr.net; prof.gozhenko@gmail.com;
[2]Communal Hospital, Truskavets', Ukraine
[3]Danylo Halyts'kyĭ National Medical University, L'viv, Ukraine nyv86@ukr.net
[4]Nicolaus Copernicus University, Torun, Poland w.zukow@wp.pl
[5]Bohomolets' OO Institute of Physiology of National Academy of Sciences, Kyïv, Ukraine i.popovych@biph.kiev.ua

Abstract
Background. We have previously shown that nitrogenous metabolites have immunomodulatory effects, both suppressor and enhancing, both in healthy rats and in humans exposed to pathogenic influences. The immunomodulatory effect of bilirubin is probably mediated through aryl hydrocarbon receptors, and uric acid through TL- and adenosine receptors of immune cells. The question of mediators of the immunomodulatory action of urea and creatinine remains open. We hypothesized the mediating role of mediators of the autonomic nervous system and adaptation hormones. The **aim** of this study is to analyze the relationships between the parameters of nitrogenous metabolites, on the one hand, and HRV markers of the parameters of the autonomic nervous system - on the other hand. **Material and methods**. The object of observation in 1997 were 19 men and 3 women who were exposed to pathogenic factors of the accident at the Chornobyl nuclear power plant during the liquidation of its consequences in 1986-87. The survey was conducted twice - on admission and after two weeks of rehabilitation at the Truskavets' Spa. The plasma and urinary concentration of the nitrogenous metabolites were determined. The state of the autonomic nervous system (ANS) was judged by the HRV parameters recorded before and after submaximal bicycle ergometric loading. **Results**. Both negative and positive metabolic-ANS correlations were revealed. Calculation of multiple correlation coefficients between individual metabolite parameters and constellations of HRV parameters revealed the

maximum vegetotropic effect of Urea plasma (R=0,700) and Uric acid urine (R=0,623). This is followed by Urea urine (R=0,531) and Creatinine plasma (R=0,457). No significant correlations were found for Creatinine urine, Uric acid plasma and Bilirubinemia. The canonical correlation between the constellation of nitrogenous metabolites, on the one hand, and the HRV markers of ANS, on the other hand, was strong: R=0,747; $\chi^2_{(28)}$=63; $p<10^{-3}$. **Conclusion**. Previously identified immunomodulatory effects of urea and creatinine are realized, possibly through cholinergic and adrenergic mechanisms.

Key words: **urea, uric acid, creatinine, bilirubin, HRV, relationships, humans.**

INTRODUCTION

We have previously shown that nitrogenous metabolites have immunomodulatory effects, both suppressor and enhancing, both in rats [10,11,29] and in humans [12,13,19,33]. The immunomodulatory effect of bilirubin is probably mediated through aryl hydrocarbon receptors [2,6,26,30], and uric acid through TL- and Adenosine receptors [1,7,15,16,22,23,35] of immune cells. The question of mediators of the immunomodulatory action of urea and creatinine remains open. We hypothesized the mediating role of mediators of the autonomic nervous system and adaptation hormones [19] in line with the concepts of neuroendocrine-immune complex [14,27] and functional-metabolic continuum [9]. The aim of this study is to analyze the relationships between the parameters of nitrogenous metabolites, on the one hand, and HRV markers of the parameters of the autonomic nervous system - on the other hand.

MATERIAL AND METHODS

The database of the Truskavetsian Scientific School of Balneology [18,28] was used for the research. The object of observation in 1997 were 19 men (26÷61 y) and 3 women (38, 40 and 47 y) with urolithiasis and chronic pyelonephritis who were exposed to pathogenic factors of the accident at the Chornobyl nuclear power plant during the liquidation of its consequences in 1986-87. According to the documents, the total effective radiation dose was 10÷25 cGy, which is most typical for this contingent [28,31]. The survey was conducted twice: on admission and after two weeks of rehabilitation at the Truskavets' Spa.

The plasma level of the nitrogenous metabolites determined: creatinine (by Jaffe's color reaction by Popper's method), urea (urease method by reaction with phenolhypochlorite), uric acid (uricase method) and bilirubin (by diazoreaction using the Jedrashik-Kleghorn-Grof method). The same metabolites, with the exception of bilirubin, were also determined in the morning urine. The analyzes were carried out according to the instructions described in the manual [8]. The analyzers "Pointe-180" ("Scientific", USA) and "Reflotron" (Boehringer Mannheim, BRD) were used with appropriate sets.

State of autonomous nervous system was assessed by the method of HRV using the "Cardio" device (Kyiv). The classical parameters of Baevskiy were analyzed: Mode (Mo), Amplitude of the Mode (AMo) and variational swing (MxDMn) as markers of the humoral channel of regulation, sympathetic and vagal tones respectively [3,4].

A feature of the design was the registration of HRV at rest (basal conditions, B) and immediately after the second bicycle ergometric load (L), which allowed the assessment of autonomic reactivity as L/B ratio.

A bicycle ergometer “Tunturi” (Finland) is used. The power of the first load was 0,5 W/kg at a pedaling frequency of 60-75 rpm. The power of the second load (after 3 min), according to the recommendations for a gentle version of the PWC test, taking into account the age of the subjects [5], was selected so that the HR at the end of the load was close to that calculated by the formula: HR = (220 - Age)•0,87.

Results processed by using the software package "Statistica 20".

RESULTS AND DISCUSSION

In presenting the results, we will follow the algorithm used in previous studies [19].

Screening of linear correlation coefficients between parameters of nitrogenous metabolites, on the one hand, and the recorded HRV parameters, on the other hand, revealed the following (Table 1).

As you can see, the level of Urea in plasma is negatively correlated with Mode, which is considered a marker, especially of circulating catecholamines, as well as other positive chronotropic factors (glucocorticoids, thyroid hormones, glucagon, etc.). It is noteworthy that the correlation coefficients are almost the same both in basal conditions (Fig. 1) and after muscle load (Fig. 2), which, of course, reduces Mode (increases HR).

