

## Therapy


UDC: 616.12-008.313.2

### PLASMA AMINO ACIDS SPECTRUM AND HOLTER ECG MONITORING INDEXES IN CORONARY ARTERY DISEASE PATIENTS WITH ATRIAL FIBRILLATION

*Melnychuk I.O., Sharayeva M.L., Kramarova V.N., Lyzogub V.G.*  
*Bogomolets National Medical University, Kyiv, Ukraine*

The research was conducted with the aim of establishing a connection between plasma amino acid peculiarities and Holter ECG monitoring indexes in Coronary Artery Disease (CAD) and Atrial Fibrillation (AF) patients. 300 patients were examined divided into 3 groups: I – 149 patients with CAD without arrhythmias, II – 124 patients with CAD and AF paroxysm, and the Control Group (CG) – 27 patients without CAD and arrhythmias. Holter ECG monitoring was performed for the patients with AF within 24 hours after sinus rhythm restoration, and for the patients without AF on the first day of observation. Plasma AA level was detected by the method of ion exchange liquid column chromatography. It was established that there is a significant increase glutamate and Branched-Chain Amino Acids (BCAA) levels in patients of the II group, and significant depletion in glycine levels comparison with the I group patients ( $p < 0.05$ ). In the II group patients, an increase in SupraVentricular (SVE) and Ventricular Extrasystoles (VE) was checked in comparison with the I group patients ( $p < 0.05$ ). Total SVE was significantly correlated with threonine ( $r = -0.316$ ), serine ( $r = -0.336$ ), glycine ( $r = -0.397$ ), isoleucine ( $r = 0.317$ ), BCAA ( $r = 0.356$ ), and glycine+serine sum ( $r = -0.302$ ),  $p < 0.05$ . AF paroxysm was significantly correlated with taurine ( $r = -0.302$ ), serine ( $r = -0.328$ ), glycine ( $r = -0.311$ ), glutamine ( $r = -0.304$ ), and glycine+serine sum ( $r = -0.379$ ),  $p < 0.05$ . Total VE was significantly correlated with glycine ( $r = -0.370$ ) and tyrosine ( $r = 0.325$ ),  $p < 0.05$ . Changes in ST-segment were significantly correlated with tyrosine ( $r = 0.307$ ), phenylalanine ( $r = 0.318$ ), and Aromatic Amino Acids (AAA) ( $r = 0.379$ ),  $p < 0.05$ . We concluded that glycine, serine, and BCAA are significantly correlated with cardiac arrhythmias. Changes in ST segment are significantly correlated with AAA levels.

**Keywords:** heart rhythm violations, ischemia, arrhythmia, metabolomics.

	<p><b>Цитуйте українською:</b> Мельничук ІО, Шараєва МЛ., Крамарєва ВН, Лизогуб ВГ. Амінокислотний спектр плазми та показники Холтерівського моніторингу ЕКГ у пацієнтів з ішемічною хворобою серця та фібриляцією передсердь. Експериментальна і клінічна медицина. 2024;93(1):12с. In press. <a href="https://doi.org/10.35339/ekm.2024.93.1.msk">https://doi.org/10.35339/ekm.2024.93.1.msk</a> [англійською].</p>
	<p><b>Cite in English:</b> Melnychuk IO, Sharayeva ML, Kramarova VN, Lyzogub VG. Plasma amino acids spectrum and Holter ECG monitoring indexes in coronary artery disease patients with atrial fibrillation. Experimental and Clinical Medicine. 2024;93(1):12p. In press. <a href="https://doi.org/10.35339/ekm.2024.93.1.msk">https://doi.org/10.35339/ekm.2024.93.1.msk</a></p>

CC BY-NC-SA

Відповідальний автор: Мельничук І.О.

✉ Україна, 01601, м. Київ,

бульвар Тараса Шевченка, 13.

E-mail: [ira.merkulova45@gmail.com](mailto:ira.merkulova45@gmail.com)

Corresponding author: Melnychuk I.O.

✉ Ukraine, 01601, Kyiv,

Taras Shevchenko Blvd, 13.

E-mail: [ira.merkulova45@gmail.com](mailto:ira.merkulova45@gmail.com)

## Introduction

Coronary Artery Disease (CAD) is the most common CardioVascular (CV) pathology in the world. At the same time, Atrial Fibrillation (AF) is the most widely spread cardiac arrhythmia. Moreover, they are known risk factors for each other and worsen each other prognosis and clinical picture. Also, CAD and AF are characterized by a quantity of the same risk factors: diabetes mellitus, dyslipidemia, obesity, inflammatory disorders, etc. All of them are closely connected with metabolic disturbances [1; 2].

