ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

DOI: 10.21802/artm.2024.1.29.99
UDC 616.12-008.313.2

GUT MICROBIOTA METABOLITES AND HOLTER ECG MONITORING IN CORONARY ARTERY DISEASE PATIENTS WITH ATRIAL FIBRILLATION

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Abstract. Gut microbiota metabolites play a clue role in human metabolism.

The aim. To analyze and find the connections between Holter ECG monitoring indexes and gut microbiota metabolites in patients with coronary artery disease and atrial fibrillation.

Materials and methods. 300 patients were divided into 3 groups: first (CAD) – 149 patients with CAD but without arrhythmias, second (CAD+AF) – 124 patients with CAD and AF paroxysm, and the control group – 27 patients without CAD and arrhythmias. Holter ECG monitoring was done for the patients with AF paroxysm 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. The levels of trimethylamine (TMA), trimethylamine-N-oxide (TMAO) in plasma, and fecal short-chain fatty acids (SCFA) were determined by gas chromatography with mass electron detection.

Results. Isocaproic and isobutyric fecal acids occurred in the I and II groups in comparison with the CG. In the II group patients an increase of TMA (16.13%), and TMAO (57.54%) levels and a decrease in their ratio (26.16%) was found in comparison with the I group, $P<0.05$. In the II group patients an increase in valeric (1128.43%) and a decrease in butyric (78.75%), isovaleric (43.71%), caprylic (99.21%) acids, middle chain fatty acids (95.54%), and the total amount of fecal SCFA (17.09%) was found in comparison with the I group, $P<0.05$. In the II group patients, an increase in supraventricular and ventricular extrasystoles was checked in comparison with the I group patients, $P<0.05$. The significant middle force correlations between rhythm abnormalities and gut microbiota metabolites were found: supraventricular extrasystoles per hour and TMA ($r=0.311$), TMAO ($r=0.364$), the total amount of fecal SCFA ($r=-0.339$), and butyric acid ($r=-0.321$); ventricular extrasystoles per hour and trimethylamine ($r=0.320$), trimethylamine-N-oxide ($r=0.373$), the total amount of fecal SCFA ($r=-0.309$), and isocaproic acid ($r=0.399$); AF episodes occurrence correlated with TMAO ($r=0.355$), butyric acid ($r=-0.312$), isobutyric acid ($r=-0.319$), middle chain fatty acids ($r=-0.334$), $P<0.05$. The significant middle force correlations between ST-segment changes and TMAO ($r=0.390$), the total amount of fecal SCFA ($r=-0.398$), unsaturated fatty acids ($r=-0.307$), butyric acid ($r=-0.336$), valeric acid ($r=0.317$) were checked, $P<0.05$. The maximum ST-episode duration was significantly correlated with TMAO ($r=0.326$), the total amount of fecal SCFA ($r=-0.391$), valeric acid ($r=-0.322$), $P<0.05$.

Conclusion. Gut microbiota metabolites (TMA, TMAO, fecal SCFA) are significantly correlated with rhythm abnormalities (supraventricular and ventricular) and ST-segment changes in CAD patients. TMA and TMAO were directly correlated with AF paroxysms, supraventricular, and ventricular rhythm abnormalities, which shows them as a new therapeutic target for patients with CAD and AF. Vice versa the total amount of fecal SCFA, butyric, and valeric acids had inversing associations with rhythm abnormalities, which present them as a promising therapeutic molecule for CAD and AF management. However, the pathogenetic mechanisms of influence gut microbiota metabolites on rhythm abnormalities and myocardial ischemia need further investigation.

Keywords: coronary artery disease, ischemia, atrial fibrillation, heart rate monitoring, gastrointestinal microbiome, fatty acids, metabolomics, heart failure.