In contrast, plasma urea correlates significantly with the marker of vagal tone only after exercise (Fig. 4), whereas in basal conditions there is no connection (Fig. 3). It should be noted that under basal conditions, normal vagus tone (0,15÷0,30 sec) [4] occurred only in 6 cases out of 44, while in 86% it was reduced, and after exercise vagus tone in 32% was normal, and another 23% - elevated.

On the other hand, the normal level of sympathetic tone (30÷50%) [4] in basal conditions occurred only in 16% of cases, and in 82% was elevated (Fig. 5). Exercise reduced the proportion of sympathicotonia to 45,5%, reciprocally increasing the proportion of vagotonia from 2% to 34% (Fig. 6). This indicates a **paradoxical** vagotonic response to the muscular load of this group of patients. Obviously, this is a manifestation of post-radiation encephalopathy [18,28,31].

Baevskyi's Stress index, which also takes into account Mode [3], is considered to be more informative for assessing the state of heart rhythm regulation systems. Eutonia is characterized by a range of 51÷199 units (or lnSI 3,93÷5,29), a range of 200÷500 units indicates sympathicotonia, and more than 500 units – hypersympathicotonia [3,21]. According to this scale, euthonia is found in only 16% of cases, while sympathicotonia - in 34%, and hypersympathicotonia - in 48%, in the only case of vagotonia.

Naturally, the level of plasma urea correlates with sympathetic tone positively, but again only after exercise (Fig. 6), whereas in basal conditions the correlation is insignificant (Fig. 5), as well as with the tone of the vagus.

Table 1. Matrix of correlations between nitrogenous metabolites and HRV parameters

Variable	Correlations						
	Urea U	UA U	Cr U	Urea P	Cr P	UA P	Bilir P
Mode Basal	-0,01	-0,04	0,09	-0,66	-0,43	-0,09	-0,07
AMo Basal	-0,35	-0,32	-0,08	-0,27	-0,16	-0,10	0,12
MxDMn Basal	0,51	0,51	-0,08	-0,13	-0,11	0,02	-0,11
ln SI Basal	-0,48	-0,43	0,03	0,14	0,10	-0,03	0,12
Mode Loading	-0,08	-0,09	0,13	-0,63	-0,42	-0,10	-0,13
AMo Loading	-0,04	0,02	0,11	0,60	0,39	0,07	-0,19
MxDMn Loading	-0,06	-0,03	0,07	-0,65	-0,43	-0,12	-0,08
ln SI Loading	0,03	0,02	-0,04	0,65	0,42	0,11	0,03
ln (SIL/SIB)	0,29	0,25	-0,05	0,48	0,31	0,11	-0,04
AMoL/AMoB	0,24	0,14	0,10	0,45	0,24	0,19	-0,23
(MxDMnL)/(MxDMnB)	-0,31	-0,33	0,04	-0,29	-0,27	-0,05	0,06

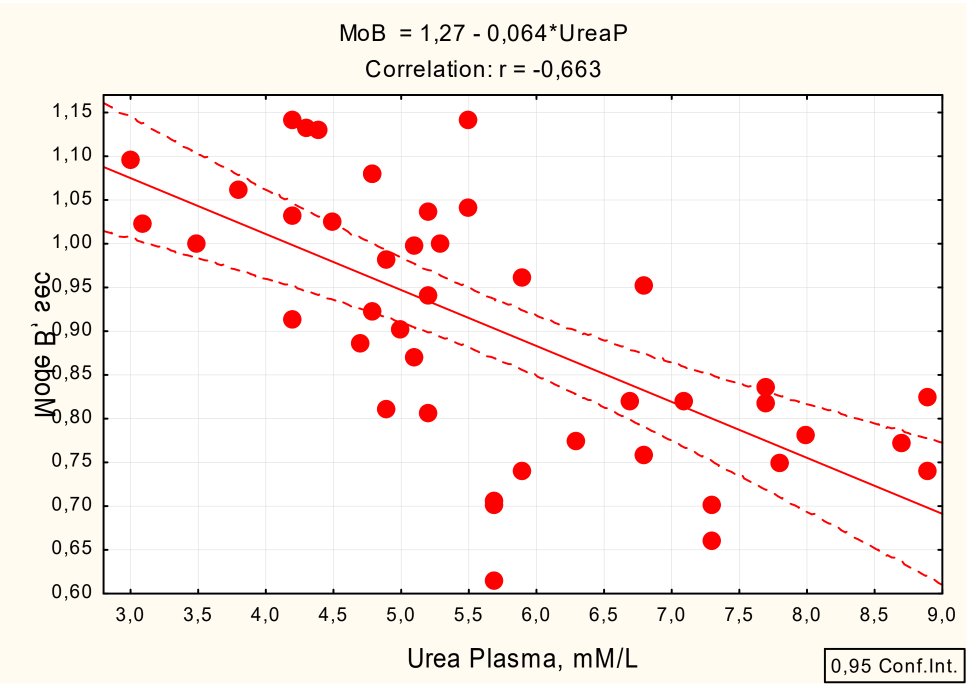


Fig. 1. Scatterplot of correlation between Urea Plasma (X-line) and Mode HRV basal (Y-line)

