Оригінальні дослідження
Original Researches

ГАСТРОЕНТЕРОЛОГІЯ
GASTROENTEROLOGY

Патологія кишечника / Bowel Pathology

UDC 616.12-008.313.2 *DOI: https://doi.org/10.22141/2308-2097.57.4.2023.573*

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

Platelet amino acid spectrum and gut microbiota, their links in patients with coronary artery disease and atrial fibrillation

For citation: Gastroenterologìa. 2023;57(4):227-233. doi: 10.22141/2308-2097.57.4.2023.573

Abstract. ***Background.*** *The aim of our work was to identify the links between platelet amino acid (AA) spectrum and gut microbiota composition in patients with coronary artery disease (CAD) and atrial fibrillation (AF) and to evaluate them.* ***Materials and methods.*** *Three hundred patients were enrolled in the study. They were divided into 3 groups: I (CAD) — 149 patients with CAD but without arrhythmias, II (CAD + AF) — 124 people with CAD and AF paroxysm, and control group (CG) — 27 individuals without CAD and arrhythmias. Platelet AA level was assessed by method of ion-exchange liquid column chromatography. Gut microbiota composition was studied by 16-S rRNA sequencing.* ***Results.*** *A significant increase in isoleucine (10.73 %), leucine (12.63 %) and a decrease in threonine (23.05 %), serine (5.06 %), glycine (32.21 %) and valine (30.83 %) platelets levels was found in patients with CAD and AF ($P < 0.05$). In addition, they had a significant increase in Bacteroides spp., Faecalibacterium prausnitzii, Actinobacter spp., Streptococcus spp., Ruminococcus spp. and a decrease in Lactobacillus spp., Bifidobacterium spp., Eubacterium rectale ($P < 0.05$). Platelet glutamine acid, valine, glycine, asparagine acid, threonine had the highest number of significant correlations with gut microbiota species ($P < 0.05$). Actinobacter spp., Blautia spp., Streptococcus spp., Akkermansia muciniphila and Roseburia inulinivorans had the highest number of significant correlations with platelet amino acids ($P < 0.05$).* ***Conclusions.*** *Platelet amino acid spectrum and gut microbiota composition in patients with coronary artery disease and atrial fibrillation are closely linked.*

Keywords: *coronary artery disease; atrial fibrillation; amino acids; blood platelets; gut microbiota composition*

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the world, which prevalence increased each year. While coronary artery disease (CAD) is the most common cardiovascular disease and one of the known risk factors of AF [1, 2]. Both diseases share associated risk factors, as dyslipidemia, inflammatory diseases, diabetes mellitus, arterial hypertension etc. CAD leads to atrial fibrosis development, which produce the reentry morphological substrate of AF. Near the half of patients with AF have CAD [3].

AF presence increased mortality 1.5–3.5 times, mostly due to stroke [1]. Because, AF is strongly associated with prothrombotic tendency, which pathogenesis is highly intricate and multifactorial. Also increased platelets activity is common for CAD patients. Activated platelets have a lot of prothrombotic and vasoactive factors. One of the important sine of platelets activation is an increasing of mean platelets volume, that shows us the morphological platelets changes. So, platelets are an important part of hemostatic balance and they directly affect prothrombotic state [4]. Each AF paroxysm is associated with platelets activation [5]. Repeated platelets activation is contributing thrombosis formation [6]. Moreover, antithrombotic therapy is essential for patients with AF and CAD because of the high risk of thrombosis, whereas a combination of antiplatelets and anticoagulants is associated with a high risk of bleeding [7].

Due to the recent data, special microbiota signature is common for AF occurrence. In large population-based study AF is characterized by positive associations with genera *Eisenbergiella*, *Enorma*, *Enterobacter*, *Kluyvera* and negative with genera *Bacteroides*, *Bifidobacterium*, *Holdemanella*, *Parabacteroides*, *Turicibacter* [8]. Also, some case-control

Для кореспонденції: Мельничук І.О., к.мед.н., доцент кафедри внутрішньої медицини № 4, Національний медичний університет імені О.О. Богомольця, бульв. Т. Шевченка, 13, м. Київ, 01601, Україна; e-mail: ira.merkulova45@gmail.com; тел.: + 380(50)2893355
For correspondence: Iryna Melnychuk, PhD, Associate Professor at the Department of Internal Medicine 4, Bogomolets National Medical University, T. Shevchenko boulevard, 13, Kyiv, 01601, Ukraine; e-mail: ira.merkulova45@gmail.com; phone: + 380(50)2893355
Full list of authors' information is available at the end of the article.

studies have shown genus and species changes in gut microbiota in AF patients. As enrichment of *Ruminococcus*, *Streptococcus*, *Enterococcus* and depletion of *Faecalibacterium*, *Alistipes*, *Oscillibacter*, *Bilophila* in AF patients. Or overgrowth of *Parabacteroides*, *Lachnoclostridium*, *Streptococcus*, *Alistipes* and reduction of *Enterobacter* was observed in AF patients in another study [9]. But these results are controversial.

Gut microbiota acts at the heart health through its metabolites toxicity: increasing plasma lipopolysaccharides (LPS), trimethylamine (TMA), trimethylamine-N-oxide (TMAO), bile acids, indole sulfate and decreasing fecal short chain fatty acids (SCFA) due to impaired intestinal barrier function [9]. That leads for autonomic remodeling (increasing sympathetic activity in heart innervation), structural remodeling (cardiac fibrosis, sell apoptosis, increasing conduction velocity) and electrical remodeling (reduction effective refractory period and increase after depolarizations) [10].

