PLASMA AND PLATELETS AMINO ACIDS IN CORONARY ARTERY DISEASE AND ATRIAL FIBRILLATION PATIENTS – ARE THEY LINKED?

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ABSTRACT

Background. The impact of circulating amino acid levels and their combinations on the pathogenesis of ischemic heart disease and atrial fibrillation is a current issue, otherwise, the platelets amino acid spectrum is still under discussion, despite the known pathogenetic role of platelets in these disorders.

Aim. To compare changes in the plasma and platelets amino acid spectrum in patients with coronary artery disease and atrial fibrillation as well as to find their connections.

Materials & Methods. 300 patients were divided into 3 groups: I group – 149 patients with coronary artery disease without arrhythmias, II group – 124 patients with coronary artery disease and atrial fibrillation paroxysm, and the control group – 27 patients without coronary artery disease and arrhythmias. Plasma and platelet amino acid levels were detected by means of ion exchange liquid column chromatography.

Results & Conclusions. In platelets amino acid spectrum, a significant rise in leucine (12.63%), isoleucine (10.73%), and Fishers' ratio (6.37%); a decrease in threonine (23.05%), valine (30.83%) levels, glycine (32.21%), serine (5.06%), and glycine+serine sum (20.51%) in group 2 patients was found compared with group 1, $p<0.05$. In the plasma amino acids spectrum, a significant increase in glutamate, branched-chain amino acids, and Fishers' ratio and a decrease in glycine in group 2 patients was checked in comparison with group 1, $p<0.05$. Only 10 moderate strength correlations were revealed between the plasma and platelets amino acid spectrum of investigated patient's groups. These changes in platelets and plasma amino acids spectrum were not significantly congruent in patients with coronary artery disease and atrial fibrillation. Plasma and platelets amino acid spectrum should be analyzed separately in patients with coronary artery disease and atrial fibrillation for further studies and evaluation of new prognostic markers and pathogenetic clues to their development.

Keywords: *myocardial ischemia, heart rhythm violations, proteins, metabolomics.*

Abbreviations:

Coronary Artery Disease (CAD), Atrial Fibrillation (AF), CardioVascular (CV), InterLeukin (IL), Amino Acids (AAs), Platelet Count (PC), Platelet Distribution Width (PDW), Mean Platelet Volume (MPV), Platelets-to-Leucocytes Ratio (PLR), Branched-Chain AAs (BCAA), Control Group (CG), Body Mass Index (BMI), Total Cholesterol (TC), Glomerular Filtration Rate (GFR), Myocardial Infarction (MI), aromatic AAs (AAAs), Sulfur Contains AA (SCAAs).

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Introduction

Coronary Artery Disease (CAD) and Atrial Fibrillation (AF) are known and widely spread CardioVascular (CV) pathology. Batta A. et al. notes that more than half of AF cases are accompanied by CAD [1]. Based on the world statistics, 16% to 28% Ukrainian population suffered from AF from 1990 to 2019 years. Moreover, data vary according to sociodemographic index quintiles – poverty leads to the worst AF prognosis and increases its quantity in the population [2]. CAD and AF are pathogenetically closely linked and have numerous similar risk factors, such as arterial hypertension, obesity, diabetes mellitus, dyslipidemia, inflammatory disease, etc. Besides, CAD is one of

the main and most important AF risk factors by itself [3; 4].

CAD and AF pathogenesis is undoubtedly closely linked with prothrombotic states. Platelet condition represents an important part of the hemostatic balance. Platelet activation is directly involved in thrombosis and inflammation processes, which are the known key factors in AF paroxysm development. Zhou P. et al. describes the importance of proinflammatory markers evaluation in prediction permanent AF development in CAD patients. They note that evaluation of InterLeukin-1 (IL-1), IL-6, IL-10 and C-reactive protein have the high predictive potential for evaluating the probability of permanent AF development [5]. Proinflammatory cytokines levels are closely linked with circulating nitrogen-contain Amino Acids (AAs) as arginine, glutamine etc. Arribas-Lopes E. et al. found that glutamine supplementation leads to significant rise of IL-6, which closely associated with increased morbidity and mortality [6]. Also, Zhang L. et al. notes that AF and CAD are characterized by a decrease in Platelet Count (PC) and a rise in Platelet Distribution Width (PDW), Mean Platelet Volume (MPV), and Platelets-to-Leucocytes Ratio (PLR). Nowadays correction platelet characteristics in CAD and AF patients is an attractive substrate for AF paroxysm development prophylaxis in CAD patients [7; 8].