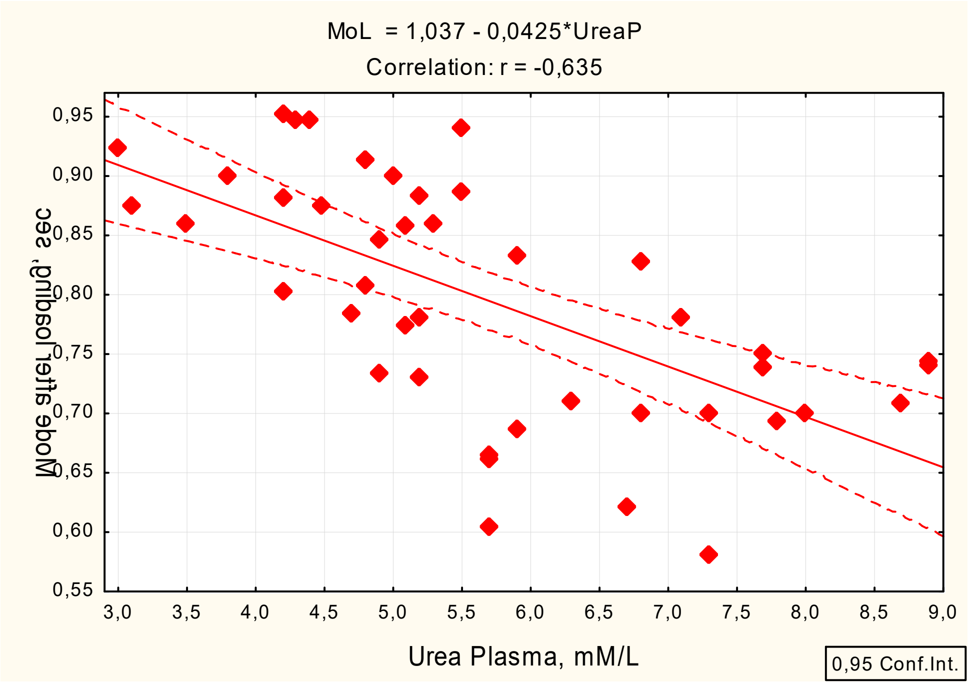


Fig. 2. Scatterplot of correlation between Urea Plasma (X-line) and Mode HRV after loading (Y-line)

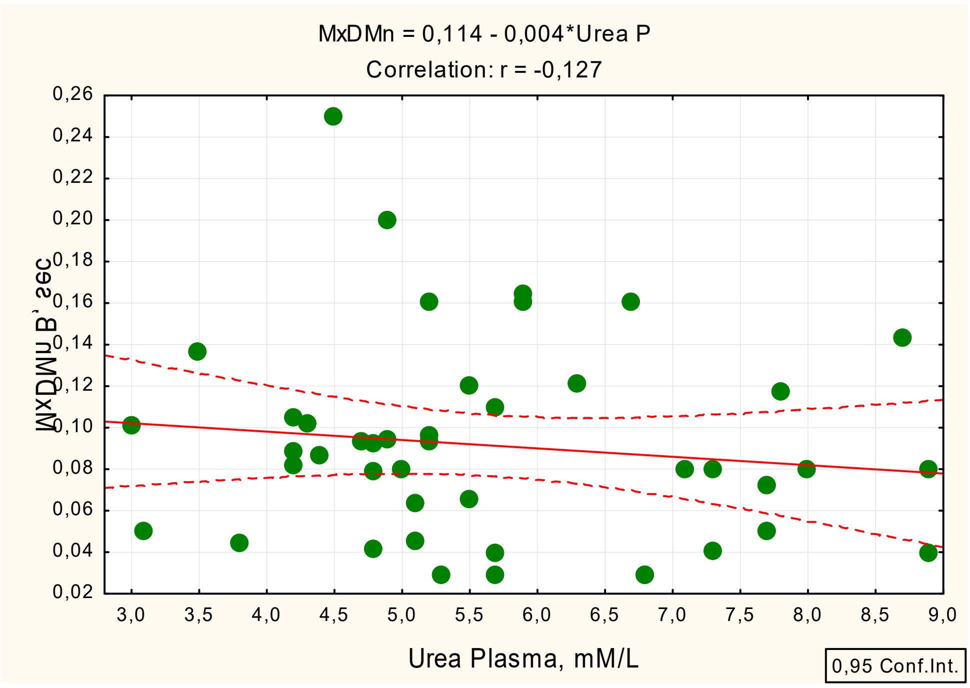


Fig. 3. Scatterplot of correlation between Urea Plasma (X-line) and MxDMn HRV basal (Y-line)

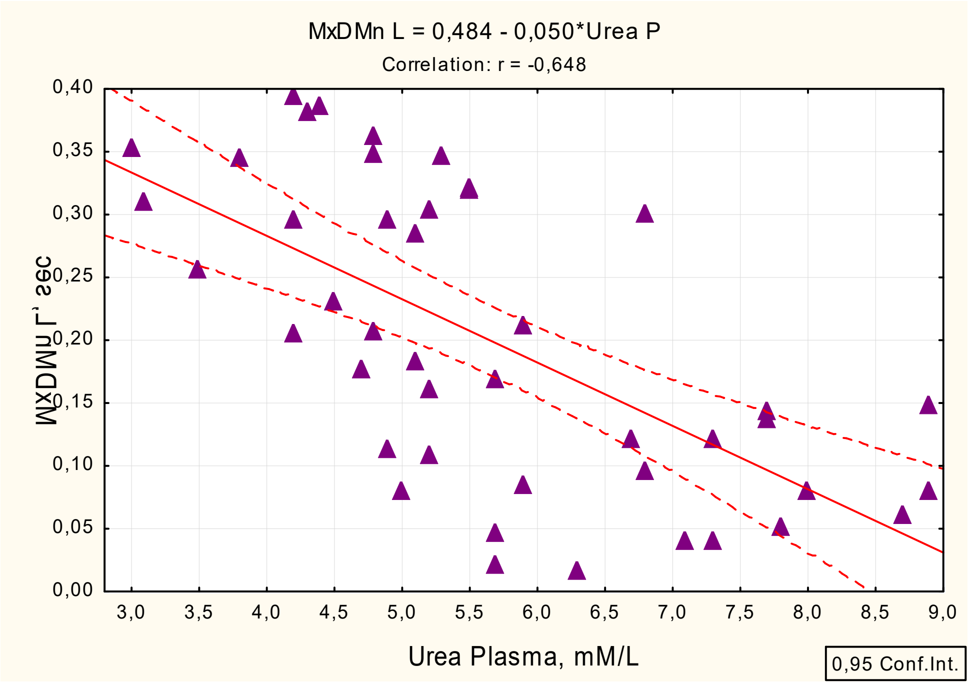


Fig. 4. Scatterplot of correlation between Urea Plasma (X-line) and MxDMn HRV after loading (Y-line)