Platelets protein composition is an important component of their morphological and functional state. Proteins changes occurs during platelets activation and highly connected with prothrombotic conditions [11]. Also, platelets hyperactivity is connected with gut microbiota metabolites, including plasma amino acids (AA) composition, TMA, TMAO levels [12].

The aim: to estimate the links between platelet AA spectrum and gut microbiota composition in patients with CAD and AF and evaluate their connections.

Materials and methods

300 patients were enrolled in the study. They were divided into 3 groups: I (CAD) — 149 patients with CAD but without arrhythmias, II (CAD + AF) — 124 patients with CAD and AF paroxysm and control group (CG) — 27 patients without CAD and arrhythmias. CAD and AF diagnosis were based on latest ESC guidelines [1, 2]. All patients were treated in the Kyiv City Clinical Hospital 12, cardiological and therapeutic departments. Diagnosis CAD was confirmed by history of coronary arteries stenotic changes during invasive coronarography. AF paroxysm was checked by resting 12 leads electrocardiography. Exclusion criteria were: reported malignancies, chronic kidney disease (glomerular filtration rate (GFR) < 60 mL/min), valvular AF, heart failure class III to IV (by New York Heart Association), thyroid pathology, inflammatory bowel disease, irritable bowel syndrome, vegetarians and vegans, pregnancy, taking probiotics and antibiotics for a month before the study. No significant difference in risk factors at baseline were seen between investigated groups. The study was conducted at the base and was approved by the ethical commission of the Kyiv City Clinical Hospital 12 (protocol No. 8 from 22/08/2018). Informed consent was obtained from all subjects in accordance with the Declaration of Helsinki.

Baseline characteristics of study patients includes age, body mass index (BMI), uric acid, total bilirubin, GFR, total cholesterol (TC) levels. Uric acid, total bilirubin, creatinine and TC were checked by Kyiv City Clinical Hospital 12 laboratory (certificate ПТ-257/21). GFR was calculated by CKD-EPI creatinine equation [13]. 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 this baseline characteristics were analyzed and compared, because it can help us to exclude their influence on obtained results.

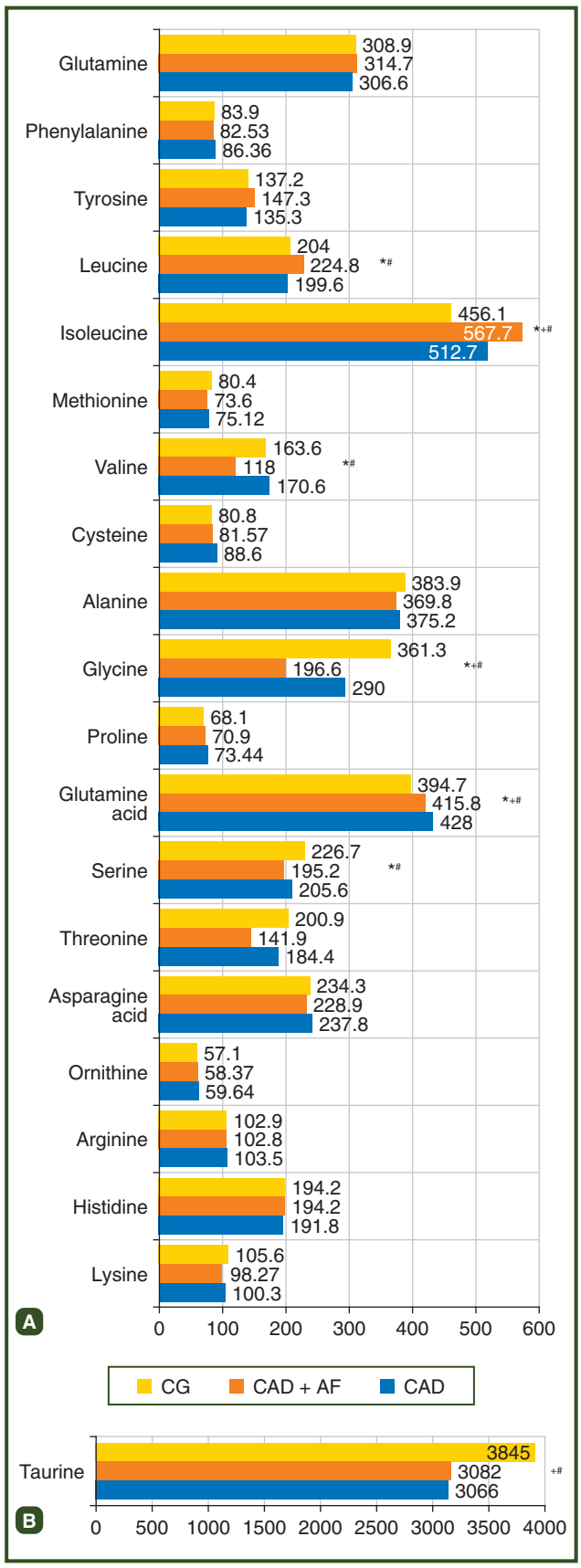
Platelets AA level was detected by method of ion exchange liquid column chromatography — such AA were identified: lysine, histidine, arginine, ornithine, taurine, asparagine acid, threonine, serine, glutamine acid, proline, glycine, alanine, cysteine, valine, methionine, isoleucine, leucine, tyrosine, phenylalanine, glutamine. Automatic amino acids analyzer T 339 (Mikrotechna, Czech Republic) were used in our study. Study was done in Bogomolets National Medical University. Blood sampling from patients was performed on an empty stomach from the cubital vein on the first day of hospitalization, before treatment. Citrated blood is centrifuged for 10 minutes at a speed of 1500 revolutions per minute. The middle layer is selected with a Pasteur pipette — the plasma is saturated with platelets. The obtained material is again centrifuged for 20 minutes at a speed of 3000 revolutions per minute. The upper supernatant liquid was collected with a Pasteur pipette, and the lower layer was washed with buffer (phosphate buffer solution pH 6.2). Washed platelets are resuspended in buffer (pH 7.4).