Metabolomic is a newer powerful tool for detection of global and cardiac-specific metabolism. It targets small molecule metabolites (sugars, nucleotides, AAs, and lipids). Proteomics is a crucial metabolomic part, which includes AAs exchange peculiarities in CV diseases [8]. The violations of AAs metabolism in CV patients are up-to-date and widely discussed in scientific society. A prevalence of studies describes circulating AAs values and their role in CV pathology pathogenesis [8; 9], but there is still a lack of data about platelets AAs composition in patients with CAD and AF.

Previous studies have shown several changes in the circulating AAs profile, which can be associated with AF development, but the obtained data are controversial. Also, She J. et al. mentioned that circulation AAs peculiarities are common for the majority of metabolic disorders, which are known as AF and CAD risk factors. The depth of metabolic disorders inherent in AF is shown by plasma AAs violations. Furthermore, therapeutic amino acids supplementation can be an attractive decision for AF paroxysm prevention and management [10]. On the other hand, Huang J. et al. described that AAs play an important role in platelet metabolism: calcium release, integrin activation, granular secretion, and shape changes [11]. For example, Branched-Chain AAs (BCAA) promote thrombosis risks [7]. Meanwhile, Bayron-Marrero Z. et al. noticed that the AAs composition of platelet receptors is crucial for CAD development and prognosis [12]. Thus, platelet proteome investigation is an up-to-date scientific problem [11]. Moreover, the changes in platelets and plasma AAs spectrum coinciding or mismatched are still unclear.

The aim of the study was to compare the changes in the plasma and platelets amino acids spectrum in patients with coronary artery disease and atrial fibrillation and to find their relations.

Materials & Methods

Mean characteristics of investigated groups are shown in *Table 1*.

Plasma and platelet AAs levels were investigated by ion exchange liquid column chromatography. Automatic amino acids analyzer T 339 (Mikrotehna, Czech Republic) was used. Blood sampling from patients was taken fasted from the cubital vein, before treatment. Citrated blood was centrifuged during 10 minutes with at a speed of 1500 revolutions per minute. For platelets collection the middle layer was selected by a Pasteur pipette, there plasma was saturated by platelets. This material was again centrifuged during 20 minutes with a speed of 3000 revolutions per minute. The upper supernatant liquid was collected by a Pasteur pipette, after the lower layer was washed by phosphate buffer solution with pH 6.2. Then washed platelets are resuspended in a buffer (pH 7.4). Twenty (20) AAs were identified in this study: arginine, lysine, alanine, ornithine, histidine, isoleucine, taurine, methionine, threonine, asparaginic acid, serine, proline, glutaminic acid, glycine, cysteine, tyrosine, valine, phenylalanine, leucine, glutamine. They include BCAAs – isoleucine, leucine, and valine; aromatic AAs (AAAs) – tyrosine and phenylalanine; Sulfur Contains AAs (SCAAs) – taurine, cysteine, and methionine [7]. All patients signed an informed consent to participate in the study.

The results were presented as mean ± standard error or for continuous variables. Pearson criterion checked variable distribution for normality. The data were compared using Wilcoxon signed-rank test or Student t-test with two critical regions by the type of distribution. Spearman's correlation analysis was used to explore their correlations [15]. MATLAB R2014a (MathWorks, Inc., USA, License No.271828) was used for calculations.

Table 1. The characteristics of investigated groups

Characteristic /group	Group 1	Group 2	Control group (CG)
Patients number	149	124	27
Patients' diagnosis (by the recent ESC guidelines [3; 4].)	CAD and without arrhythmias	AF paroxysm and CAD	without CAD and arrhythmias
Diagnosis conformation	coronary artery stenotic changes during invasive coronary angiography in history	12 leads electrocardiography at rest	exclusion by Holter ECG and history
Baseline characteristics	age, gender, Body Mass Index (BMI), Total Cholesterol (TC), total bilirubin, uric acid, Glomerular Filtration Rate (GFR), and Myocardial Infarction (MI), stroke, diabetes mellitus in history		
Exclusion criteria	reported malignancies, heart failure Class III to IV (by New York Heart Association [13]), thyroid pathology, chronic kidney disease (GFR <60 ml/min), valvular AF, irritable bowel syndrome, inflammatory bowel disease, vegetarians and vegans, pregnancy, usage of the probiotics and antibiotics for a three month before the study.		
Ethical improvement of the protocol	in the ethical commission of Kyiv City Clinical Hospital No.12 (No.8 on August 22, 2018). Informed consent was obtained from all subjects according to the Declaration of Helsinki [14].		
Study location	the cardiological and therapeutic departments of Kyiv City Clinical Hospital No.12 in 2018–2023 years		
Study laboratory	laboratory in Kyiv City Clinical Hospital No.12 (certificate # ІІТ – 257/21).		