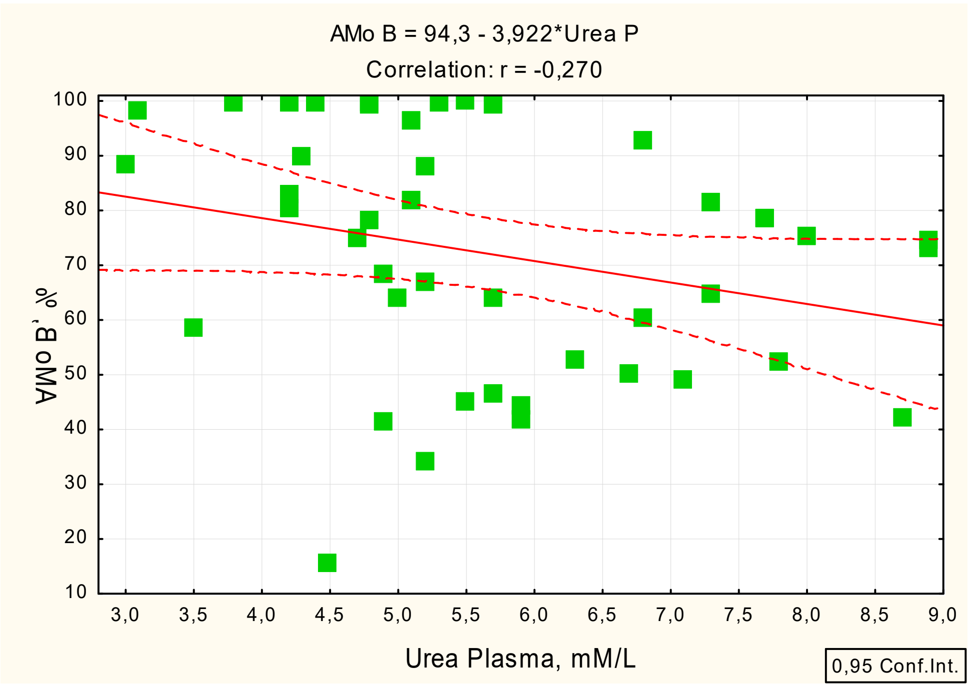


Fig. 5. Scatterplot of correlation between Urea Plasma (X-line) and AMo HRV basal (Y-line)

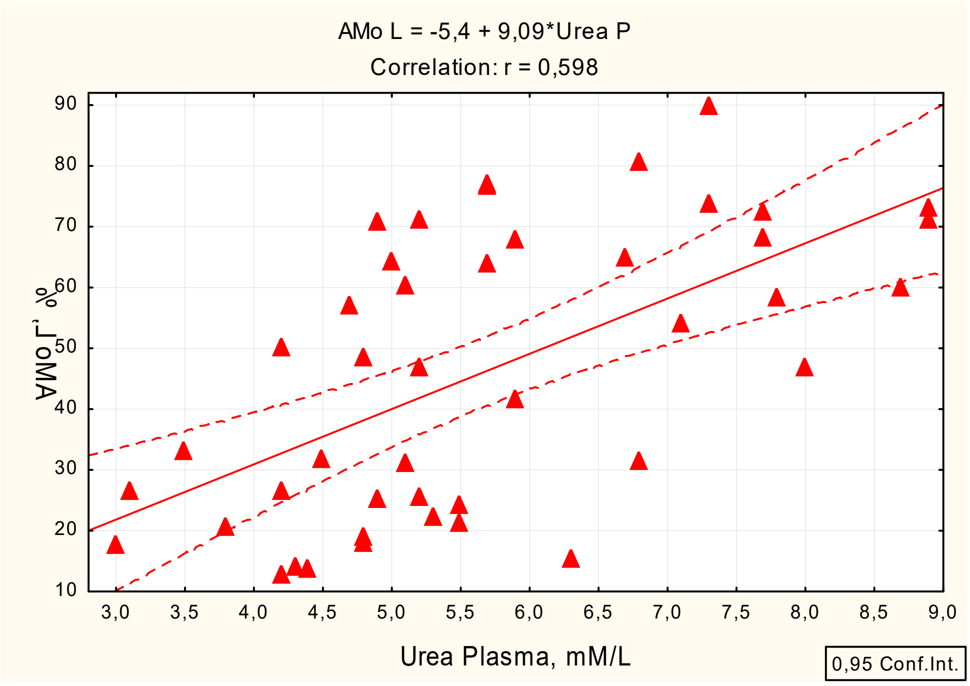


Fig. 6. Scatterplot of correlation between Urea Plasma (X-line) and AMo HRV after loading (Y-line)

Another parameter of regulatory systems is autonomic reactivity, the quantitative measure of which is the ratio of the stress index standing to such lying (SIS/SILd) [3]. Normal (sympathicotonic) reactivity is indicated by SIS/SILd in the range of 0,7÷1,5 at SILd>91 units, 0,9÷1,8 at SILd 90÷61 units, 1,0÷2,5 at SILd 60÷30 units. For a more convenient logarithmic scale, the corresponding ranges are: -0,36÷0,405; -0,10÷0,59; 0÷0,92. As the sympathetic tone increases both at transition from a lying position to standing, and in response to physical activity, this scale, in our opinion, is quite acceptable and concerning the ln(SIL/SIB) ratio applied by us. Accepting this, we state normal autonomic reactivity only in 16% of cases, while in 64% of cases there was asympathicotonic reactivity, and in 20% - hypersympathicotonic (Fig. 7). The same figure illustrates the positive correlation between autonomic reactivity and plasma urea levels.