Determination of the gut microbiota composition was carried out using quantitative PCR qRT-PCR using primers for the 16S rRNA gene and taxon-specific primers. Such domains were checked: bacteria — *Firmicutes* (*Lactobacillus* spp., *Faecalibacterium prausnitzii*, *Enterococcus* spp., *Blautia* spp., *Streptococcus* spp., *Eubacterium rectale*, *Roseburia inulinivorans*, *Ruminococcus* spp.), *Bacteroides* (*Bacteroides* spp., *Bacteroides thetaiotaomicron*, *Prevotella* spp.) and other (*Bifidobacterium* spp., *Escherichia coli*, *Akkermansia muciniphila*, *Acinetobacter* spp.), and archaea (*Methanobrevibacter smithii* and *Methanosphaera stadmanae*).

Results were presented as mean ± standard error or [95% confidence interval (CI)] for continuous variables or as a number for categorical variables. Data were compared using Wilcoxon signed-rank test or Student t-test with two critical

Table 1 — Baseline characteristics of study sample, mean ± standard error

Characteristic/group	I group	II group	CG	P I–II	P II-CG	P I-CG
Age (years)	67.71 ± 3.90	67.96 ± 0.94	56.25 ± 2.18	> 0.05	> 0.05	> 0.05
BMI (kg/m^2)	27.02 ± 0.33	26.93 ± 0.43	28.12 ± 2.10	> 0.05	> 0.05	> 0.05
Total bilirubin (mmol/l)	11.30 ± 0.09	12.40 ± 0.08	11.70 ± 0.11	> 0.05	> 0.05	> 0.05
Uric acid (mmol/l)	380.50 ± 28.16	404.90 ± 36.11	310.20 ± 29.12	> 0.05	< 0.05	< 0.05
GFR (ml/min)	62.03 ± 2.31	67.73 ± 1.98	84.01 ± 5.48	> 0.05	< 0.05	< 0.05
TC (mmol/l)	5.73 ± 0.37	6.18 ± 0.31	4.32 ± 0.21	> 0.05	< 0.05	< 0.05



Notes (here and in Fig. 2): * — P < 0.05 I–II groups; + — I group vs CG; # — II group vs CG.

Figure 1 — Platelets AA spectrum in the investigated groups, μmol/l: A — platelets A spectrum; B — platelets taurine level

regions by the type of distribution; Spearman's rank correlation coefficient [14]. All calculations were done in MATLAB R2014a (license number 271828).

Results

At first baseline characteristics of investigated groups were analyzed. All investigated groups were similar by age, BMI and total bilirubin values. I and II groups patients were characterized by increase of TC (by 32.64 and 43.06 %, respectively), uric acid (by 22.66 and 30.53 %) and decrease of GFR (by 26.16 and 19.38 %) in comparison with CG. Data are shown in Table 1.

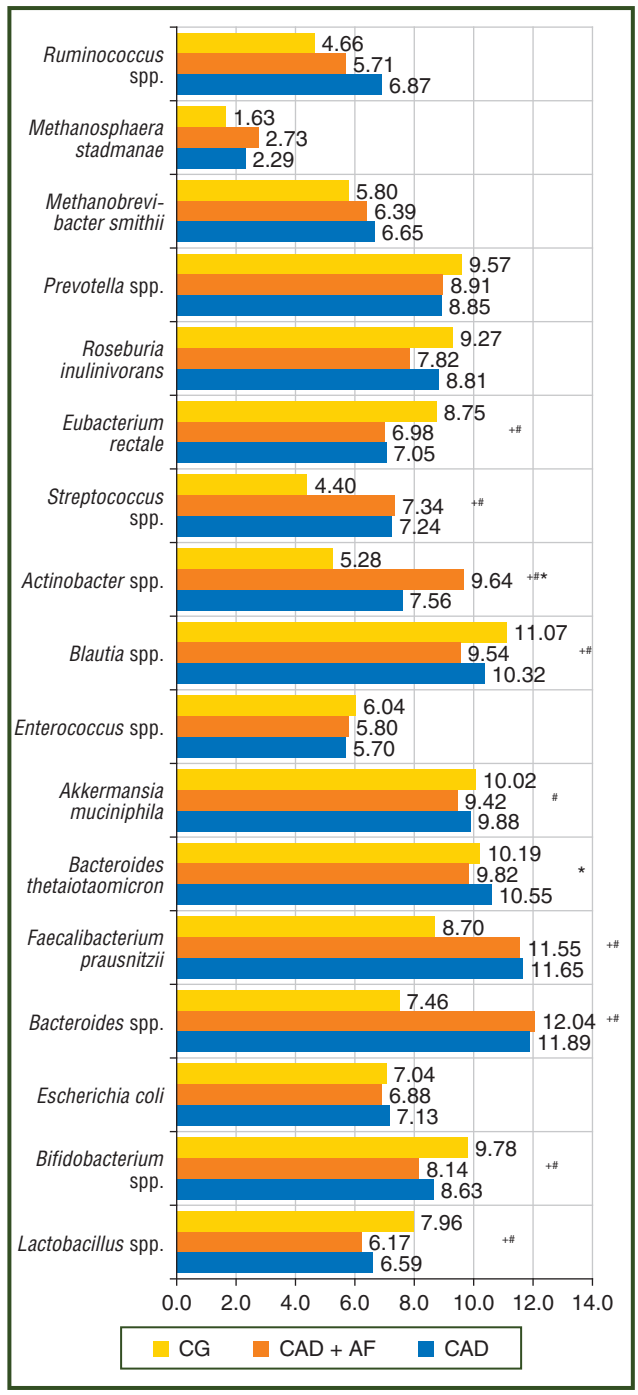


Figure 2 — Gut microbiota composition in the investigated groups, mean [95% CI], lg/CFU/ml