Circulating Amino Acids (AA) are the promising molecules implicated in CV disease pathogenesis. Their role is as biomarkers for CV disease prediction or as a potential therapeutic target for disease treatment and prevention. According to the latest data, an increase in circulating leucine and tyrosine levels and a decrease in glycine, serine, and alanine levels are closely associated with CV pathology [3]. Branch-Chain Amino Acids (BCAAs) are crucial in metabolic disturbances pathogenesis. Their rise leads to the overactivation of the mammalian Target Of Rapamycin (mTOR) signaling pathway, which is a central regulator of cellular metabolism, and can provoke insulin resistance. Also, a rise of circulating BCAAs leads to their angiotensin-II-induced atrial accumulation, which aggravates tissue fibrosis and mitochondrial oxidation and is possibly linked to AF. Moreover, BCAAs are responsible for platelet activity, promoting their activation and degranulation by thrombomodulin-3 propionylation catabolites, which is an important part of CAD pathogenesis [4]. Aromatic Amino Acids (AAA) and their metabolites can be used as independent CV

event predictors and are closely connected with gut microbiota conditions [5]. Also, according to the big population studies BCAA and AAA are directly associated with arterial hypertension and significantly correlated with each other. Moreover, reported their associations with obesity, diabetes mellitus, hyperuricemia, and thyroid dysfunction [4–6]. So, the role of circulating AA in CV disease pathogenesis is undoubtful, but their changes in patients with arrhythmias are still under discussion.

**The aim of study** – to analyze the connections between plasma amino acid features and Holter ECG monitoring indexes in coronary artery disease and atrial fibrillation patients.

## Materials and Methods

We explored 300 patients in our study. They were divided into 3 groups: I – 149 patients with CAD but without arrhythmias, II – 124 patients with CAD and AF paroxysm, and the Control Group (CG) – 27 patients without CAD and arrhythmias. CAD and AF diagnoses were based on the latest ESC guidelines [5; 6]. All patients were investigated in the Kyiv City Clinical Hospital No.12 in the cardiological and therapeutic departments in 2018–2023. Diagnosis CAD was confirmed by a history of coronary artery stenotic changes during invasive coronary angiography. AF paroxysm was checked by resting 12 leads electrocardiography. Exclusion criteria were: heart failure Class III to IV (by New York Heart Association), thyroid pathology, reported malignancies, chronic kidney disease (Glomerular Filtration Rate, GFR <60 mL/min), valvular AF, inflammatory bowel disease, irritable bowel syndrome, vegetarians and vegans, pregnancy, usage of probiotics and antibiotics for a month be-

fore the study. No significant difference in risk factors at baseline was seen between investigated groups. The study was conducted at the base and was approved by the ethical commission of the Kyiv City Clinical Hospital No.12 (Protocol No.8 on August 22, 2018). Informed consent was obtained from all patients according to Declaration of Helsinki. Baseline characteristics of the study patients include age, gender, history of Myocardial Infarction (MI), stroke, diabetes mellitus, obesity, Body Mass Index (BMI), uric acid, total bilirubin, GFR, and Total Cholesterol (TC) levels. Uric acid, total bilirubin, creatinine, and TC were checked by the Kyiv City Clinical Hospital No.12 laboratory (certificate "ІІТ" (Cyrillic) – 257/21). Advanced age, obesity, hypercholesterolemia, high stages of chronic kidney disease, gout, and hyperbilirubinemia are known risk factors of AF paroxysm development [1]. That's why these baseline characteristics were analyzed and compared because it can help us to exclude their influence on obtained results.

Holter ECG monitoring was performed for the patients with AF within 24 hours after sinus rhythm restoration, and for the patients without AF on the first day of observation. A channel Holter ECG monitor (Cardiosens\_K, Kharkiv, 2014) was used. We assessed Holter monitoring in V1, aVF, and V5 leads during 24 hours. Arrhythmia and conduction abnormalities, ST-segment, and QTc monitoring were evaluated by Holter ECG. Studied main indexes were: maximum heart rate (HR, bpm), minimum HR (bpm), average HR (bpm), total number of Supraventricular Extrasystoles (SVE), number of pairs SVE, number of groups SVE, number of Supraventricular Tachycardia (SVT) episodes, longest duration of SVT, maximum HR of SVT episode, number of SVE's per hour, number of AF paroxysm, longest duration of AF paroxysm, total number of Ventricular Extrasystoles (VE), number of pairs

VE, number of groups VE, number of ventricular tachycardia (VT) episodes, longest duration of VT, maximum HR of VT episode, number of VE's per hour, number of pauses more than 3 sec, maximum ST depression (mkV), maximum ST elevation (mkV), maximum ST duration (min) [7].

Plasma AA level was detected by method of ion exchange liquid column chromatography – such AA were identified: lysine, histidine, arginine, ornithine, taurine, asparaginate, threonine, serine, glutamate, proline, glycine, alanine, cysteine, valine, methionine, isoleucine, leucine, tyrosine, phenylalanine, glutamine, ammonia. They include BCAA – isoleucine, leucine, and valine; AAA – tyrosine and phenylalanine; sulfur contains AA (SCAA) – taurine, cysteine, and methionine [6]. Blood sampling from patients was performed on an empty stomach from the cubital vein on the day of hospitalization.

Results were presented as mean  $\pm$  standard error or [95% Confidence Interval (CI)] for continuous variables or as a number for categorical variables. The Pearson criterion checked variable distribution for normality. Data were compared using the Wilcoxon signed-rank test or Student t-test with two critical regions by the type of distribution; Spearman's rank correlation coefficient [8]. All calculations were done in MATLAB R2014a (License number 271828, MathWorks, Inc., USA).

### Results

The baseline characteristics in the investigated groups were checked. Significant differences in age, gender, BMI, total bilirubin, and smoking history were not found,  $p < 0.05$ . In the I and II groups uric acid (by 22.66% and 30.53% respectively) and TC (by 32.64% and 43.06% respectively) levels were higher and GFR (by 26.16% and 19.38% respectively) was lower than in CG ( $p < 0.05$ ). In the I and II groups were patients with obesity, diabetes mellitus, stroke, or MI history, such cases were absent in CG (Table 1).