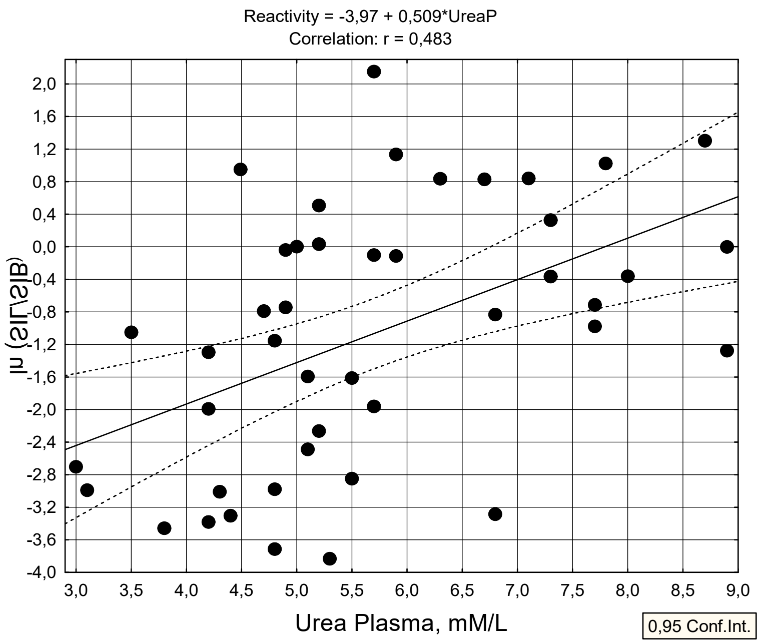


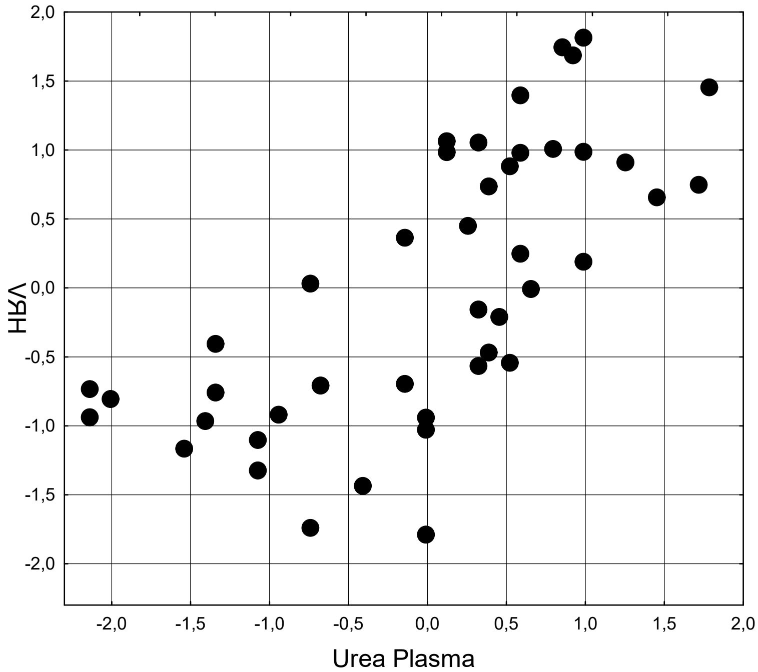
Fig. 7. Scatterplot of correlation between Urea P (X-line) and ANS Reactivity (Y-line)

In the next step of the analysis, a regression model was constructed for each plasma and urine nitrogenous metabolite by stepwise exclusion until the maximum level of adjusted R^2 was reached. As a result, it turned out that some regression models included parameters with an insignificant correlation coefficient, while some parameters with a significant correlation were outside the model.

From the regression model it follows that Urea plasma downregulates basal sympathetic tone and exercise-induced vagal tone, while upregulates the autonomic reactivity and level of circulating catecholamines. Judging by adjusted R^2, the rate of autonomic modulation is 44% (Table 2 and Fig. 8).

Table 2. Regression Summary for Urea Plasma
R=0,700; R^2=0,489; Adjusted R^2=0,437; $F_{(4,4)}$=9,3; $p<10^{-4}$

		Beta	St. Err. of Beta	B	SE of B	$t_{(39)}$	p-level
Variables	r		Intercpt	12,96	3,18	4,08	0,0002
MxDMn HRV after loading, sec	-0,65	-0,959	0,378	-12,328	4,866	-2,53	0,015
Mode HRV after loading, sec	-0,66	-0,327	0,231	-4,885	3,452	-1,42	0,165
AMo HRV basal, %	-0,27	-0,379	0,321	-0,026	0,022	-1,18	0,244
ln(SIL/SIB) as ANS Reactivity	0,48	-0,915	0,541	-0,867	0,513	-1,69	0,099



R=0,700; R^2=0,489; $\chi^2_{(4)}$=26,9; $p<10^{-4}$; Λ Prime=0,511
Fig. 8. Scatterplot of canonical correlation between Urea Plasma level (X-line) and parameters of HRV (Y-line)