The study was conducted according to the department scientific research project "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).

Results

All baseline characteristics were investigated in the observed patients. In groups 1 and 2, TC (32.64% and 43.06% respectively) and uric acid (22.66% and 30.53% respectively) levels were increased and GFR (by 26.16% and 19.38% respectively) was decreased in comparison with CG ($p<0.05$). In groups 1–2 included patients with stroke, or MI history, diabetes mellitus, obesity, such cases was not in CG. In both investigated groups no significant difference was found in the age and gender, total bilirubin, BMI, and smoking history ($p<0.05$). The data are shown in *Table 2*.

Platelet AAs spectrum was analyzed in investigated patients. Thus, in group 1 demonstrated a decrease in taurine (20.26%), serine (9.31%), and glycine (19.73%) and an increase in isoleucine (12.41%) level versus the CG ($p<0.05$). And group 2 showed decline in threonine (29.37%), taurine (19.84%), glycine (45.59%), serine (13.90%), and valine (27.87%), and a rise in leucine (10.20%), isoleucine (24.47%) levels versus the CG ($p<0.05$). In group 2, a decrease in serine (5.06%), threonine (23.05%), valine (30.83%), glycine (32.21%), and an increase in leucine (12.63%), and isoleucine (10.73%) levels were observed versus group 1 ($p<0.05$). The data are shown in *Fig. 1*.

The platelets AAs combinations were detected for a deeper understanding of propionic violations in investigated groups. In group 2 patients, an increase in AAAs (13.58%), BCAAs (10.34%), Fishers' ratio (26.50%), and a significant decrease in SCAAs (19.25%) and glycine+serine sum (32.91%) versus the CG ($p<0.05$) were found. In group 1 patients a significant increase in BCAAs (7.28%), Fishers' ratio (18.93%), and a decrease in SCAAs (19.52%) and glycine+serine sum (15.60%) ver-sus the CG, $p<0.05$ were revealed. In group 2 patients an increase in Fishers' ratio (6.37%) and a significant decrease in glycine+serine sum (20.51%) versus group 1 ($p<0.05$) were present. The data are presented in *Fig. 2*.

Table 2. The baseline characteristics of the study groups, mean ± standard error

Characteristic /group	Group 1	Group 2	CG
Age (years)	67.71±3.90	67.96±0.94	56.25±2.18
Men (%)	48.99	47.97	48.15
Smoking (%)	51.01	41.46	40.74
History of myocardial infarction (%)	30.87^{+}	26.02$^{\#}$	0
History of stroke (%)	8.72^{+}	8.13$^{\#}$	0
Diabetes mellitus (%)	18.12^{+}	14.63$^{\#}$	0
Obesity (%)	8.84^{+}	12.0$^{\#}$	0
BMI (kg/m^2)	27.02±0.33	26.93±0.43	27.12±2.10
Total bilirubin (mmol/l)	11.3±0.09	12.4±0.08	11.7±0.11
Uric acid (mmol/l)	380.5±28.16^{+}	404.9±36.11$^{\#}$	310.2±29.12
GFR (ml/min)	62.03±2.31^{+}	67.73±1.98$^{\#}$	84.01±5.48
TC (mmol/l)	5.73±0.37^{+}	6.18±0.31$^{\#}$	4.32±0.21

Notes: $^{+}$ – (p<0.05) I group – CG; $^{\#}$ – (p<0.05) II group – CG; * – (p<0.05) I–II groups.

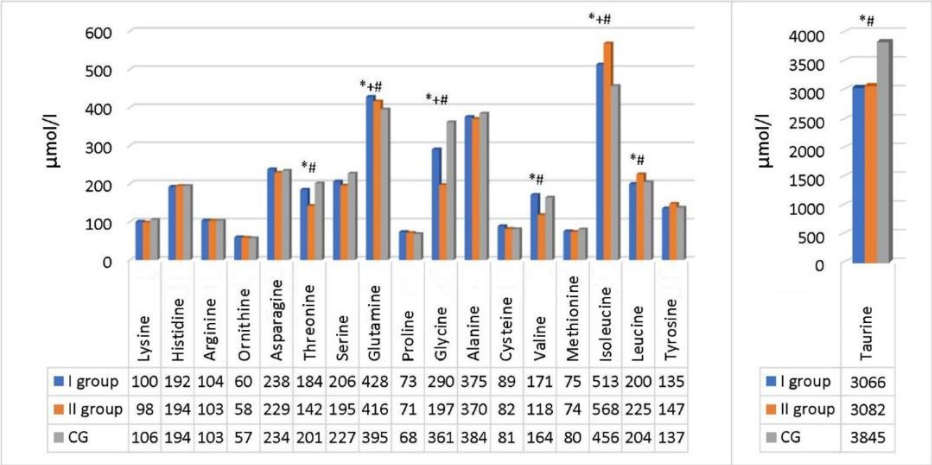

Fig. 1. Platelets amino acids profile in investigated groups, µmol/l.