Introduction. Atrial fibrillation (AF) is the most common cardiac arrhythmia in adults. It is associated with an increase in morbidity and mortality. On the other side, coronary artery disease (CAD) is the most common cardiac pathology in the world. CAD is present in nearly half of AF incidents. CAD and AF together worsen the prognosis and clinical picture of each other. At the same time, they share a lot of the same risk factors: diabetes mellitus, dyslipidemia, obesity, inflammatory diseases, and heart failure, which belong to the important characteristics of human metabolism [1, 2].

The human body contains nearly the same number of microbial cells as its cells. Microbial biomass is mostly localized in the cecum and proximal colon [3]. Gut microbiota regulates carbohydrates, proteins, and lipids metabolism, and supports energy homeostasis. Its violations are an important pathogenetic factor in arterial hypertension, diabetes mellitus, dyslipidemia, obesity, inflammatory diseases, and heart failure development [4]. Disturbances in the gut microbiota composition and its functionality can disrupt gut barrier function, which leads to metabolomic endotoxemia. Gut microbiota metabolites play a clue role in human metabolism [5]. They are trimethylamine (TMA), trimethylamine-N-oxide (TMAO), lipopolysaccharide (endotoxin), bile acids, and short-chain fatty acids (SCFAs). TMAO is the most extensively studied gut microbiota metabolite, which is involved in AF pathogenesis. According to animal studies rise in TMAO is associated with structural and autonomic cardiac remodeling, which is the basis for re-entry formation. SCFAs are also important participants in AF pathogenesis. They are crucial for intestinal barrier function, and regulate immune answer [3]. SCFAs have cardioprotective properties: decrease atrial remodeling, prevent ectopic activity, normalize atrial effective refractory period and sarcoplasmic-reticulum Ca^{2+} release by inhibiting NLRP3-inflammasome

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

activity, and regulate T cell and T helper cell homeostasis [6, 7]. Moreover, SCFAs are different in their beneficial and harmful properties [3].

There is no doubt that Holter ECG monitoring is a reliable and widely spread diagnostic method. According to the latest guidelines, it is indicated to patients with AF paroxysms to determine the best treatment strategy or heart rate control management and for CAD patients with a new episode of ischemia clinical features. Also, it is used for the patients who were prescribed amiodarone to control QTc interval monitoring. In any case, Holter ECG monitoring is used for rhythm abnormalities and ST-segment change detection [8].

So, analysis of the correlations between Holter ECG monitoring findings and gut microbiota metabolites in patients with CAD and AF is an interesting and up-to-date scientific goal.

The aim. To analyze and find the connections between Holter ECG monitoring indexes and gut microbiota metabolites in patients with coronary artery disease and atrial fibrillation.

Materials and methods. 300 patients were involved in the study. They were divided into 3 groups: first (CAD) – 149 patients with CAD but without arrhythmias, second (CAD+AF) – 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 [1, 2]. All patients were treated in the Kyiv City Clinical Hospital No. 12 in cardiological and therapeutic departments in 2018-2023 years. 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. All patients had heart failure stage B or C [9]. 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, prescribing probiotics and antibiotics for a month before 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 # 8 from 22/08/2018). Informed consent was obtained from all subjects by the 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 – 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. There were studied main indexes: 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) [8].

The level of TMAO, and TMA plasma was determined by gas chromatography with mass electron detection. They were extracted from blood plasma into acid by adding internal standards [10]. The patient's blood sampling was performed on an empty stomach from the cubital vein on the day of hospitalization. Fecal SCFA was checked by gas chromatography with mass electron detection. We determined nine fatty acids in the collected samples – acetic acid (C2:0), propionic acid (C3:0), butyric acid (C4:0), isobutyric acid (C4:1), valeric acid (C5:0), isovaleric acid (C5:1), caproic acid (C6:0), isocaproic acid (C6:1) and caprylic acid (C8:0). These fatty acids include saturated (SFA) – acetic (C2:0), propionic (C3:0), butyric (C4:0), valeric (C5:0), caproic (C6:0), caprylic (C8:0) acids; and unsaturated (USFA) – isobutyric (C4:1), isovaleric (C5:1), isocaproic (C6:1) acids. Middle-chain fatty acids (MCFA) include caproic acid (C6:0), isocaproic acid (C6:1), and caprylic acid (C8:0). Also, the total amount of fecal SCFA (TA SCFA) was determined [9].