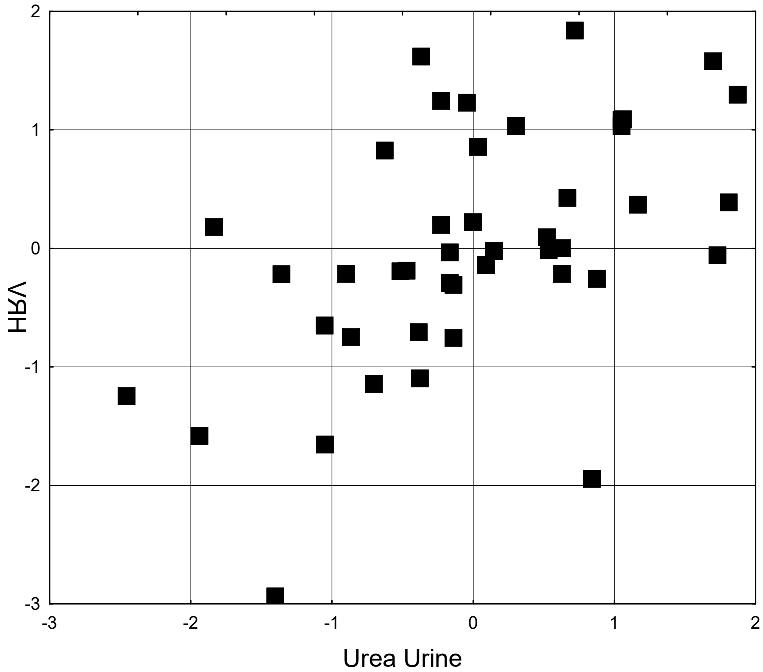
Urea urine also downregulates basal sympathetic tone and upregulates the autonomic reactivity while upregulates the vagal tone. Judging by adjusted R^2, the rate of autonomic modulation is 28% (Table 3 and Fig. 9).

Creatinine plasma upregulates both exercise-induced vagal tone and the autonomic reactivity. Judging by adjusted R^2, the rate of autonomic modulation is 21% (Table 4 and Fig. 10).

Uric acid urine upregulates the autonomic reactivity and basal vagal tone while downregulates its exercise-induced change as well as basal Stress index. Judging by adjusted R^2, the rate of autonomic modulation is 39% (Table 5 and Fig. 11).

Table 3. Regression Summary for Urea Urine
$R=0{,}531$; $R^2=0{,}282$; Adjusted $R^2=0{,}228$; $F_{(3,4)}=5{,}2$; $p=0{,}004$

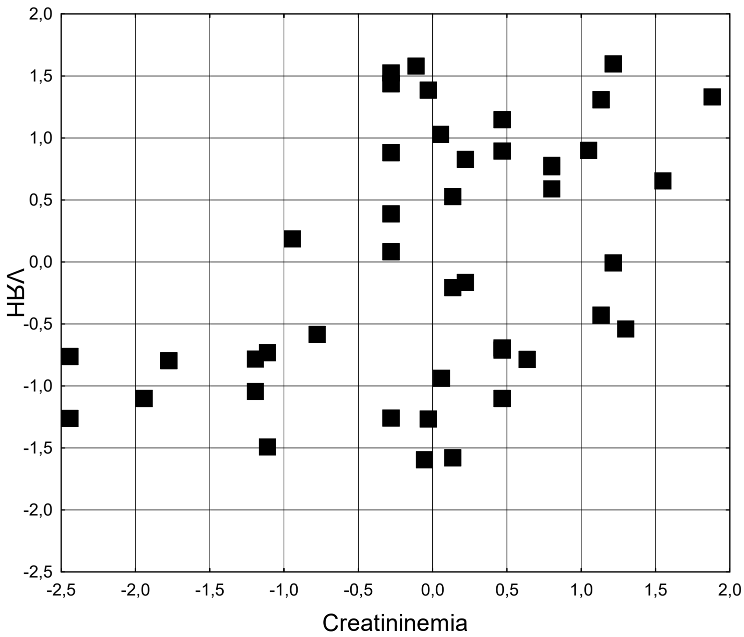
		Beta	St. Err. of Beta	B	SE of B	$t_{(39)}$	p-level
Variables	r		Intercpt	265,3	141,7	1,87	0,068
MxDMn HRV basal, sec	0,51	0,639	0,216	1395	472	2,96	0,005
ln(SIL/SIB) as ANS Reactivity	0,29	0,248	0,273	16,34	17,99	0,91	0,369
AMo HRV basal, %	-0,35	0,335	0,354	1,604	1,692	0,95	0,349



$R=0{,}531$; $R^2=0{,}282$; $\chi^2_{(3)}=13{,}4$; $p=0{,}004$; Λ Prime=0,718
Fig. 9. Scatterplot of canonical correlation between Urea Urine level (X-line) and parameters of HRV (Y-line)

Table 4. Regression Summary for Creatinine Plasma
$R=0{,}457$; $R^2=0{,}209$; Adjusted $R^2=0{,}170$; $F_{(2,4)}=5{,}4$; $p=0{,}008$

		Beta	St. Err. of Beta	B	SE of B	$t_{(39)}$	p-level
Variables	r		Intercpt	96,5	4,36	22	10^{-6}
MxDMn HRV after loading, sec	0,43	-0,711	0,292	-73,2	30,1	-2,43	0,019
ln(SIL/SIB) as ANS Reactivity	0,31	-0,318	0,292	-2,41	2,22	-1,09	0,284



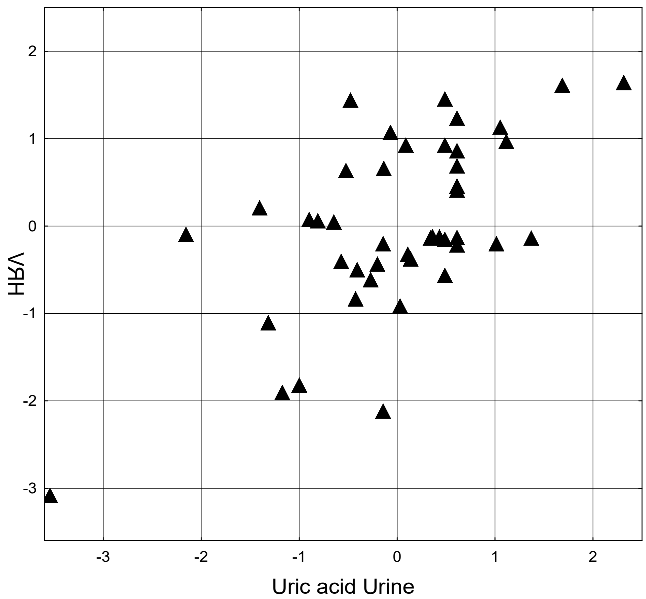
$R=0,457$; $R^2=0,209$; $\chi^2_{(2)}=9,6$; $p=0,008$; Λ Prime=0,791