Notes: $^{+}$ – (p<0.05) I group – CG; $^{\#}$ – (p<0.05) II group – CG; * – (p<0.05) I–II groups, CG – control group.

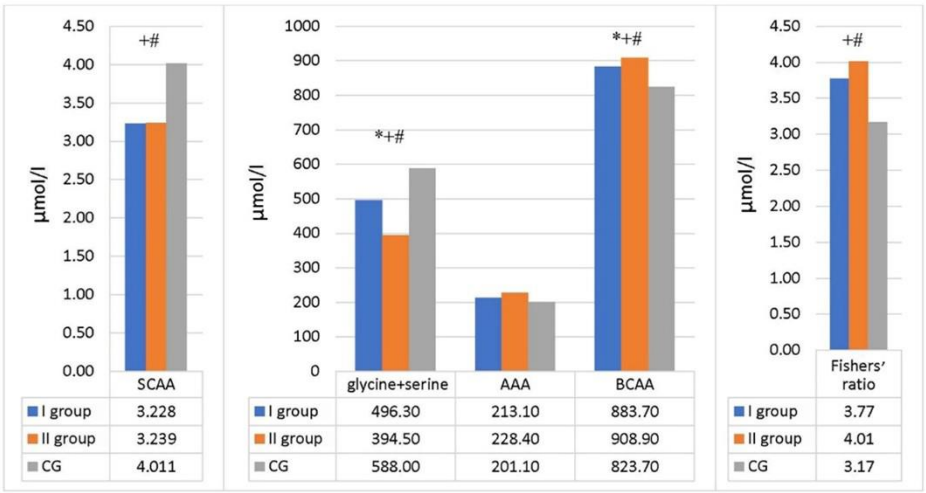

Fig. 2. Platelets amino acids combinations in investigated groups, µmol/l

Notes: $^{+}$ – (p<0.05) I group – CG; $^{\#}$ – (p<0.05) II group – CG; * – (p<0.05) I–II groups; CG – control group; BCAA – branched chain amino acids; AAA – aromatic amino acids; SCAA – sulfur contain amino acids.

The plasma AAs spectrum was analyzed in investigated groups. In group 1 patients a significant decrease in glycine, valine, and alanine levels was detected versus the CG ($p<0.05$). In group 2 patients an increase in glutamate, and a significant decrease in glycine, valine, alanine, serine, and glutamine levels were revealed compared with the CG ($p<0.05$). In group 2, a rise in glutamate and a significant depletion in glycine levels were detected versus group 1, $p<0.05$.

The data are presented in *Fig. 3* and *Table 3*.