Table 1. Baseline characteristics of the study groups, mean ± standard error

Group Characteristic	I group	II group	CG	P1-2	P2-CG	P1-CG
Age (years)	67.71±3.90	67.96±0.94	56.25±2.18	p>0.05	p>0.05	p>0.05
Men (%)	48.99	47.97	48.15	p>0.05	p>0.05	p>0.05
Smoking (%)	51.01	41.46	40.74	p>0.05	p>0.05	p>0.05
History of myocardial infarction (%)	30.87	26.02	0	p>0.05	p<0.05	p<0.05
History of stroke (%)	8.72	8.13	0	p>0.05	p<0.05	p<0.05
Diabetes mellitus (%)	18.12	14.63	0	p>0.05	p<0.05	p<0.05
Obesity (%)	8.84	12.00	0	p>0.05	p<0.05	p<0.05
BMI (kg/m <sup>2</sup> )	27.02±0.33	26.93±0.43	27.12±2.10	p>0.05	p>0.05	p>0.05
Total bilirubin (mmol/l)	11.30±0.09	12.40±0.08	11.7±0.11	p>0.05	p>0.05	p>0.05
Uric acid (mmol/l)	380.50±±28.16	404.90±±36.11	310.2±±29.12	p>0.05	p<0.05	p<0.05
GFR (ml/min)	62.03±2.31	67.73±1.98	84.01±5.48	p>0.05	p<0.05	p<0.05
TC (mmol/l)	5.73±0.37	6.18±0.31	4.32±0.21	p>0.05	p<0.05	p<0.05

Notes: BMI – Body Mass Index, GFR – Glomerular Filtration Rate, TC – Total Cholesterol, CG – Control Group; P1-2 – Probability between I and II groups; P2-CG – Probability between II and control groups; P1-CG – Probability between I and control groups.

Holter ECG monitoring results were investigated in our study. The average Holter monitoring duration has lasted for (22.13±±0.22) hours. The supraventricular and ventricular arrhythmia and ST-segment changes have significant differences between the investigated groups.

Supraventricular rhythm abnormalities are characterized by changes in HR, SVE, and AF paroxysms. The I and II groups were characterized by significant depletion in average (9.38% and 14.14%, consequently) and minimum HR (13.82% and 11.36%, consequently) in comparison with the CG (p<0.05). The II group had a significant decrease in average HR (5.26%) in comparison with the I group (p<0.05). In the I group patients a significant increase in SVEs per hour, total SVE, single SVE, pair SVE, group SVE, SVT, and its duration

were detected in comparison with the CG (p<0.05). In the II group patients a significant increase in SVEs per hour, total SVE, single SVE, pair SVE, group SVE, SVT, its duration, AF paroxysm, and its duration were detected in comparison with the CG (p<0.05). In the II group patients a significant increase in SVEs per hour, total SVE, single SVE, pair SVE, AF paroxysm, and its duration were detected in comparison with the I group (p<0.05).

Ventricular arrhythmias presented VE and VT. In the I group patients a significant increase in VEs per hour, total VE, single VE, pair VE, and group VE were detected in comparison with the CG (p<0.05). In the II group patients a significant increase in VEs per hour, total VE, single VE, pair VE, and group VE were detected in comparison with the CG (p<0.05). In the II group pa-

tients a significant increase in VEs per hour, total VE, single VE, and pair VE were detected in comparison with the I group ( $p < 0.05$ ). At the same time, VT episodes and pauses of more than 3 seconds were not detected in the investigated groups.

ST-segment changes include ST elevation and depression, and their duration. ST elevation and depression episodes were not observed in the CG and a significant difference in ST-segment changes was not found ( $p < 0.05$ ). The data are shown in *Table 2*.

*Table 2. Holter ECG monitoring indexes in investigated groups, mean ± standard error [95% CI].*