In this study platelets AA spectrum in I and II groups was compared with CG. During data analysis in the I group in comparison with CG was found significant increasing isoleucine (by 12.41 %), levels and decreasing taurine (by 20.26 %), serine (by 9.31 %) and glycine (by 19.73 %) levels. In II group in comparison with CG significant increasing isoleucine (by 24.47 %), leucine (by 10.20 %) and decreasing taurine (by 19.84 %), threonine by (29.37 %), serine (by 13.90 %), glycine (by 45.59 %) and valine (by 27.87 %) levels. Also, in II group in comparison with the I group significant increasing isoleucine (by 10.73 %), leucine (by 12.63 %) and decreasing threonine (by 23.05 %), serine (by 5.06 %), glycine (by 32.21 %) and valine (by 30.83 %) levels were detected. A general overview of investigated groups plasma AA levels is provided in Fig. 1.

Gut microbiota composition was estimate in investigated groups. By the species analysis results in the II group comparing with I group is significant increasing *Actinobacter* spp. and decreasing *Blautia* spp., *Roseburia inulinivorans*, *Bacteroides thetaiotaomicron*; in the II group comparing with CG is significant increasing *Bacteroides* spp., *Faecalibacterium prausnitzii*, *Actinobacter* spp., *Streptococcus* spp. and decreasing *Lactobacillus* spp., *Bifidobacterium* spp., *Akkermansia muciniphila*, *Blautia* spp., *Eubacterium rectale*; in the I group comparing with CG is significant increasing *Bacteroides* spp., *Faecalibacterium prausnitzii*, *Actinobacter* spp., *Streptococcus* spp., *Ruminococcus* spp. *and* decreasing *Lactobacillus* spp., *Bifidobacterium* spp., *Eubacterium rectale*. Results are presented in the Fig. 2.

The correlation analysis between platelets AA spectrum and the clinical and laboratory characteristics, gut microbiota composition of the examined groups was done. Gut microbiota composition and platelets AA spectrum had the largest amount of correlations in such species as *Actinobacter* spp. (total number = 9), *Blautia* spp. (total number = 8), *Streptococcus* spp. (total number = 7), *Akkermansia muciniphila* (total number = 7) and *Roseburia inulinivorans* (total number = 7); also, such AA as glutamine acid (total number = 11), valine (total amount = 10), glycine (total number = 9), asparagine acid (total number = 9) and threonine (total number = 8). At the same time, the highest amount of correlations was between TC level and platelets AA (total