Results were presented as mean ± 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 [11]. All calculations were done in MATLAB R2014a (License number 271828).

Results. The baseline characteristics were analyzed in the investigated groups. 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, $P<0.05$. Also, in the I and II groups were patients with obesity, diabetes mellitus, stroke, or MI history, such cases were absent in CG. The data are shown in Table 1.

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

Table 1

Baseline characteristics of the study groups, mean ± standard error

Characteristic /group	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	12.0	0	P>0,05	P<0,05	P<0,05
BMI (kg/m^2)	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)	11.3±0.09	12.4±0.08	11.7±0.11	P>0,05	P>0,05	P>0,05
Uric acid (mmol/l)	380.5±28.16	404.9±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

We analyzed Holter ECG monitoring results in our study. The average Holter monitoring duration has lasted for 22,13±0.22 hours. A significant difference in the supraventricular and ventricular arrhythmia and ST-segment changes was found between the investigated groups.

Supraventricular rhythm abnormalities are characterized by changes in HR, SVE, and AF paroxysms. The II group had a significant decrease in average HR (5.26%) in comparison with the I group, P<0.05. 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. 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. 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.

Ventricular arrhythmias presented VE and VT. In the II group patients 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. 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. 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 or mean [95% CI]

Characteristic /group	I group	II group	CG	P1-2	P2-CG	P1-CG
Maximum HR, bpm	110.20±2.48	106.6±3.89	109.8±3.97	P>0.05	P>0.05	P>0.05
Minimum HR, bpm	45.6±1.68	46.9±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 [95% CI 24-43]	729 [95% CI 331-982]	7 [95% CI 0-15]	P<0.05	P<0.05	P<0.05
SVE single	32 [95% CI 24-43]	502 [95% CI 307-766]	7 [95% CI 0-15]	P<0.05	P<0.05	P<0.05
SVE pair	0 [95% CI 0-3]	27 [95% CI 8-42]	0	P<0.05	P<0.05	P<0.05
SVE group	0 [95% CI 0-1]	5 [95% CI 0-9]	0	P>0.05	P<0.05	P<0.05
SVT	0 [95% CI 0-1]	0 [95% CI 0-1]	0	P>0.05	P<0.05	P<0.05
Longest SVT, sec.	0 [95% CI 0-16]	0 [95% CI 0-42]	0	P>0.05	P<0.05	P<0.05

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

SVEs per hour	8 [95% CI 3-17]	38 [95% CI 11-112]	0 [95% CI 0-2]	P<0.05	P<0.05	P<0.05
AF paroxysm	0	0 [95% CI 0-1]	0	P<0.05	P<0.05	P>0.05
Longest AF paroxysm, sec.	0	0 [95% CI 0-44]	0	P<0.05	P<0.05	P>0.05
VE total	0 [95% CI 0-3]	3 [95% CI 0-15]	0 [95% CI 0-1]	P<0.05	P<0.05	P<0.05
VE single	0 [95% CI 0-3]	3 [95% CI 0-15]	0	P<0.05	P<0.05	P<0.05
VE pair	0 [95% CI 0-2]	3 [95% CI 0-15]	0	P<0.05	P<0.05	P<0.05
VE group	0 [95% CI 0-1]	0 [95% CI 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 [95% CI 5-19]	32 [95% CI 17-41]	0 [95% CI 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 [95% CI 0-3]	0 [95% CI 0-6]	0	P>0.05	P<0.05	P<0.05
Maximum ST depression, mkV	0 [95% CI 0-118]	0 [95% CI 0-124]	0	P>0.05	P<0.05	P<0.05
Maximum ST elevation, mkV	0 [95% CI 0-133]	0 [95% CI 0-112]	0	P>0.05	P<0.05	P<0.05
Maximum ST episode duration, minutes	2 [95% CI 1-5]	2 [95% CI 1-5.5]	0	P>0.05	P<0.05	P<0.05