Fig. 10. Scatterplot of canonical correlation between Creatinine Plasma level (X-line) and parameters of HRV (Y-line)

Table 5. Regression Summary for Uric acid Urine

$R=0,623$; $R^2=0,388$; Adjusted $R^2=0,326$; $F_{(4,4)}=6,2$; $p=0,0006$

		Beta	St. Err. of Beta	B	SE of B	$t_{(39)}$	p-level
Variables	r		Intercpt	-10,5	4,65	-2,22	0,030
MxDMn HRV basal, sec	0,51	2,204	0,633	36,61	10,51	3,48	0,001
ln(SIL/SIB) as ANS Reactivity	0,25	-0,277	0,246	-0,139	0,123	-1,13	0,266
ln SI basal, units	-0,43	1,823	0,650	1,704	0,607	2,81	0,008
(MxDMn) L/(MxDMn) B	-0,33	-0,403	0,265	-0,120	0,079	-1,52	0,136



$R=0,623$; $R^2=0,388$; $\chi^2_{(4)}=19,7$; $p=0,0006$; Λ Prime=0,612

Fig. 11. Scatterplot of canonical correlation between Uric acid Urine (X-line) and parameters of HRV (Y-line)

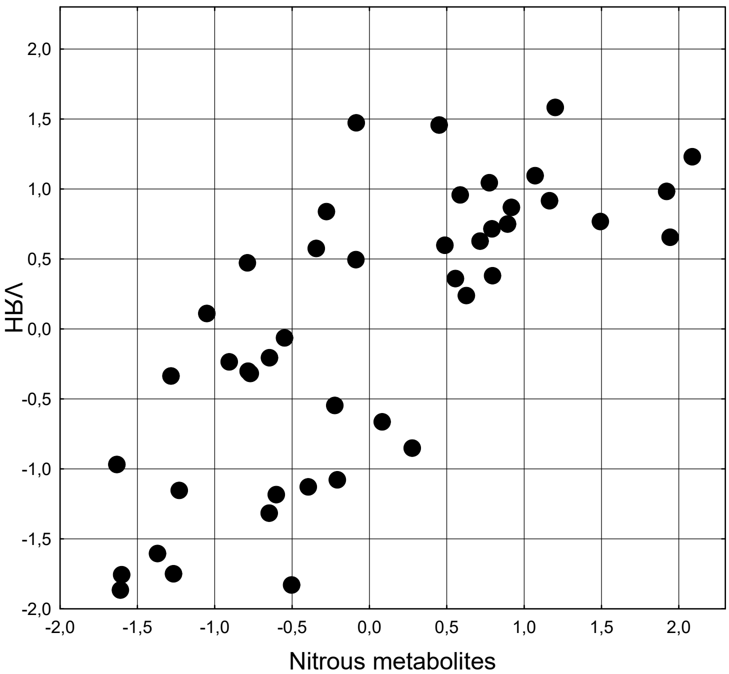
No significant correlations were found for Creatinine urine, Uric acid plasma and Bilirubinemia.

At the final stage, following the accepted algorithm, the canonical correlation between the parameters of nitrogenous metabolism, on the one hand, and the parameters of ANS - on the other hand, is analyzed.

As a result of canonical analysis, two pairs of canonical roots were formed. Nitrogenous root of the first pair (Table 6), judging by the factor loads, represents mainly Urea and Creatinine plasma, and to a lesser extent Uric acid and Urea urine, but inversely. The ANS root of the first pair contains inversely information about mainly the vagal tone both exercise-induced and basal as well as its change while direct information about exercise-induced level of circulating catecholamines and basal Stress index and its change after load. The vegetotropic effect of these nitrogenous metabolites, judging by the coefficient of determination, is 55,8% (Fig. 12).

Table 6. Factor load on first pair of canonical roots of nitrogenous metabolites and HRV parameters

Left set	**Root 1**
Urea Plasma	**0,892**
Creatininemia	**0,552**
Uric acid Urine	**-0,332**
Urea Urine	**-0,239**
Right set	**Root 1**
MxDMn after loading	-0,819
MxDMn basal	-0,390
(MxDMn) L/(MxDMn) B	-0,157
AMo basal	-0,208
Mode after loading	-0,784
ANS Reactivity	0,507
Stress Index basal	0,393



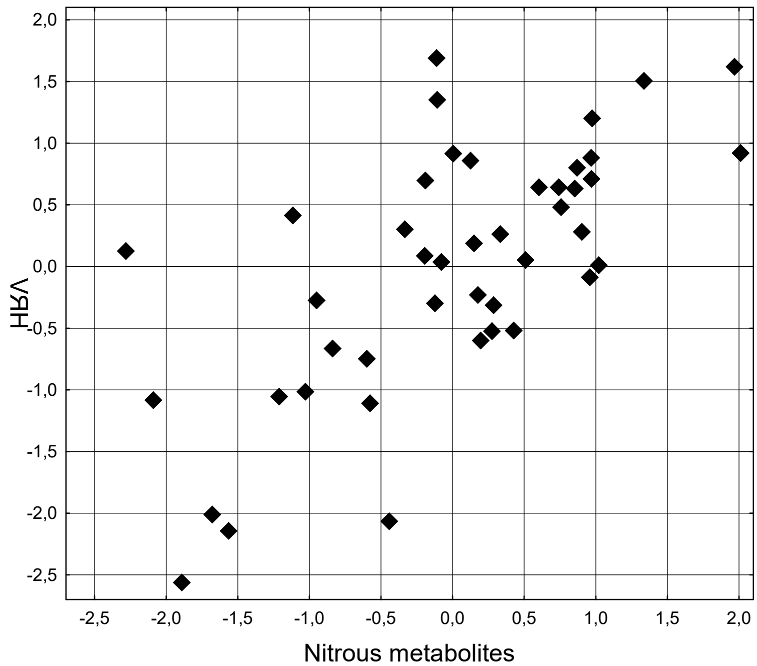
R=0,747; R^2=0,558; $\chi^2_{(28)}$=63; p=0,0002; Λ Prime=0,184