Group	I group	II group	CG	P1-2	P2-CG	P1-CG
Characteristic						
Maximum HR, bpm	110.20± ±2.48	106.60± ±3.89	109.80± ±3.97	$p > 0.05$	$p > 0.05$	$p > 0.05$
Minimum HR, bpm	45.60± ±1.68	46.90± ±1.66	52.91± ±1.30	$p > 0.05$	$p < 0.05$	$p < 0.05$
Average HR, bpm	66.98± ±0.99	63.46± ±1.24	73.91± ±2.20	$p < 0.05$	$p < 0.05$	$p < 0.05$
SVE total	36 [24–43]	729 [331–982]	7 [0–15]	$p < 0.05$	$p < 0.05$	$p < 0.05$
SVE single	32 [24–43]	502 [307–766]	7 [0–15]	$p < 0.05$	$p < 0.05$	$p < 0.05$
SVE pair	0 [0–3]	27 [8–42]	0	$p < 0.05$	$p < 0.05$	$p < 0.05$
SVE group	0 [0–1]	5 [0–9]	0	$p > 0.05$	$p < 0.05$	$p < 0.05$
SVT	0 [0–1]	0 [0–1]	0	$p > 0.05$	$p < 0.05$	$p < 0.05$
Longest SVT, sec.	0 [0–16]	0 [0–42]	0	$p > 0.05$	$p < 0.05$	$p < 0.05$
SVEs per hour	8 [3–17]	38 [11–112]	0 [0–2]	$p < 0.05$	$p < 0.05$	$p < 0.05$
AF paroxysm	0	0 [0–1]	0	$p < 0.05$	$p < 0.05$	$p > 0.05$
Longest AF paroxysm, sec.	0	0 [0–44]	0	$p < 0.05$	$p < 0.05$	$p > 0.05$
VE total	0 [0–3]	3 [0–15]	0 [0–1]	$p < 0.05$	$p < 0.05$	$p < 0.05$
VE single	0 [0–3]	3 [0–15]	0	$p < 0.05$	$p < 0.05$	$p < 0.05$
VE pair	0 [0–2]	3 [0–15]	0	$p < 0.05$	$p < 0.05$	$p < 0.05$
VE group	0 [0–1]	0 [0–2]	0	$p > 0.05$	$p < 0.05$	$p < 0.05$
VT	0	0	0	$p > 0.05$	$p > 0.05$	$p > 0.05$
Longest VT, sec.	0	0	0	$p > 0.05$	$p > 0.05$	$p > 0.05$
VE's per hour	14 [5–19]	32 [17–41]	0 [0–1]	$p < 0.05$	$p < 0.05$	$p < 0.05$
Pauses more than 3 sec.	0	0	0	$p > 0.05$	$p > 0.05$	$p > 0.05$
Longest pauses, sec.	0	0	0	$p > 0.05$	$p > 0.05$	$p > 0.05$
Changes ST segment, quantity episodes	0 [0–3]	0 [0–6]	0	$p > 0.05$	$p < 0.05$	$p < 0.05$
Maximum ST depression, mkV	0 [0–118]	0 [0–124]	0	$p > 0.05$	$p < 0.05$	$p < 0.05$
Maximum ST elevation, mkV	0 [0–133]	0 [0–112]	0	$p > 0.05$	$p < 0.05$	$p < 0.05$

*Continuation of Table 2*

Characteristic /group	I group	II group	CG	P1-2	P2-CG	P1-CG
Maximum ST episode duration, minutes	2 [1–5]	2 [1–5.5]	0	p>0.05	p<0.05	p<0.05

Notes: HR – Heart Rate, SVE – SupraVentricular Extrasystoles, SVT – SupraVentricular Tachycardia, AF – Atrial Fibrillation, VE – Ventricular Extra-systoles, VT – Ventricular Tachycardia, CG – Control Group; P1-2 – Probability between I and II groups; P2-CG – Probability between II and control groups; P1-CG – Probability between I and control groups.

The plasma AA spectrum was analyzed in investigated groups. In the I group patients a significant decrease in glycine, valine, and alanine levels was found in comparison with the CG (p<0.05). In the II group patients a significant increase in glutamate, and a significant decrease in glycine, valine,

alanine, serine, and glutamine levels were checked in comparison with the CG (p<0.05). In the II group, a significant rise in glutamate and a significant depletion in glycine levels were detected in comparison with the I group (p<0.05). The data are shown in *Table 3*.

*Table 3. Plasma amino acid spectrum in CAD patients with or without AF compared with the control group, mean [95% CI], μmol/l*

Group Amino acid	I group	II group	CG	P1-2	P2-CG	P1-CG
Lysine	25.35 [19.44; 133.33]	29.84 [19.36; 112.24]	91.83 [17.18; 181.32]	p>0.05	p>0.05	p>0.05
Histidine	11.52 [9.48; 53.04]	10.32 [9.60; 46.48]	46.49 [5.56; 63.38]	p>0.05	p>0.05	p>0.05
Arginine	13.13 [8.57; 87.5]	22.96 [9.12; 79.55]	62.09 [6.63; 119.32]	p>0.05	p>0.05	p>0.05
Ornithine	16.04 [10.01; 122.22]	22.09 [11.78; 88.00]	75.59 [7.85; 179.89]	p>0.05	p>0.05	p>0.05
Taurine	12.04 [4.80; 29.41]	7.87 [4.30; 45.29]	23.97 [3.28; 53.37]	p>0.05	p>0.05	p>0.05
Asparaginate	4.82 [1.42; 6.08]	3.95 [1.83; 4.39]	4.43 [0.79; 9.39]	p>0.05	p>0.05	p>0.05
Threonine	21.19 [12.87; 63.22]	17.65 [14.23; 69.54]	61.82 [10.97; 91.46]	p>0.05	p>0.05	p>0.05
Serine	15.08 [13.70; 52.17]	20.64 [13.49; 29.37]	60.18 [11.51; 103.45]	p>0.05	p<0.05	p>0.05
Glutamate	18.67 [15.64; 29.41]	25.23 [21.51; 36.76]	17.57 [7.34; 20.15]	p<0.05	p<0.05	p>0.05
Proline	25.00 [16.33; 63.46]	23.33 [16.67; 82.50]	80.23 [13.33; 115.38]	p>0.05	p>0.05	p>0.05
Glycine	31.18 [20.95; 147.90]	28.04 [21.50; 44.82]	189.00 [56.56; 281.40]	p<0.05	p<0.05	p<0.05