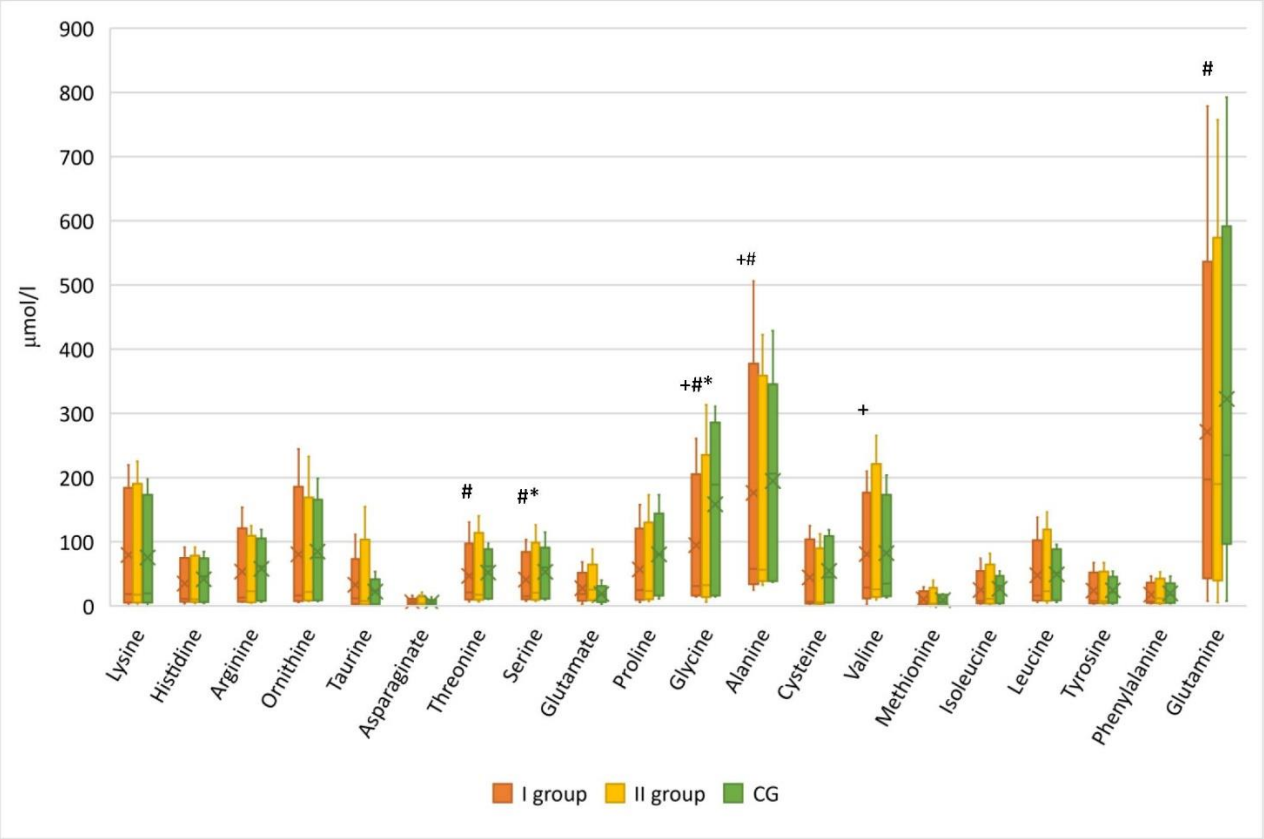

Fig. 3. Plasma amino acids spectrum in investigated groups, µmol/l

Notes: $^{+}$ – ($p<0.05$) I group – CG; $^{\#}$ – ($p<0.05$) II group – CG; * – ($p<0.05$) I–II groups; CG – control group.

Table 3. Plasma amino acids spectrum in investigated groups, µmol/l

Characteristic /group	Group 1	Group 2	CG	$p_{G1–G2}$	$p_{G2–CG}$	$p_{G1–CG}$
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

Characteristic /group	Group 1	Group 2	CG	$p_{G1–G2}$	$p_{G2–CG}$	$p_{G1–CG}$
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
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
Phenylalanine	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

Also, plasma AAs were combined according to their biochemical properties and exchange and these results were compared in investigated groups. In group 2, a rise in BCAAs and Fishers' ratio was found versus group 2 (p<0.05). In group 2, a significant rise in BCAAs and Fishers' ratio and a decrease in glycine+serine sum was found versus the CG (p<0.05). In group 1, a rise in Fishers' ratio and a decrease in glycine+serine sum was present versus the CG, p<0.05.

The data are presented in *Fig. 4* and *Table 4*.

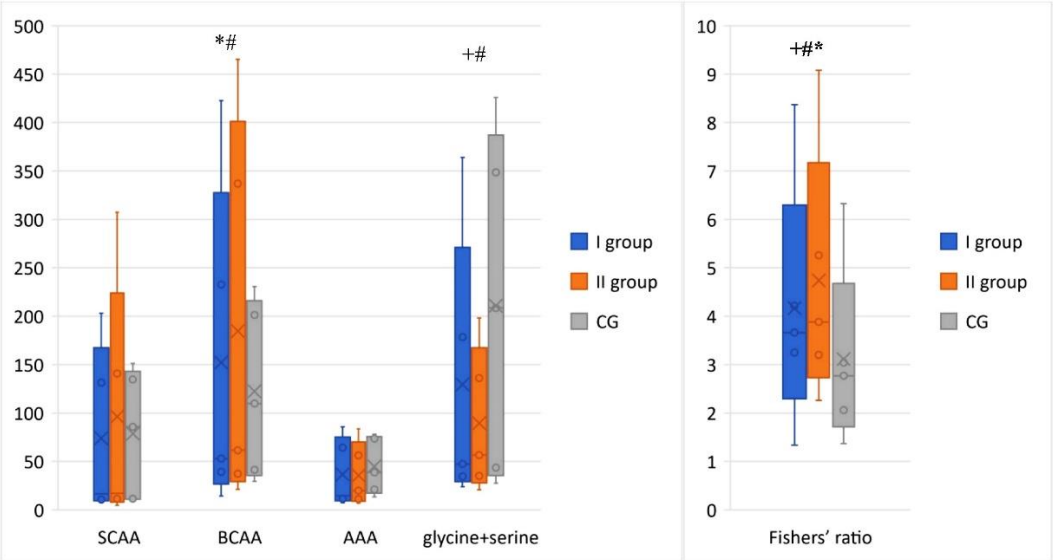

Fig. 4. Plasma amino acid combinations in investigated groups, μmol/l

Notes: $^{+}$ – ($p<0.05$) I group – CG; $^{\#}$ – ($p<0.05$) II group – CG; * – ($p<0.05$) I–II groups; CG – control group; BCAA – branched chain amino acids; AAA – aromatic amino acids; SCAA – sulfur contain amino acids.