Fig. 12. Scatterplot of canonical correlation between nitrogenous metabolites (X-line) and parameters of HRV (Y-line). First pair of canonical roots

The nitrogenous root of the second pair (Table 7) represents mainly Uric acid and Urea urine, and to a lesser extent Urea and Creatinine plasma. Note the same sign of the factor loads. This constellation of nitrogenous metabolites primarily downregulates basal sympathetic tone and stress index, as well as exercise-induced vagal tone and its change while upregulates the basal vagal tone, ANS reactivity and level of circulating catecholamines. The vegetotropic effect of these nitrogenous metabolites is 45,6% (Fig. 13).

Table 7. Factor load on second pair of canonical roots of nitrogenous metabolites and HRV parameters

Left set	**Root 2**
Uric acid Urine	**-0,853**
Urea Urine	**-0,691**
Urea Plasma	**-0,272**
Creatininemia	-0,138
Right set	**Root 2**
AMo basal	0,708
(MxDMn) L/(MxDMn) B	0,689
Stress Index basal	0,684
MxDMn after loading	0,430
MxDMn basal	-0,787
ANS Reactivity	-0,711
Mode after loading	0,501



R=0,676; R^2=0,456; $\chi^2_{(18)}$=32; p=0,020; Λ Prime=0,416

Fig. 13. Scatterplot of canonical correlation between nitrogenous metabolites (X-line) and parameters of HRV (Y-line). Second pair of canonical roots

Our data on the vegetotropic activity of Uric acid are ambiguous. Thus, no significant relationships were found between HRV parameters and uricemia, instead, vagotonic activity of uricosuria was noted. Interestingly, the data of other authors are also ambiguous. In particular, Shehab AM et al [32] in patients with chronic heart failure also found no significant linear correlation between allopurinol-induced changes in serum Uric acid concentrations and changes in parameters of HRV (SDNN and RMSSD as markers of vagal tone) and mean heart rate. While Kunikullaya KU et al [20] found that serum Uric acid levels were high in prehypertensives and hypertensives as compared to normal subjects; further, there was statistically significant correlation seen between Uric acid levels and sympathetic domain parameters particularly among prehypertensives. Passos RS et al [25] showed that the hyperuricemic older adults exhibited significant higher values for V0% and lower values for V2% parameters when compared to normouricemic older adults. These results suggesting a sympathovagal imbalance in hyperuricemic older adults, characterized by greater sympathetic predominance (0 V%) and lower vagal modulation (2 V%) at rest conditions.

Instead, we found a significant positive correlation between plasma urea and creatinine with sympathetic tone, but only after exercise, whereas in basal conditions the correlation was weakly negative. Another ambiguity is manifested in a significant positive correlation of urinary urea, but not urinary creatinine with basal vagal tone. Unfortunately, there is no one to compare our data with, as we could not find analogues on PubMed/PMC resources.

Despite all these contradictions, given the well-documented autonomic-immune relationships [24,34], our data provide good reason to believe that the immunotropic activity of urea and creatinine, as well as uric acid is realized through the autonomic nervous system through adreno- and cholinoreceptors of immunocytes.

The analysis of 10 most important basic life support systems of human body — cardiovascular (CVS), respiratory (RS), nervous (NS), digestive (DS), endocrine (ES), immune (IS), excretory (EXS), brain (BS), musculo-skeletal (MSS), hematopoietic (HS) was carried out. Based on this analysis two levels of ensuring the reliability of organism's work were revealed: sequential and parallel.The system of logical equations for reduced sequential system is: Ys1 = CVS RS BS, where is the notation for the conjunctions of set elements. The system of logical equations for the reduced parallel system is: Ys2 = NS DS ES IS HS EXS MSS, where is the disjunction of the scheme elements. Visualization of human STC changes the concept of the kinetics of age-related changes in the organism and the role of determinants of health as a stable factor accompanying a uniform, smooth transition from the most pronounced functions of the body to their gradual extinction. For human STC is formulated the following regularity kinetics of involutionary processes: after 30 years of age in the human body morphological changes regress in arithmetic progression, and the functions of organs in a geometric one. Assumption of health as a state redundancy of functions is suggested [36].

The research is devoted to the fundamental issue of medicine and biology – the study of factors limiting the life span of a person. As a model, the system of adaptation of the human body to the forces of natural gravity is chosen, the disadaptation to which manifests itself in falls and everyday injuries. The object of the study was the selection of severe fractures of bone tissue due to fall, taken in the age aspect. Statistical and meta-analytical research methods were used. It is shown that the age-related increase in mortality due to household falls, coming to severe bone fractures, is non-linear and increases in geometric progression. As a result of the coincidence of the age characteristics of bone fragility and age-related kidney function, an assumption is made about the role of involution of the renal tissue in the development of osteoporosis in the elderly and the need for a new approach to the prevention of osteoporosis and domestic injuries [37].

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ACCORDANCE TO ETHICS STANDARDS

Tests in patients are conducted in accordance with positions of Helsinki Declaration 1975 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.

Conflict of Interest. The authors declare that there is no conflict of interest that could be perceived as interfering with publication of the article.
Competing Interests. The authors declare that they have no competing interests.
Informed Consent. Informed consent was obtained from all individual participants included in the study. All subjects of the institutional survey gave consent for anonymized data to be used for publication purposes.
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