*Continuation of Table 3*

Group Amino acid	I group	II group	CG	P1-2	P2-CG	P1-CG
Alanine	57.86 [45.64; 145.29]	56.25 [48.31; 131.65]	206.28 [40.47; 345.24]	p>0.05	p<0.05	p<0.05
Cysteine	6.52 [5.32; 78.95]	5.69 [5.21; 39.47]	44.83 [5.32; 88.45]	p>0.05	p>0.05	p>0.05
Valine	28.56 [22.44; 142.86]	25.89 [19.48; 137.50]	34.87 [13.97; 82.86]	p>0.05	p>0.05	p<0.05
Methionine	2.71 [2.07; 9.18]	3.97 [2.64; 11.09]	6.03 [2.37; 16.13]	p>0.05	p>0.05	p>0.05
Isoleucine	8.33 [5.78; 31.50]	11.02 [6.86; 36.17]	31.38 [5.34; 46.88]	p>0.05	p>0.05	p>0.05
Leucine	16.35 [12.70; 61.54]	23.07 [12.90; 63.46]	51.87 [12.90; 92.31]	p>0.05	p>0.05	p>0.05
Tyrosine	8.01 [5.84; 35.71]	7.69 [5.96; 15.07]	21.10 [9.57; 44.12]	p>0.05	p>0.05	p>0.05
Phenyl- alanine	6.79 [6.08; 23.53]	12.14 [6.69; 24.12]	17.64 [5.56; 29.41]	p>0.05	p>0.05	p>0.05
Glutamine	78.22 [57.14; 337.26]	74.01 [51.19; 164.44]	234.79 [96.18; 398.53]	p>0.05	p<0.05	p>0.05

Notes: CG – Control Group; P1-2 – Probability between I and II groups; P2-CG – Probability between II and control groups; P1-CG – Probability between I and control groups.

Also, we combined plasma AA according to their biochemical properties and exchange and compared these results for investigated groups. In the II group, a significant rise in BCAA was found in comparison with the I group (p<0.05). In the II group, a significant rise in BCAA and a de-

crease in glycine+serine sum was found in comparison with the CG (p<0.05). In the I group, a significant decrease in glycine+serine sum was checked in comparison with the CG (p<0.05). The data are shown in *Table 4*.

*Table 4. Plasma amino acid combinations in CAD patients with or without AF compared with the control group, mean [95% CI], μmol/l*

Group Characteristic	I group	II group	CG	P1-2	P2-CG	P1-CG
SCAA	16.6 [11.29; 124.88]	17.19 [11.80; 133.10]	85.76 [10.73; 139.83]	p>0.05	p>0.05	p>0.05
BCAA	52.84 [40.73; 214.77]	61.55 [54.41; 260.92]	109.88 [38.63; 215.67]	p<0.05	p<0.05	p>0.05
AAA	14.54 [11.40; 60.29]	19.85 [11.69; 47.63]	38.74 [14.30; 77.63]	p>0.05	p>0.05	p>0.05
glycine+serine	47.40 [34.78; 188.10]	56.55 [39.73; 95.82]	208.52 [28.07; 363.95]	p>0.05	p<0.05	p<0.05

Notes: SCAA – sulfur-contains amino acids, BCAA – branched chain amino acids, AAA – aromatic amino acids, CG – Control Group; P1-2 – Probability between I and II groups; P2-CG – Probability between II and control groups; P1-CG – Probability between I and control groups.

The correlation analysis between plasma AA spectrum, their combinations, and Holter ECG monitoring findings was done in our study. Spearman's correlation analysis was used to explore their correlations. The largest amount of correlations was checked between Holter ECG monitoring indexes and glycine (total number = 7), threonine (total number = 5), BCAA (total number = 5), and glycine+serine sum (total number = 5). The highest amount of correlations was found between total SVE (total number = 6) and plasma amino acids. Total SVE was significantly correlated with thre-

onine ( $r=-0.316$ ), serine ( $r=-0.336$ ), glycine ( $r=-0.397$ ), isoleucine ( $r=0.317$ ), BCAA ( $r=0.356$ ), and glycine+serine sum ( $r=-0.302$ ),  $p<0.05$ . AF paroxysm was significantly correlated with taurine ( $r=-0.302$ ), serine ( $r=-0.328$ ), glycine ( $r=-0.311$ ), glutamine ( $r=-0.304$ ), and glycine+serine sum ( $r=-0.379$ ),  $p<0.05$ . Total VE was significantly correlated with glycine ( $r=-0.370$ ) and tyrosine ( $r=0.325$ ),  $p<0.05$ . Changes in ST-segment were significantly correlated with tyrosine ( $r=0.307$ ), phenylalanine ( $r=0.318$ ), and AAA ( $r=0.379$ ),  $p<0.05$ . The data are presented in *Figure*.