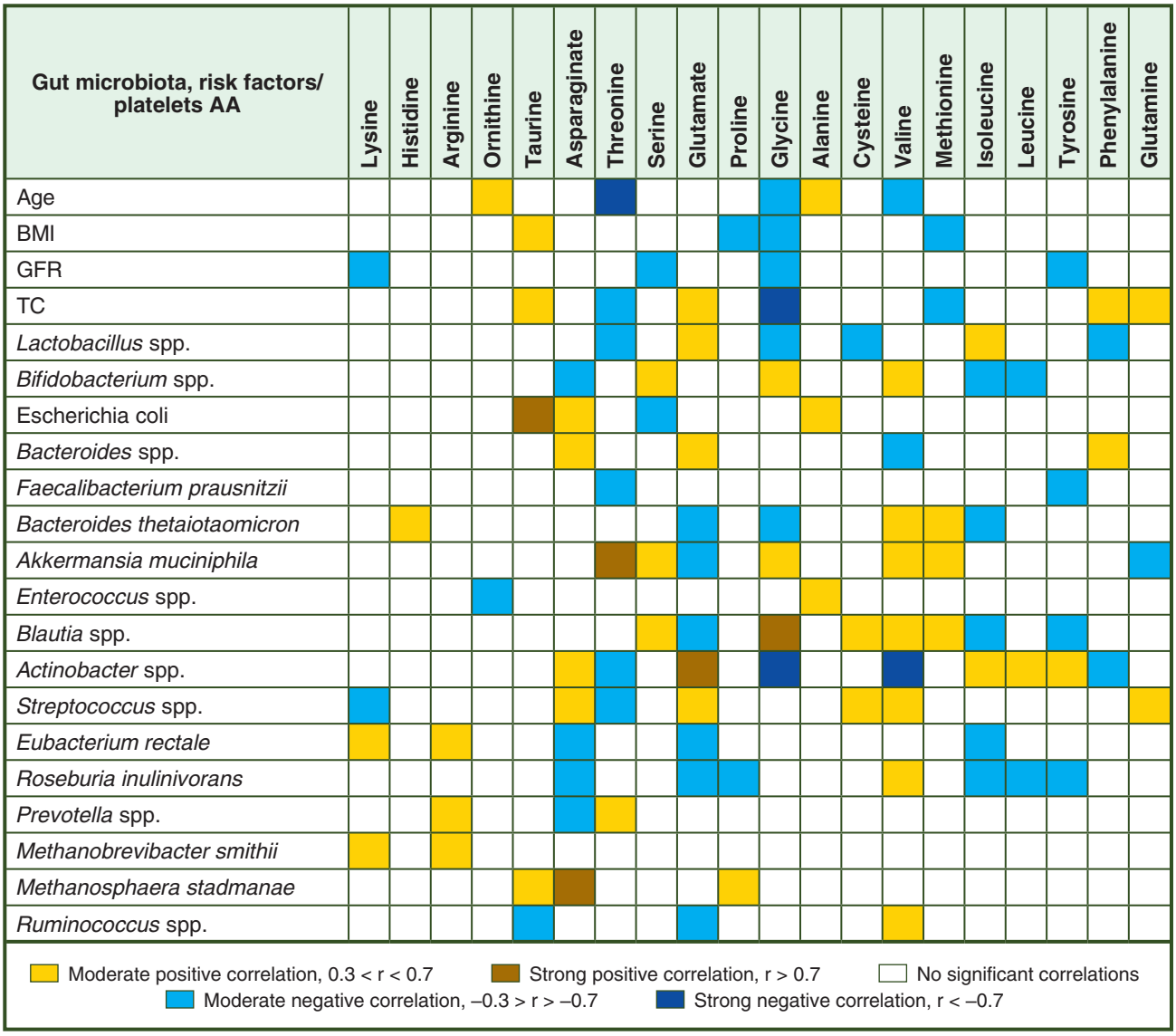


Figure 3

number = 7). Strong correlations ($P < 0.05$) were found between: taurine and *Escherichia coli* (r = 0.714), asparaginate and *Methanosphaera stadmanae* (r = 0.716), threonine and age (r = –0.727), threonine and *Akkermansia muciniphila* (r = 0.703), glutamate and *Actinobacter* spp. (r = 0.744), glycine and total cholesterol (r = –0.715), glycine and *Blautia* spp. (r = 0.708), glycine and *Actinobacter* spp. (r = –0.769), valine and *Actinobacter* spp. (r = –0.736). All correlations are shown in the Fig. 3.

Discussion

Unfortunately, it is no evidence about platelets AA spectrum in patients with AF and CAD. But, due to literature data, platelets AA profile changes are present for their risk factors, as diabetes mellitus [15], etc. So, platelets AA spectrum in patients with AF and CAD was checked first time in our work.

The role of platelets in AF pathogenesis is undoubted. Such platelets morphological and functional characteristics as platelet count, mean platelets volume, platelet distribution width, platelet factor 4, beta thromboglobulin and p-selectin are closely linked with AF paroxysm occurrence and consequent stroke. Platelets volume, distribution and factors of activity are significantly higher, but platelets count is lower in AF patients. But it is still no evidence about deep pathophysiological plot of this changes [4]. Moreover, platelets condition plays an important role in myocardial inflammation and regulates myocardial reperfusion in during myocardial ischemia [16]. It means, platelets characteristics in patients with AF and CAD are interesting pathogenetic aim for investigations.

According to the latest data, BCAA (leucine, isoleucine, valine) takes part in platelets activation. Isoleucine, leucine and valine concurrently used BCAA aminotranspherase and dehydrogenase in their metabolism. In our work significant increasing isoleucine and leucine platelets levels in AF patients was present. At the same time valine was significantly decreased, that can be explained by highly increased valine metabolism in activated platelets. In the animal experiment α-ketoisovaleric acid, which is valine catabolite, is able to activate platelets. Also, BCAA involved in the integrin αIIbβ3-mediated bidirectional signaling pathway which can modulate platelets activation. Moreover, BCAAs enhanced propionylation of tropomodulin-3 what can lead for platelets hyperactivity [17]. So, role of AA metabolism in AF paroxysm formation in CAD patients is undoubted.

Gut microbiota composition is an important part of human health. Its influence on the host life is made by its metabolites, including fecal SCFA. They are presented mainly by acetic, propionic, butyric, valeric acids. BCAA and SCFA are strongly corelated with each other [18]. SCFA, especially valerate and butyrate, are also able to increase platelets activity. On the other hand, high level of fecal butyrate increases permeability of intestinal cellular barrier. CAD is commonly associated with low fecal SCFA, especially butyrate [19]. Due to the animal studies, SCFA production is associated with *Bifidobacterium*, *Bacteroides*, *Actinobacter*, *Ruminococcus*, *Roseburia*, *Bilophila*, *Coprococcus* species [20]. In our study, also *Bifidobacterium*, *Bacteroides*, *Actinobacter*, *Ruminococcus*, *Roseburia*, *Blautia*, *Akkermansia* are significantly correlated with BCAAs.

On the other hand, glycine, serine, threonine, taurine platelets levels were significantly higher in patients with AF and CAD in our study. By the animal studies, glycine reduces platelets aggregation by activating calcium flux through glycine-gated chlorine channels in white blood cells, macrophages and platelets [21]. Glycine deficiency leads to hyperlipidemia by some data. In our study also, total cholesterol plasma level and platelets glycine level were significantly corelated. *Clostridia*, *Actinobacteria*, *Bacteroides* are associated with glycine level reduction. In our study *Actinobacter* spp. and *Bacteroides thetaiotaomicron* have significantly negative correlations with platelets glycine levels. Glycine and serine exchange are closely linked. Threonine is also a known glycine resort in microbial and human metabolism [22].