TMA, TMAO, and their ratio levels were examined. In the II and I groups a significant rise in TMA (22.50% and 42.25% respectively), TMAO (50.00% and 136.31% respectively) levels and a decrease in TMA/TMAO ratio (18.59% and 39.89% respectively) were found in comparison with CG, P<0.05. In the II group significant rise of TMA (16.13%), and TMAO (57.54%) levels, and a decrease in TMA/TMAO ratio (26.16%) was obtained in comparison with the I group, P<0.05. The data are shown in Figure 1.

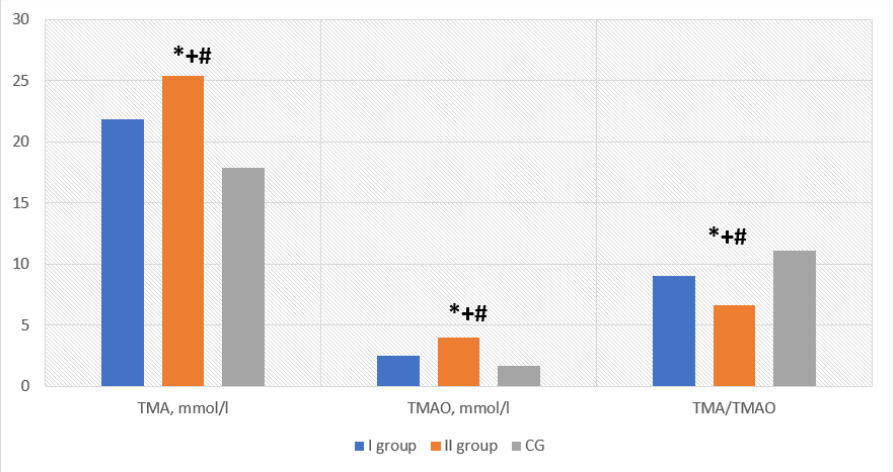

Fig.1. TMA, TMAO, and their ratio in investigated groups, mmol/l.
Notes: *-P<0.05 I-II groups; +-P<0.05 I group – CG; #-P<0.05 II group – CG

Fecal SCFA composition was examined in investigated groups. In the I group was a significant rise in isovaleric acid (165.58%), USFA (485.44%), and a decrease in butyric (63.36%), valeric (97.75%), caproic (93.39%) acids, TA SCFA (29.52%%), MCFA (66.04%) was found in comparison with CG, P<0.05. In the II group a significant rise in acetic (62.35%) and a decrease in butyric (92.21%), valeric (72.36%), caprylic (99.84%) acids, TA SCFA (41.57%) was obtained in comparison with CG, P<0.05. In the II group was a significant increase in valeric (1128.43%) and a decrease in butyric (78.75%), isovaleric (43.71%), caprylic (99.21%) acids, MCFA (95.54%), and TA SCFA (17.09%) was checked in comparison with the I group, P<0.05. Isocaproic and isobutyric fecal acids were absent in the CG samples, but they appeared in the I and II group's patients' results. The data are shown in Figures 2 and 3.