Table 4. Plasma amino acid combinations in investigated groups, μmol/l

Characteristic/group	Group 1	Group 2	CG	$p_{G1–G2}$	$p_{G2–CG}$	$p_{G1–CG}$
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
Fishers' ratio	3.66 [3.31; 4.04]	3.88 [3.29; 4.52]	2.77 [1.97; 3.14]	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

The correlation analysis between plasma and platelet AAs spectrum was done in the study. The biggest number of correlations was checked between the plasma AAs spectrum and asparagine acid (total number = 3). The largest amount of correlations was found between platelet AAs spectrum and glutamic acid (total number = 3). The data are presented in *Fig. 5*.

In sum, in this study the plasma and platelet AAs spectrum and their combinations were revealed and compared in group 1 (patients with CAD and without arrhythmias), group 2 (patients with CAD and AF), and control group (patients without CAD and AF). The correlation analysis between plasma and platelets AAs spectrum was performed to reveal their associations.

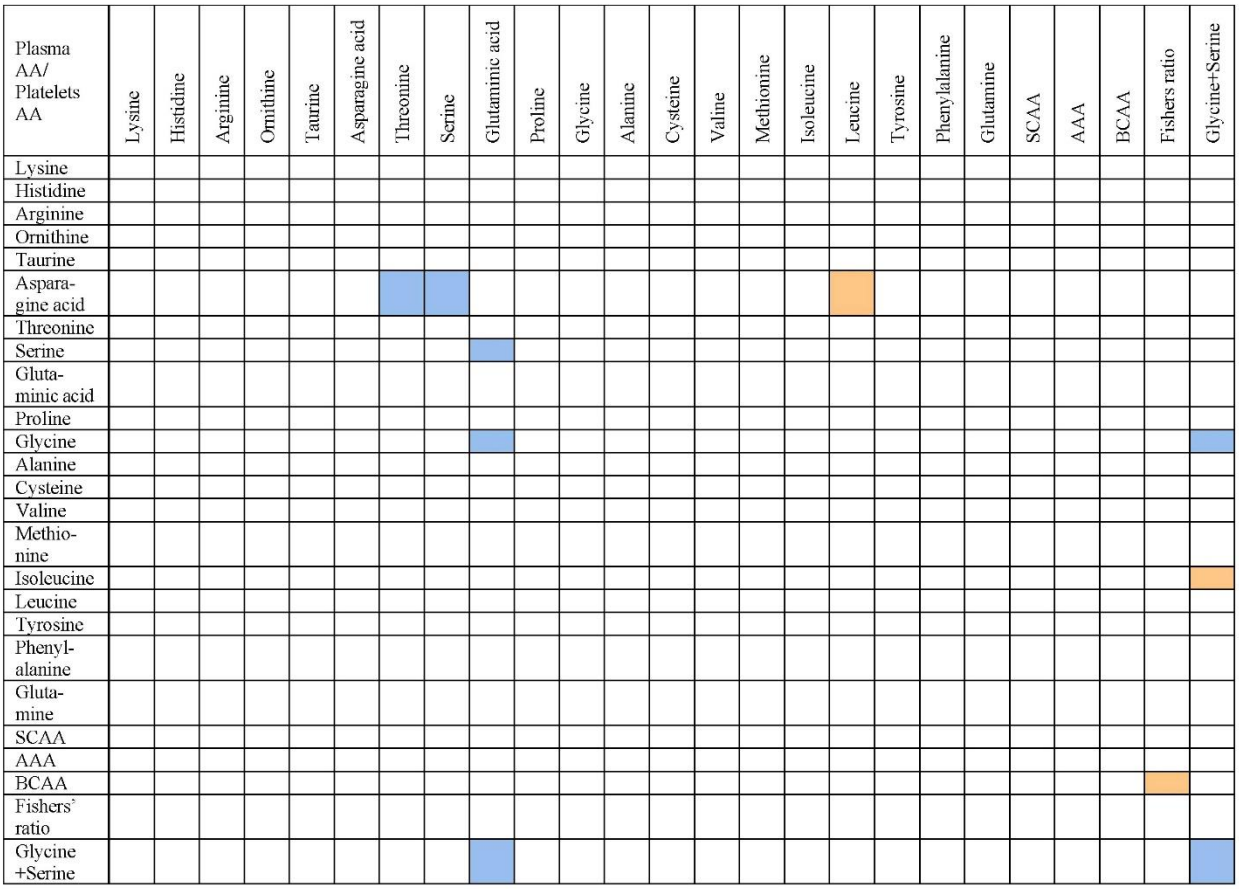

Fig. 5. Correlation matrices between plasma and platelet amino acids spectrum, $p<0.05$