So, gut microbiota and platelets AA profile have strong connections what approved by appearance of strong correlations between their components: taurine and *Escherichia coli* (r = 0.714), asparaginate and *Methanosphaera stadmanae* (r = 0.716), threonine and *Akkermansia muciniphila* (r = 0.703), glutamate and *Actinobacter* spp. (r = 0.744), glycine and *Blautia* spp. (r = 0.708), glycine and *Actinobacter* spp. (r = –0.769), valine and *Actinobacter* spp. (r = –0.736). By the animal studies, taurine assimilation is closely linked with *Escherichia coli* metabolism. Also, taurine assimilation by *Escherichia coli* depends by the iron presence and SCFA content [23]. Asparaginic acids exchange is closely connected with archaea activity and is crucial for their metabolism [24]. *Akkermansia muciniphila* is widely discussed as a new probiotic bacterium. Threonine supplementation promotes its proliferation in rats and in human feces [25]. *Blautia* spp. is an also promising discussed new probiotic. Its decrease is linked with glycine metabolism in animal studies. *Blautia* spp. and glycine are decrease in aging and low fibers diet, also in animal models [26]. In *Actinobacter* spp. glycine derived pathways are N-oxygenase and amino acid-carrier protein ligase, which regulates bacterial biosynthesis and genes activity [27]. On the one hand, increase of BCAA is commonly associated with metabolic disorders (diabetes mellitus, dyslipidemia) [12], also *Actinobacter* spp. have proatherosclerotic and proinflammatory properties [28]. But *Actinobacter* spp. includes variety of species, which influenced in BCAA metabolism in different way. Some of them use valine in the top of metabolites in connection with ɣ-aminobutyric acid [29], what can explain obtained strong negative connections between valine and *Actinobacter* spp. obtained in our study.

In conclusion, gut microbiota is directly linked with platelets amino acids profile. Gut microbiota composition answer for intestinal amino acids exchange, what plays crucial role for all human organism. Probiotics administration can modulate not only gut microbiota composition, but also amino acids profile. Because they improved amino acids and minerals absorption from the nutrients, decries inflammation, normalize lipids exchange [30]. Of course, the type of used probiotic is important and should be performed individually [31]. Moreover, by the latest data some amino acids have strong probiotic properties. For example, in animal studies glycine can decrease endotoxin production, improve anti-inflammatory response, increase non-pathogenic *Escherichia coli* production, potentiate *Lactobacterium* and *Bifidobacterium* activity, etc. [32, 33]. In our study glycine also

had the largest number of the strong correlations with gut microbiota composition. So, glycine can be used as a promising component in probiotic treatment strategy for patients with CAD and AF.

Conclusions

Platelet amino acids spectrum and gut microbiota composition in patients with coronary artery disease and atrial fibrillation are closely linked:

1. Significant increasing isoleucine (10.73 %), leucine (12.63 %) and decreasing threonine (23.05 %), serine (5.06 %), glycine (32.21 %) and valine (30.83 %) platelets levels in patients with coronary artery disease and atrial fibrillation was found ($P < 0.05$).

2. Significant increasing *Bacteroides* spp., *Faecalibacterium prausnitzii*, *Actinobacter* spp., *Streptococcus* spp., *Ruminococcus* spp. and decreasing *Lactobacillus* spp., *Bifidobacterium* spp., *Eubacterium rectale* in patients with coronary artery disease and atrial fibrillation was determined ($P < 0.05$).

3. Platelets glutamine acid, valine, glycine, asparagine acid, threonine had the highest number of significant correlations with gut microbiota species ($P < 0.05$).

4. *Actinobacter* spp., *Blautia* spp., *Streptococcus* spp., *Akkermansia muciniphila* and *Roseburia inulinivorans* had the most pronounced amount of significant correlations with platelets amino acids ($P < 0.05$).

5. Strong correlations were found between ($P < 0.05$): taurine and *Escherichia coli* ($r = 0.714$), asparaginate and *Methanosphaera stadmanae* ($r = 0.716$), threonine and age ($r = –0.727$), threonine and *Akkermansia muciniphila* ($r = 0.703$), glutamate and *Actinobacter* spp. ($r = 0.744$), glycine and total cholesterol ($r = –0.715$), glycine and *Blautia* spp. ($r = 0.708$), glycine and *Actinobacter* spp. ($r = –0.769$), valine and *Actinobacter* spp. ($r = –0.736$).

References

1. Hindricks G, Potpara T, Dagres N, et al. ESC Scientific Document Group. 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 Feb 1;42(5):373-498. doi:10.1093/eurheartj/ehaa612.

2. Knuuti J, Wijns W, Saraste A, et al. ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020 Jan 14;41(3):407-477. doi:10.1093/eurheartj/ehz425.

3. Michniewicz E, Mlodawska E, Lopatowska P, Tomaszuk-Kazberuk A, Malyszko J. Patients with atrial fibrillation and coronary artery disease - Double trouble. Adv Med Sci. 2018 Mar;63(1):30-35. doi:10.1016/j.advms.2017.06.005.

4. Liu X, Yu S, Liang T, Chen L, Zhang H. Mean Platelet Volume to Platelet Count Ratio Predicts Left Atrial Stasis in Patients with Non-Valvular Atrial Fibrillation. Int J Gen Med. 2023 Mar 3;16:847-858. doi:10.2147/IJGM.S395305.

5. Li D, Li Y, Ding H, Wang Y, Xie Y, Zhang X. Cellular Senescence in Cardiovascular Diseases: From Pathogenesis to Therapeutic Challenges. J Cardiovasc Dev Dis. 2023 Oct 23;10(10):439. doi:10.3390/jcdd10100439.

6. De Simone I, Baaten CCFMJ, Gibbins JM, et al. Repeated platelet activation and the potential of previously activated platelets to contribute to thrombus formation. J Thromb Haemost. 2023 May;21(5):1289-1306. doi:10.1016/j.jtha.2023.01.006.

7. Ishii M, Kaikita K, Yasuda S, et al. Risk prediction score for clinical outcome in atrial fibrillation and stable coronary artery disease. Open Heart. 2023 May;10(1):e002292. doi:10.1136/openhrt-2023-002292.

8. Palmu J, Börschel CS, Ortega-Alonso A, et al. Gut microbiome and atrial fibrillation-results from a large population-based study. EBioMedicine. 2023 May;91:104583. doi:10.1016/j.ebiom.2023.104583.