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

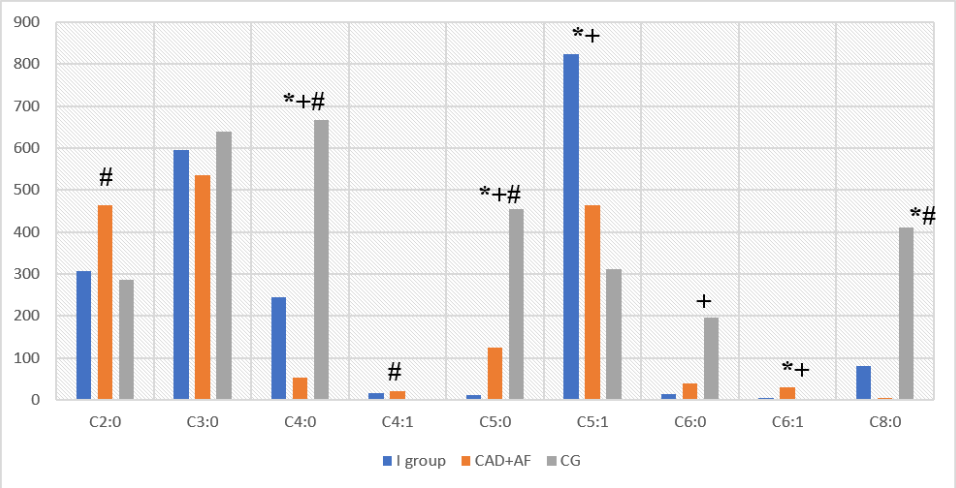

Fig. 2. Fecal short-chain fatty acids in investigated groups, mg/g
Notes: *-P<0.05 I-II groups; +-P<0.05 I group – CG; #-P<0.05 II group – CG

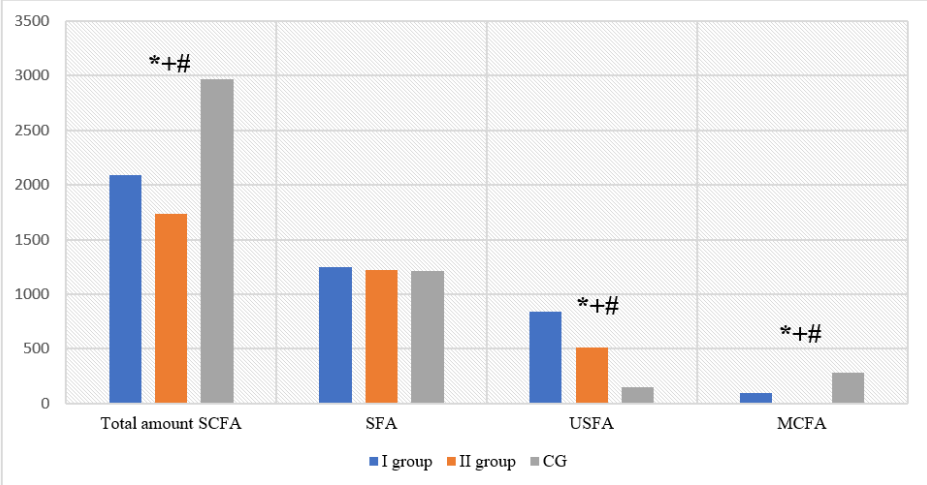

Fig. 3. Fecal short-chain fatty acids in investigated groups, mg/g
Notes: *-P<0.05 I-II groups; +-P<0.05 I group – CG; #-P<0.05 II group – CG.

The correlation analysis between gut microbiota metabolites and Holter ECG monitoring findings was done in our study. Spearman's correlation analysis was used to explore their correlations. The largest number of significant correlations was checked between Holter ECG monitoring indexes and TMAO (total number = 12), TMA (total number = 8), and TA SCFA (total number =8). The highest number of correlations was found between ST segment changes (total number = 5) and gut microbiota metabolites. The data are presented in Table 3.

Discussion. An increase in circulating TMAO is closely associated with cardiovascular events and mortality. Moreover, the rise of TMAO is a possible promoter of neurological disorders, cancers, and chronic diseases, such as obesity, dyslipidemia, diabetes mellitus, heart failure, inflammatory diseases, etc. [12]. According to literature data high circulating TMAO levels are directly associated with AF, but it is no differences between permanent and paroxysmal AF forms. Despite this, the pathogenetic mechanisms of TMAO influence at AF paroxysm formation are still unclear. TMAO functions are diversified. It takes part in hormonal homeostasis, cholesterol and bile acids metabolism, promotes oxidative stress, triggers apoptosis and macrophage activity, has pro-inflammatory properties, is associated with reduced renal function, contributes to intestinal and blood-brain barriers, etc. [3, 12]. The proarrhythmic effect of TMAO can be explained in that it increases sympathetic activity and decreases conduction velocity by promoting cardiac fibrosis, cell apoptosis, and connection lateralization [3]. In our study plasma TMAO level is directly correlated with supraventricular and ventricular arrhythmias, and ischemic changes, which confirms the previous explanation.