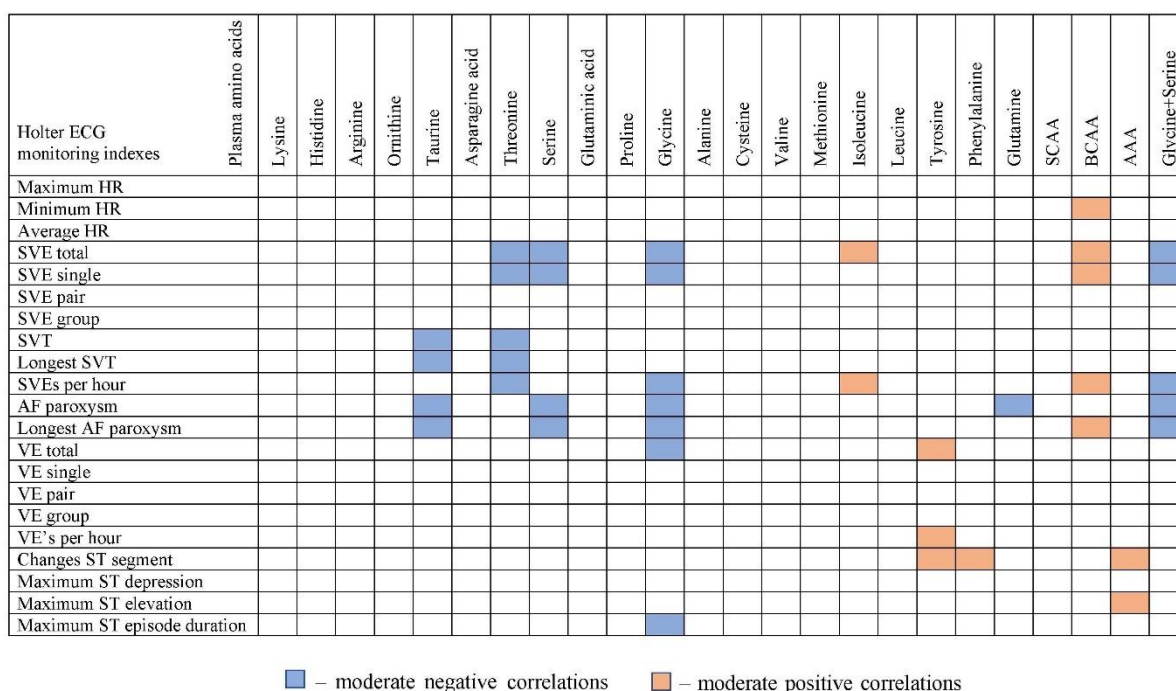


Fig. Correlation heatmap in plasma amino acids spectrum and Holter ECG monitoring indexes.

Notes: SCAA – Sulfur-Contain Amino Acids, BCAA – branched chain amino acids, AAA – Aromatic Amino Acids, HR – Heart Rate, SVE – SupraVentricular Extrasystoles, SVT – SupraVentricular Tachycardia, AF – Atrial Fibrillation, VE – Ventricular Extrasystoles,  $p<0.05$ .

**Discussion**

According to our results plasma glycine and serine levels were inversing associated with cardiac arrhythmia. Also, plasma gly-

cine levels were significantly lower in CAD patients with and without AF. Previous studies suggested that glycine has cardioprotective properties, can regulate lipids



and glucose metabolism, and prevents platelets and immune cell activation [9; 10]. Moreover, a decrease in circulating glycine level is associated with CV diseases, such as myocardial infarction, arterial hypertension, hypertrophic cardiomyopathy, and metabolic disorders, such as diabetes mellitus and dyslipidemia [3; 9; 11]. In animal studies, the glycine antihypertensive effect is explained by endogenous glycine receptor  $\alpha 2$  activation, which stimulates the release of transforming growth factor  $\beta$  and endothelin-1 cardiomyocytes [11]. In experimental studies, dilated cardiomyopathy is associated with serine metabolism violations, by alterations in non-glycolytic glucose metabolism in cardiomyocytes [12].

According to our results, threonine was also inversing correlated with supraventricular arrhythmias. The serine/threonine phosphorylation mechanism plays a crucial role in cardiomyocyte depolarization and is an important part of cardiac arrhythmogenic state, including AF development [13].

In this study, taurine was also inversing correlated with supraventricular arrhythmias. Taurine is widely known as a famous antioxidant, which can prevent cardiac apoptosis and fibrosis, and regulates intracellular calcium homeostasis [14].

According to our data AAA (tyrosine and phenylalanine) were directly significantly correlated with changes in ST-segment. In experimental studies, the rise in circulating phenylalanine and tyrosine levels associated with myocardial infarction, by increase in oxidative stress and inflammation in cardiomyocytes [15].

Despite of numerosity of data about AA's role in cardiomyocyte metabolism, and their influence on CV disease development, their pathogenetic role is still unclear. Most data are based on experimental, or animal studies. So, the associations between AA exchange alterations and arrhythmias in CAD patients is up-to-date and important scientific question.

## Conclusions

According to our study results the plasma amino acid peculiarities and their associations with Holter ECG monitoring indexes were analyzed:

1. in the patients with coronary artery disease and atrial fibrillation a significant rise in glutamate and branched-chain amino acids, and a significant depletion in glycine levels was found in comparison with coronary artery disease patients without arrhythmia ( $p < 0.05$ );

2. in the patients with coronary artery disease and atrial fibrillation an increase in supraventricular and ventricular extrasystoles was checked in comparison with patients with coronary artery disease and without atrial fibrillation ( $p < 0.05$ );

3. total SVE was significantly correlated with threonine ( $r = -0.316$ ), serine ( $r = -0.336$ ), glycine ( $r = -0.397$ ), isoleucine ( $r = 0.317$ ), BCAA ( $r = 0.356$ ), and glycine+serine sum ( $r = -0.302$ ) ( $p < 0.05$ );

4. AF paroxysm was significantly correlated with taurine ( $r = -0.302$ ), serine ( $r = -0.328$ ), glycine ( $r = -0.311$ ), glutamine ( $r = -0.304$ ), and glycine+serine sum ( $r = -0.379$ ) ( $p < 0.05$ );

5. total VE was significantly correlated with glycine ( $r = -0.370$ ) and tyrosine ( $r = 0.325$ ) ( $p < 0.05$ );

6. changes in ST-segment were significantly correlated with tyrosine ( $r = 0.307$ ), phenylalanine ( $r = 0.318$ ), and AAA ( $r = 0.379$ ) ( $p < 0.05$ ).