Notes: – moderate negative correlations; – moderate positive correlations;
BCAA – branched chain amino acids; AAA – aromatic amino acids; SCAA – sulfur contain amino acids.

Discussion

Evaluation of plasma AAs features in patients with CV pathology is widely used. Several studies describe changes in plasma AAs profile in patients with arterial hypertension [16], coronary artery disease, heart failure [17], atrial fibrillation [8], etc. According to the obtained data patients with CAD and AF paroxysm were characterized by BCAAs, AAAs, glycine, serine, and threonine exchange violations in comparison with CAD and without arrhythmias group, what can imply their role in AF paroxysm development. Also, Fisher's ratio was increased in CAD patients with and without AF congruently.

These data are matched with the literature overview. According to Zhang L. et al. study, AF paroxysm is closely appropriate with glycine, serine, and threonine exchange [8]. Chu C. et al. noticed that their metabolism in cardiomyocytes is closely linked, and they can be a precursor of each other. Glycine metabolism is indirectly closely developed with the one-carbon metabolism pathway, which provides homocysteine regulation, DNA methylation, generation of methyl donors, and other components of antioxidative action. Glycine is also improving nitric oxide synthesis, thereby increasing central arterial pressure and arterial stiffens. According to several studies, it has anti-inflammatory and antilipidemic properties, thereby preventing atherosclerosis development [18; 19]. Cifuentes F. et al. described that, glycine depletion is associated with autonomic dysregulation, thereby an increase in sympathetic activity and cardiac autonomic remodeling formation [20]. Furthermore, the glycine, serine, and threonine metabolism pathway play a crucial role in energy regulation [18]. According to Gao X. et al. data, serine regulates mitochondrial activity, thereby cell formation and proliferation. Mitochondrial serine metabolism is thought to be considered for

cellular NADPH production. Precisely serine exchange is closely linked with lipids and indirectly with glucose exchange. Nucleotide synthesis, redox balance, and alteration of sphingolipids metabolism are intricately, but tightly connected with serine level [21]. In the Mesubi O. et al. animal experiment, serine-threonine protein kinases are abundant in the myocardium thereby linked with membrane excitability, calcium homeostasis, matrix remodeling, apoptosis, which are the basis for atrial remodeling and AF paroxysm development [22]. Tang Q. et al. noticed that serine and threonine in intestinal barrier permeability conduction and mucin production, are the crucial part of microbial endotoxemia development [23]. According to Gawalko M. et al. overview, gut microbiota, and its metabolites, which include AAs, play an important role in AF pathogenesis and are a remarkable part of most metabolomic studies [24]. Gut microbiota and AAs exchange relations are interesting and up-to-date scientific topic, which can be useful in the search of a new AF paroxysm prevention and management therapeutic strategies [25]. This study presents deeper insight into relations between platelets and plasma amino acids, but their links with gut microbiota composition are also interesting scientific question.

Also, BCAAs plasma levels and Fisher's ratio were increased in patients with CAD and AF. According to Karadeniz A. et al., increase of BCAAs concentrations regulates the mTOR signaling pathway, which is a central regulator of cellular metabolism, that improves insulin resistance and provokes low-grade chronic inflammation. Redundant BCAAs is addicted to atrial accumulation, which aggravates tissue fibrosis and mitochondrial oxidation. Moreover, BCAAs improved platelet activity, leading to their activation and degranulation by promoting thrombomodulin-3 propionylation [26]. Yang S. et al. mentioned that it is no wonder that glycine, serine, threonine, and BCAAs metabolism disruption are associated with life-threatening ventricular arrhythmias [27]. In Zhang J. et al. animal experiments, a rise of circulating BCAAs (mostly leucine and isoleucine) is associated with hypertriglyceridemia, thereby CV pathology via the mTOR/SREBP-1/betatrophin pathway. Moreover, BCAAs increase indirectly associated with diabetes mellites and fatty liver. Interesting, circulating BCAAs levels can be successfully reduced by metformin supplementation [28]. AAAs are involved in inflammatory processes by their impact on T lymphocytes and macrophage function. Tyrosine plays an important role in nitric oxide production. Phenylalanine is a precursor of adrenaline, noradrenaline, and thyroid hormones. Undoubtedly, all described mechanisms take part in CVD development [18]. Fishers' ratio is a known marker of CV events. It is calculated as BCAAs/AAAs circulating values. Thus, an increase in BCAAs and a decrease in AAAs are the important characteristic of investigated patients [8].