On the other hand, fecal TA SCFA levels are inversing correlated with supraventricular and ventricular arrhythmias, and ischemic changes. Decreased fecal TA SCFA is commonly associated with intestinal barrier disruption and proinflammatory conditions. TA SCFA is correlated with C-reactive protein and interleukin-6. SCFA deficiency leads to activation of protein 3 (NLRP3) inflammasome, which is typical for atrial cardiomyocytes and can exhibit ectopic activity, altered sarcoplasmic-reticulum Ca^{2+} release, shortened atrial effective refractory period, and atrial hypertrophy [13]. In the mice model, lack of SCFA is connected with elevated P wave duration, reflecting atrial conduction function violations [14].

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

Table 3

Correlation matrices between gut microbiota metabolites and Holter ECG monitoring indexes

Holter ECG monitoring indexes / Platelet amino acids	TMA	TMAO	TA SCFA	C 2:0	C 3:0	C 4:0	C 4:1	C 5:0	C 5:1	C 6:0	C 6:1	C 8:0	SFA	USFA	MCFA
Maximum HR	0.152	0.042	-0.137	0.035	0.040	0.024	-0.010	-0.035	0.059	-0.025	-0.081	0.177	0.124	0.025	0.141
Minimum HR	0.377*	0.314*	-0.280	-0.109	-0.255	0.032	0.257	-0.291	0.081	-0.003	-0.159	-0.060	-0.229	0.120	-0.066
Average HR	0.007	0.100	-0.263	0.107	-0.189	-0.086	0.334*	-0.288	0.008	0.038	-0.061	-0.112	-0.088	0.043	-0.110
SVE total	0.343*	0.394*	-0.311*	0.275	0.237	-0.331*	-0.254	-0.232	-0.016	-0.133	-0.037	0.104	0.102	-0.099	-0.008
SVE single	0.313*	0.387*	-0.339*	0.194	0.259	-0.313*	-0.242	-0.226	0.022	-0.123	-0.045	0.102	0.101	-0.063	-0.011
SVE pair	0.209	0.321*	-0.217	0.175	0.202	-0.136	-0.147	-0.235	-0.051	-0.098	-0.027	0.100	0.070	-0.081	-0.107
SVE group	0.110	0.304*	0.130	0.128	0.271	-0.186	-0.153	-0.198	-0.096	0.057	-0.017	0.187	0.137	-0.131	-0.216
SVT	0.316*	0.309*	0.142	0.012	0.195	-0.204	-0.061	-0.238	-0.176	0.035	0.048	0.146	0.238	-0.213	-0.254
Longest SVT	0.328*	0.316*	0.138	0.014	0.192	-0.202	-0.061	-0.237	-0.179	0.035	0.053	0.140	0.236	-0.216	-0.209
SVEs per hour	0.311*	0.364*	-0.339*	0.217	0.250	-0.321*	-0.242	-0.217	0.075	-0.128	-0.045	0.114	0.112	-0.065	-0.011
AF paroxysm	0.082	0.355*	-0.190	0.185	0.051	-0.312*	-0.319*	-0.298	-0.017	0.053	-0.096	-0.277	0.066	-0.025	-0.334*
Longest AF paroxysm	0.099	0.316*	-0.192	0.184	0.048	-0.218	-0.335*	-0.300	-0.024	0.048	-0.057	-0.280	0.072	-0.032	-0.302*
VE total	0.318*	0.066	-0.384*	0.275	0.280	-0.108	-0.156	0.111	-0.059	0.052	0.129	-0.279	0.106	-0.088	-0.150
VE single	0.298	-0.066	-0.101	0.278	0.283	-0.123	-0.150	0.110	-0.060	0.066	0.118	-0.279	0.117	-0.089	-0.182
VE pair	0.282	0.022	-0.141	0.105	0.140	-0.260	0.081	0.187	-0.093	0.136	0.270	-0.084	0.108	-0.099	0.170
VE group	0.020	0.089	-0.032	0.048	-0.040	-0.062	-0.119	-0.134	0.032	-0.129	-0.096	-0.129	-0.128	0.032	-0.186
VE's per hour	0.320*	0.373*	-0.309*	0.011	0.072	-0.045	0.005	0.292	-0.064	0.179	0.399*	-0.179	0.079	-0.049	0.047
Changes ST segment	0.142	0.390*	-0.398*	-0.185	0.224	-0.307*	-0.182	-0.336*	0.273	-0.054	-0.070	-0.025	0.117	0.317*	-0.069