## Perspectives for further research

Despite of numerosity of data about AA's role in cardiomyocyte metabolism, and their influence on CV disease development, their pathogenetic role is still unclear. Most data are based on experimental, or animal studies. So, the associations between AA exchange alterations and arrhythmias in CAD patients is up-to-date and important scientific question.

### Financing

This study did not receive external funding. The study was done according to the department scientific study work "Changes in protein, carbohydrate and lipid metabolism in patients with coronary heart disease

and arterial hypertension with heart rhythm disorders, possibilities of drug correction" 2021–2023 (state registration number 0121U108875).

**Conflicts of interest** is absent.

### References

1. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, et al. Corrigendum to: 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42(40):4194. DOI: 10.1093/eurheartj/ehab648. Erratum for: *Eur Heart J*. 2021;42(5):373-498. PMID: 34520521.
2. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al.; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41(3):407-77. DOI: 10.1093/eurheartj/ehz425. Erratum in: *Eur Heart J*. 2020;41(44):4242. PMID: 31504439.
3. Hu S, Lin Z, Hu MJ, Tan JS, Guo TT, Huang X, Hua L. Causal relationships of circulating amino acids with cardiovascular disease: a trans-ancestry Mendelian randomization analysis. *J Transl Med*. 2023;21(1):699. DOI: 10.1186/s12967-023-04580-y. PMID: 37805555.
4. Karadeniz A, Babayigit E, Gorenek B. Could Branched-Chain Amino Acids Be a New Landmark in Metabolic Syndrome and Cardiac Arrhythmias? *Can J Cardiol*. 2022;38(8):1326. DOI: 10.1016/j.cjca.2022.03.008. PMID: 35306103.
5. Nemet I, Li XS, Haghikia A, Li L, Wilcox J, Romano KA, et al. Atlas of gut microbe-derived products from aromatic amino acids and risk of cardiovascular morbidity and mortality. *Eur Heart J*. 2023;44(32):3085-96. DOI: 10.1093/eurheartj/ehad333. PMID: 37342006.
6. Mahbub MH, Yamaguchi N, Hase R, Takahashi H, Ishimaru Y, Watanabe R, et al. Plasma Branched-Chain and Aromatic Amino Acids in Relation to Hypertension. *Nutrients*. 2020;12(12):3791. doi: DOI: 10.3390/nu12123791. PMID: 33322015.
7. Sandau KE, Funk M, Auerbach A, Barsness GW, Blum K, Cvach M, et al.; American Heart Association Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Cardiovascular Disease in the Young. Update to Practice Standards for Electrocardiographic Monitoring in Hospital Settings: A Scientific Statement from the American Heart Association. *Circulation*. 2017;136(19):e273-344. PMID: 28974521. DOI: 10.1161/CIR.0000000000000527.
8. Faizi N, Alvi Y. *Biostatistics Manual for Health Research*. Elsevier; 2023. 290 p.
9. Wittemans LBL, Lotta LA, Oliver-Williams C, Stewart ID, Surendran P, Karthikeyan S, et al. Assessing the causal association of glycine with risk of cardio-metabolic diseases. *Nat Commun*. 2019;10(1):1060. DOI: 10.1038/s41467-019-08936-1. PMID: 30837465.
10. Melnychuk IO. Platelets amino acids profile and cardiometabolic risk factors in patients with coronary artery disease and atrial fibrillation. *The world of medicine and biology*. 2023;4(86):110-4. DOI: 10.26724/2079-8334-2023-4-86-110-114.
11. Lu Y, Zhu X, Li J, Fang R, Wang Z, Zhang J, et al. Glycine prevents pressure overload induced cardiac hypertrophy mediated by glycine receptor. *Biochem Pharmacol*. 2017;123:40-51. DOI: 10.1016/j.bcp.2016.11.008. PMID: 27836671.

12. Perea-Gil I, Seeger T, Bruyneel AAN, Termglinchan V, Monte E, Lim EW, et al. Serine biosynthesis as a novel therapeutic target for dilated cardiomyopathy. *Eur Heart J*. 2022;43(36):3477-89. DOI: 10.1093/eurheartj/ehac305. PMID: 35728000.
13. Ai X, Yan J, Pogwizd SM. Serine-threonine protein phosphatase regulation of Cx43 dephosphorylation in arrhythmogenic disorders. *Cell Signal*. 2021;86:110070. DOI: 10.1016/j.cellsig.2021.110070. PMID: 34217833.
14. Jong CJ, Sandal P, Schaffer SW. The Role of Taurine in Mitochondria Health: More Than Just an Antioxidant. *Molecules*. 2021;26(16):4913. DOI: 10.3390/molecules26164913. PMID: 34443494.
15. Al-Sadoon I, Wittmann I, Kun S, Ahmann M, Konyi A, Verzar Z. Assessment of serum phenylalanine and tyrosine isomers in patients with ST-segment elevation vs non-ST-segment elevation myocardial infarction. *J Clin Lab Anal*. 2021;35(2):e23613. DOI: 10.1002/jcla.23613. PMID: 33043503.