9. Al-Kaisey AM, Figgett W, Hawson J, Mackay F, Joseph SA, Kalman JM. Gut Microbiota and Atrial Fibrillation: Pathogenesis, Mechanisms and Therapies. Arrhythm Electrophysiol Rev. 2023 Apr 19;12:e14. doi:10.15420/aer.2022.33.

10. Rashid S, Noor TA, Saeed H, et al. Association of gut microbiome dysbiosis with the progression of atrial fibrillation: A systematic review. Ann Noninvasive Electrocardiol. 2023 Jul;28(4):e13059. doi:10.1111/anec.13059.

11. Scopelliti F, Cattani C, Dimartino V, Mirisola C, Cavani A. Platelet Derivatives and the Immunomodulation of Wound Healing. Int J Mol Sci. 2022 Jul 28;23(15):8370. doi:10.3390/ijms23158370.

12. Duttaroy AK. Role of Gut Microbiota and Their Metabolites on Atherosclerosis, Hypertension and Human Blood Platelet Function: A Review. Nutrients. 2021 Jan 3;13(1):144. doi:10.3390/nu13010144.

13. Meeusen JW, Kasozi RN, Larson TS, Lieske JC. Clinical Impact of the Refit CKD-EPI 2021 Creatinine-Based eGFR Equation. Clin Chem. 2022 Mar 31;68(4):534-539. doi:10.1093/clinchem/hvab282.

14. Faizi N, Alvi Y. Biostatistics Manual for Health Research: A Practical Guide to Data Analysis. Cambridge, MA: Elsevier Science; 2023. 290 p.

15. Chen D, Zhao X, Sui Z, et al. A multi-omics investigation of the molecular characteristics and classification of six metabolic syndrome relevant diseases. Theranostics. 2020 Jan 12;10(5):2029-2046. doi:10.7150/thno.41106.

16. Schöte JP, Manke MC, Hemmen K, et al. Platelet-Derived MicroRNAs Regulate Cardiac Remodeling After Myocardial Ischemia. Circ Res. 2023 Mar 31;132(7):e96-e113. doi:10.1161/CIRCRESAHA.122.322459.

17. Xu Y, Jiang H, Li L, et al. Branched-Chain Amino Acid Catabolism Promotes Thrombosis Risk by Enhancing Tropomodulin-3 Propionylation in Platelets. Circulation. 2020 Jul 7;142(1):49-64. doi:10.1161/CIRCULATIONAHA.119.043581.

18. Ramos-Garcia V, Ten-Doménech I, Moreno-Giménez A, et al. GC-MS analysis of short chain fatty acids and branched chain amino acids in urine and faeces samples from newborns and lactating mothers. Clin Chim Acta. 2022 Jul 1;532:172-180. doi:10.1016/j.cca.2022.05.005.

19. Anderson G, Rodriguez M, Reiter RJ. Multiple Sclerosis: Melatonin, Orexin, and Ceramide Interact with Platelet Activation Coagulation Factors and Gut-Microbiome-Derived Butyrate in the Circadian Dysregulation of Mitochondria in Glia and Immune Cells. Int J Mol Sci. 2019 Nov 5;20(21):5500. doi:10.3390/ijms20215500.

20. Mesnage R, Grundler F, Schwiertz A, Le Maho Y, Wilhelmi de Toledo F. Changes in human gut microbiota composition are linked to the energy metabolic switch during 10 d of Buchinger fasting. J Nutr Sci. 2019 Nov 12;8:e36. doi:10.1017/jns.2019.33.

21. Karolczak K, Guligowska A, Kostanek J, Soltysik B, Kostka T, Watala C. The amino acid content in the daily diet of seniors negatively correlates with the degree of platelet aggregation in a sex- and agonist-specific manner. Aging (Albany NY). 2022 Aug 19;14(18):7240-7262. doi:10.18632/aging.204229.

22. Rom O, Liu Y, Liu Z, et al. Glycine-based treatment ameliorates NAFLD by modulating fatty acid oxidation, glutathione synthesis, and the gut microbiome. Sci Transl Med. 2020 Dec 2;12(572):eaaz2841. doi:10.1126/scitranslmed.aaz2841.

23. Nishikawa M, Shen L, Ogawa K. Taurine dioxygenase (tauD)-independent taurine assimilation in Escherichia coli. Microbiology (Reading). 2018 Nov;164(11):1446-1456. doi:10.1099/mic.0.000723.

24. Lubkowski J, Wlodawer A. Structural and biochemical properties of L-asparaginase. FEBS J. 2021 Jul;288(14):4183-4209. doi:10.1111/febs.16042.

25. Miyata T, Mizushima T, Miyamoto N, et al. Skate-skin mucin, rich in sulfated sugars and threonine, promotes proliferation of Akkermansia muciniphila in feeding tests in rats and in vitro fermentation using human feces. Biosci Biotechnol Biochem. 2022 Feb 24;86(3):397-406. doi:10.1093/bbb/zbac003.

26. Kadyan S, Park G, Wang B, Nagpal R. Dietary fiber modulates gut microbiome and metabolome in a host sex-specific manner in a murine model of aging. Front Mol Biosci. 2023 Jun 15;10:1182643. doi:10.3389/fmolb.2023.1182643.

27. He HY, Ryan KS. Glycine-derived nitronates bifurcate to O-methylation or denitrification in bacteria. Nat Chem. 2021 Jun;13(6):599-606. doi:10.1038/s41557-021-00656-8.

28. Khan I, Khan I, Jianye Z, et al. Exploring blood microbial communities and their influence on human cardiovascular disease. J Clin Lab Anal. 2022 Apr;36(4):e24354. doi:10.1002/jcla.24354.