Despite this, the plasma AAs spectrum is characterized by high variability. It depends on the numerosity of external and internal factors, such as age, gender, diet, physical activity [29], coexistent diseases, mental state, stress [30], etc. This can be a limitation for further plasma AAs investigations. Moreover, the plasma and serum AA spectrum can be different, which needs further investigation and what can be the cause of misunderstanding in circulating AAs values analysis.

The evidence points out that the role of platelets in AF paroxysm pathogenesis is increasing. Platelets AAs composition is corelated with transthoracic echocardiography indexes. Left atrium characteristics are directly related with leucine level and inversely with alanine and serine levels. At the same time, left ventricular indices correlated with serine, threonine, alanine, arginine, and isoleucine levels, what proved the role of such platelet's changes in prothrombotic state development [31]. Huang J. et al. noticed that the platelet activation process is connected with its unique proteomic changes [32], which can be not congruent with cardiomyocytes and plasma features. In the Song Y. et al. experimental study it was suggested that AAAs derivates can activate platelets and mediate thrombosis via adrenergic receptor activation. Their production is connected with gut microbiota composition via a rise of pathogenic strains, such as Streptococcus spp., Enterococcus spp., and Ruminococcus spp., which can induce AF via an increase of trimethylamine-N-oxide, indole sulfate, and primary bile acids circulation [33]. The topic of thrombosis-associated metabolomics is understudied, and has a big potential for new biomarkers identification. Extracellular glycine is characterized by antithrombotic properties via CD8+ T-cell activation, which interacts with extracellular toxicity and thrombogenesis [34]. Huang K. et al. noticed that the prothrombotic state is closely linked with metabolic disorders, via gut microbiota metabolites that include AAs profile by itself and their derivates, such as trimethylamine-N-oxide, etc. several gut microbiota metabolites potentiating cytosolic phospholipase

A2 activation and platelets hyperresponsiveness, via inhibition of integrin α2β1. Thus, gut microbiota condition and its metabolites, including AA profile and its derivates are attractive potential therapeutic targets for thrombosis prevention [35].

Therefore, plasma and platelets AAs spectrum both are an important characteristic of human health, forming AF and CAD pathogenesis at different points, which can provide a further prognosis of pathological process development and can be the target for secondary prophylaxis and treatment.

Presented study is mostly explained the obtained peculiarities in platelets and plasma AAs changes and their links during AF paroxysm in CAD patients. The limitations are the lack of previous studies in this area and variability of plasma AAs spectrum.

Conclusions

In this study plasma and platelet amino acids spectrum features in patients with coronary artery disease and atrial fibrillation were analyzed and compared, but reliable relationships were not found. In platelets amino acids spectrum, a significant decrease in serine (5.06%), threonine (23.05%), valine (30.83%), glycine (32.21%) levels, and glycine+serine sum (20.51%) and an increase in leucine (12.63%), isoleucine (10.73%), and Fishers' ratio (6.37%) in patients with coronary artery disease and atrial fibrillation was found compared with patients with coronary artery disease and without atrial fibrillation, $p<0.05$. In the plasma amino acids spectrum, a significant increase in glutamate, branched chain amino acids, and Fishers' ratio and a decrease in glycine in patients with coronary artery disease and atrial fibrillation was checked compared with patients with coronary artery disease and without atrial fibrillation, $p<0.05$. Ten (10) moderate strength correlations were revealed between plasma and platelets amino acids spectrum of investigated patient's groups. Therefore, according to the obtained data, the changes in platelets and plasma amino acids spectrum are not congruent. But they give us insight, which amino acids metabolism violation can lead to atrial fibrillation paroxysm formation in coronary artery disease patients. The obtained data are important for understanding the mechanism of action therapeutical amino acids administration in patients with coronary artery disease and atrial fibrillation. Besides, these results can help to choose the best amino acid or its combination for investigated pathologies and comorbidities.

The comparison of cardiomyocyte and platelet, plasma, and leucocyte amino acid profiles in patients with atrial fibrillation and coronary artery disease will be an interesting item for a deeper understanding of their pathophysiology.

DECLARATIONS:

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Data Transparency

The data can be requested from the authors.

Statement of Ethics

The authors have no ethical conflicts to disclosure.

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Consent for publication

All authors give their consent to publication.

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