ISSN 2521-1455 (Print)
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Maximum ST depression	0.043	0.404*	-0.318*	-0.183	0.207	-0.326*	-0.186	-0.295	0.262	-0.047	-0.075	-0.040	0.122	0.303*	-0.072
Maximum ST elevation	0.158	0.319*	-0.114	0.140	0.095	-0.197	-0.181	-0.302*	0.255	-0.211	0.150	-0.159	0.181	0.212	-0.089
Maximum ST episode duration	0.108	0.326*	-0.391*	-0.172	0.227	-0.274	-0.179	-0.322*	0.184	-0.061	-0.065	-0.034	0.099	0.231	-0.081

Notes: *- correlations with moderate or strong force (r>0.3 or r<-0.3), P<0.05

Isobutyric acid is inversing correlated with AF paroxysm occurrence and duration and occurred in patients in AF and CAD due to our data. In little studies, isobutyric acid also increased in AF patients [15]. Isobutyric and isovaleric acids also increased in older patients with heart failure and sarcopenia [16]. Butyric acid is inversing correlated with SVE and ST-segment changes in our investigation. Butyric acid has anti-inflammatory and insulin sensitivity-increasing effects [3]. Also, in animal experiments, butyric acid shows antihypertensive, anti-ischemic, and cardioprotective properties [17].

Thus, the influence of gut microbiota metabolites and the role of their changes in AF and CAD pathogenesis exists and needs further investigation.

Conclusions.

In our work gut microbiota metabolites and Holter ECG monitoring indexes were analyzed and correlated in patients with coronary artery disease and atrial fibrillation:

1. Isocaproic and isobutyric fecal acids occurred in coronary artery disease and atrial fibrillation patients' samples in comparison with the control group;
2. In the patients with atrial fibrillation and coronary artery disease, an increase of trimethylamine (16.13%), and trimethylamine-N-oxide (57.54%) levels and a decrease in their ratio (26.16%) was found in comparison with coronary artery disease patients without arrhythmia, P<0.05;
3. In the patients with atrial fibrillation and coronary artery disease increase in valeric (1128.43%) and a decrease in butyric (78.75%), isovaleric (43.71%), caprylic (99.21%) acids, middle chain fatty acids (95.54%) and the total amount of fecal short chain fatty acids (17.09%) was found in comparison with coronary artery disease patients and without arrhythmia, P<0.05;
4. 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;
5. The significant middle force correlations between rhythm abnormalities and gut microbiota metabolites were found: supraventricular extrasystoles per hour and trimethylamine (r=0.311), trimethylamine-N-oxide (r=0.364), the total amount of fecal short-chain fatty acids (r=-0.339), and butyric acid (r=-0.321), ventricular extrasystoles per hour and trimethylamine (r=0.320), trimethylamine-N-oxide (r=0.373), the total amount of fecal short-chain fatty acids (r=-0.309), and isocaproic acid (r=0.399), P<0.05;
6. The significant middle force correlations between ST-segment changes and trimethylamine-N-oxide (r=0.390), the total amount of fecal short-chain fatty acids (r=-0.398), unsaturated fatty acids (r=-0.307), butyric acid (r=-0.336), valeric acid (r=0.317) were checked, P<0.05.