29. Ma Q, Mo X, Zhang Q, et al. Comparative metabolomic analysis reveals different evolutionary mechanisms for branched-chain amino acids production. Bioprocess Biosyst Eng. 2020 Jan;43(1):85-95. doi:10.1007/s00449-019-02207-5.

30. Jäger R, Mohr AE, Carpenter KC, et al. International Society of Sports Nutrition Position Stand: Probiotics. J Int Soc Sports Nutr. 2019 Dec 21;16(1):62. doi:10.1186/s12970-019-0329-0.

31. Zhai L, Wu J, Lam YY, Kwan HY, Bian ZX, Wong HLX. Gut-Microbial Metabolites, Probiotics and Their Roles in Type 2 Diabetes. Int J Mol Sci. 2021 Nov 27;22(23):12846. doi:10.3390/ijms222312846.

32. Ciszewski A, Jarosz Ł, Marek A, et al. Effect of combined in ovo administration of zinc glycine chelate (Zn-Gly) and a multistrain probiotic on the modulation of cellular and humoral immune responses in broiler chickens. Poult Sci. 2023 Sep;102(9):102823. doi:10.1016/j.psj.2023.102823.

33. Hirayama S, Nakao R. Glycine significantly enhances bacterial membrane vesicle production: a powerful approach for isolation of LPS-reduced membrane vesicles of probiotic Escherichia coli. Microb Biotechnol. 2020 Jul;13(4):1162-1178. doi:10.1111/1751-7915.13572.

Received 02.10.2023
Revised 14.10.2023
Accepted 23.10.2023

Information about authors

Iryna Melnychuk, PhD, Associate Professor at the Department of Internal Medicine 4, Bogomolets National Medical University, Kyiv, Ukraine; e-mail: ira.merkulova45@gmail.com; phone: + 380(50)2893355; https://orcid.org/0000-0002-0659-1476

Sharayeva M.L., PhD, Associate Professor at the Department of Internal Medicine 4, Bogomolets National Medical University, Kyiv, Ukraine, email: malesha.kyiv@gmail.com, https://orcid.org/0000-0002-8891-7336

Kramarova V.N., MD, PhD, Professor at the Department of Internal Medicine 4, Bogomolets National Medical University, Kyiv, Ukraine, email: victoriia.kramarova@gmail.com, https://orcid.org/0000-0003-2978-3320

Lyzogub V.H., MD, PhD, Professor, Head of the Department of Internal Medicine 4, Bogomolets National Medical University, Kyiv, Ukraine, email: vglizogub@gmail.com, https://orcid.org/0000-0003-3603-7342

Conflicts of interests. Authors declare the absence of any conflicts of interests and own financial interest that might be construed to influence the results or interpretation of the manuscript.

Perspectives of subsequent scientific research. Platelets amino acids profile and gut microbiota composition correction will be interesting approach for further investigations.

Information about funding. This study did not receive external funding. The study was done according the department scientific research 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)

Authors' contribution. *Lyzogub V.H.* — concept and methodology; *Sharayeva M.L.*, *Kramarova V.N.* — review; *Melnychuk I.O.* — data collection, analysis, review, writing and administration.

Мельничук І.О., Шараєва М.Л., Крамарова В.Н., Лизогуб В.Г.
Національний медичний університет імені О.О. Богомольця, м. Київ, Україна

Амінокислотний спектр тромбоцитів та мікробіом кишечника, їх зв'язок у пацієнтів з ішемічною хворобою серця та фібриляцією передсердь

Резюме. ***Актуальність. Мета роботи:*** виявити зв'язок між амінокислотним (АК) спектром тромбоцитів і складом мікробіоти кишечника в пацієнтів з ішемічною хворобою серця (ІХС) й фібриляцією передсердь (ФП) та оцінити його. ***Матеріали та методи.*** У дослідження було включено 300 пацієнтів. Їх розподілили на 3 групи: першу — 149 осіб з ІХС без аритмій, другу — 124 пацієнти з ІХС та пароксизмом ФП і контрольну групу — 27 пацієнтів без ІХС та аритмій. Рівень АК тромбоцитів визначали методом іонообмінної рідинної колонкової хроматографії. Склад кишкової мікробіоти оцінювали шляхом 16-S рРНК секвенування. ***Результати.*** У пацієнтів із ІХС та ФП було виявлено значне підвищення рівня ізолейцину (10,73 %), лейцину (12,63 %) і зниження рівня треоніну (23,05 %), серину (5,06 %), гліцину (32,21 %) і валіну (30,83 %) тромбоцитів ($P < 0,05$). Також зареєстровано збільшення кількості *Bacteroides* spp., *Faecalibacterium prausnitzii*, *Actinobacter* spp., *Streptococcus* spp., *Ruminococcus* spp. і зниження *Lactobacillus* spp., *Bifidobacterium* spp., *Eubacterium rectale* ($P < 0,05$). Глутамінова кислота, валін, гліцин, аспарагінова кислота, треонін мали найвищу кількість значущих кореляцій зі складом кишкової мікробіоти ($P < 0,05$). *Actinobacter* spp., *Blautia* spp., *Streptococcus* spp., *Akkermansia muciniphila* та *Roseburia inulinivorans* мали найбільше значущих кореляцій з АК тромбоцитів ($P < 0,05$). ***Висновки.*** Амінокислотний спектр тромбоцитів і склад мікробіоти кишечника в пацієнтів з ішемічною хворобою серця та фібриляцією передсердь тісно пов'язані.

Ключові слова: ішемічна хвороба серця; фібриляція передсердь; амінокислоти; тромбоцити; склад мікробіоти кишечника