*Мельничук І.О., Шараєва М.Л., Крамарева В.Н., Лизогуб В.Г.*

#### **АМІНОКИСЛОТНИЙ СПЕКТР ПЛАЗМИ ТА ПОКАЗНИКИ ХОЛТЕРІВСЬКОГО МОНІТОРИНГУ ЕКГ У ПАЦІЄНТІВ З ІШЕМІЧНОЮ ХВОРОБОЮ СЕРЦЯ ТА ФІБРИЛЯЦІЄЮ ПЕРЕДСЕРДЬ**

Дослідження проведено з метою встановлення зв'язку між особливостями амінокислотного складу плазми та показниками холтерівського моніторингу ЕКГ у хворих на Ішемічну Хворобу Серця (ІХС) та Фібриляцію Передсердь (ФП). Обстежено 300 пацієнтів, які були розподілені на 3 групи: I (ІХС без аритмій) – 149 пацієнтів, II (ІХС та ФП) – 124 хворих, Контрольна Група (КГ) – 27 пацієнтів без ІХС та аритмії. Холтерівське моніторування ЕКГ проводили хворим з ФП протягом 24 годин після відновлення синусового ритму, а пацієнтам без ФП – у першу добу спостереження. Рівень АК у плазмі крові визначали методом іонообмінної рідинної колонкової хроматографії. Встановлено, що у хворих II групи присутнє достовірне підвищення рівня глутамату та амінокислот з розгалуженим ланцюгом (Branched-Chain Amino Acids, ВСАА), а також достовірне зниження рівня гліцину порівняно з пацієнтами I групи ( $p < 0,05$ ). У хворих II групи відзначено збільшення надшлуночкових (НШЕ) та шлуночкових екстрасистол (ШЕ) порівняно з хворими I групи ( $p < 0,05$ ). Загальна кількість НШЕ достовірно корелювала з треоніном ( $r = -0,316$ ), серином ( $r = -0,336$ ), гліцином ( $r = -0,397$ ), ізолеїцином ( $r = 0,317$ ), ВСАА ( $r = 0,356$ ) і сумою гліцин+серин ( $r = -0,302$ ) плазми ( $p < 0,05$ ). Пароксизм ФП достовірно корелював з таурином ( $r = -0,302$ ), серином ( $r = -0,328$ ), гліцином ( $r = -0,311$ ), глутаміном ( $r = -0,304$ ) і сумою гліцин+серин ( $r = -0,379$ ) плазми ( $p < 0,05$ ). Загальна кількість ШЕ достовірно корелювала з гліцином ( $r = -0,370$ ) і тирозином ( $r = 0,325$ ) плазми,  $p < 0,05$ . Зміни сегмента ST достовірно корелювали з тирозином ( $r = 0,307$ ), фенілаланіном ( $r = 0,318$ ) та ароматичними АК ( $r = 0,379$ ) плазми ( $p < 0,05$ ). Ми дійшли висновку, що гліцин, серин і ВСАА достовірно корелюють із серцевими аритміями. Зміни сегмента ST достовірно корелюють з рівнями ароматичних АК.

**Ключові слова:** порушення серцевого ритму, ішемія, аритмія, метаболоміка.

*Надійшла до редакції 18.01.2023*

**Information about the authors:**

*Melnychuk Iryna* – PhD, associate professor, Internal Medicine Department No.4, Bogomolets National Medical University, Kyiv, Ukraine

Address: Ukraine, 01601, Kyiv, Taras Shevchenko Blvd, 13.

E-mail: [ira.merkulova45@gmail.com](mailto:ira.merkulova45@gmail.com)

ORCID: 0000-0002-0659-1476.

*Sharayeva Maryna* – PhD, associate professor, Internal Medicine Department No.4, Bogomolets National Medical University, Kyiv, Ukraine

Address: Ukraine, 01601, Kyiv, Taras Shevchenko Blvd, 13.

E-mail: [malesha.kyiv@gmail.com](mailto:malesha.kyiv@gmail.com)

ORCID: 0000-0002-8891-7336.

*Kramarova Viktoriia* – MD, PhD, professor, Internal Medicine Department No.4, Bogomolets National Medical University, Kyiv, Ukraine

Address: Ukraine, 01601, Kyiv, Taras Shevchenko Blvd, 13.

E-mail: [viktoriia.kramarova@gmail.com](mailto:viktoriia.kramarova@gmail.com)

ORCID: 0000-0003-2978-3320.

*Lyzogub Viktor* – MD, PhD, professor, chief of Internal Medicine Department No.4, Bogomolets National Medical University, Kyiv, Ukraine

Address: Ukraine, 01601, Kyiv, Taras Shevchenko Blvd, 13.

E-mail: [vglizogub@gmail.com](mailto:vglizogub@gmail.com)

ORCID: 0000-0003-3603-7342.