Perspectives of subsequent scientific research. Pathogenetic mechanisms of influence gut microbiota metabolites on rhythm abnormalities and myocardial ischemia need further investigation.

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. The author declares that there is no conflict of interest regarding this research, including financial, personal, authorship, or other nature, which could affect the research and its results presented in this article.

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УДК 616.12-008.313.2

МЕТАБОЛІТИ МІКРОБІОМУ КИШКІВНИКА ТА ХОЛТЕРІВСЬКИЙ МОНІТОРИНГ ЕКГ У ПАЦІЄНТІВ ІЗ ІШЕМІЧНОЮ ХВОРОБОЮ СЕРЦЯ ТА ФІБРИЛЯЦІЄЮ ПЕРЕДСЕРДЬ

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Резюме. Мета. Виявити зв'язки між показниками холтерівського моніторування (ХМ) ЕКГ і метаболітами кишкової мікробіоти в пацієнтів із ішемічною хворобою серця (ІХС) та фібриляцією передсердь (ФП).

Матеріали й методи: 300 пацієнтів було розподілено на 3 групи: перша (ІХС) – 149 пацієнтів із ІХС без аритмій, друга (ІХС+ФП) – 124 пацієнти з ІХС та пароксизмом ФП, контрольна група (КГ) – 27 пацієнтів без ІХС і аритмії. ХМ ЕКГ проводили хворим із пароксизмом ФП упродовж 24 годин після відновлення синусового ритму, а пацієнтам без ФП – у першу добу спостереження. Рівень триметиламіну (ТМА), триметиламін-N-оксиду (ТМАО) в плазмі та фекальних коротко ланцюгових жирних кислот (КЛЖК) визначали за допомогою газової хроматографії з мас-електронною детекцією.

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

Результати. Ізокапронова й ізомасляна ЖК у калі з'являлись у пацієнтів I та II груп порівняно з КГ. У хворих II групи виявлено підвищення рівнів ТМА (16,13%), ТМАО (57,54%) та зниження їх співвідношення (26,16%) порівняно з I групою, P<0,05. У пацієнтів II групи спостерігалося підвищення вмісту валеріанової (1128,43 %) та зниження вмісту масляної (78,75 %), ізовалеріанової (43,71 %), каприлової (99,21 %) кислот, середньоланцюгових ЖК (95,54 %), загальної кількості фекальних КЛЖК (17,09 %) порівняно з I групою, P<0,05. Виявлено кореляції між суправентрикулярними екстрасистолами за годину та ТМА (r=0,311), ТМАО (r=0,364), загальною кількістю фекальних КЛЖК (r=-0,339), масляною ЖК (r=-0,321); шлуночковими екстрасистолами за годину та ТМА (r=0,320), ТМАО (r=0,373), загальною кількістю фекальних КЛЖК (r=-0,309), ізокапроновою ЖК (r=0,399); змінами сегмента ST і ТМАО (r=0,390), загальною кількістю фекальних КЛЖК (r=-0,398), ненасичених ЖК (r=-0,307), масляної ЖК (r=-0,336), валеріанової ЖК (r=0,317), P<0,05.

Висновок: Метаболіти кишкової мікробіоти (ТМА, ТМАО, фекальні КЛЖК) достовірно корелюють із порушеннями серцевого ритму (суправентрикулярними та шлуночковими) й змінами сегмента ST.

Фінансування: це дослідження не мало зовнішнього фінансування. Дослідження виконано в рамках науково-дослідної роботи кафедри «Зміни білкового, вуглеводного та ліпідного обміну у хворих на ішемічну хворобу серця та артеріальну гіпертензію з порушеннями серцевого ритму, можливості медикаментозної корекції» 2021-2023 (номер держреєстрації 0121U108875).

Ключові слова: ішемічна хвороба серця, ішемія, фібриляція передсердь, холтерівське моніторування ЕКГ, мікробіом кишківника, жирні кислоти, метаболоміка, серцева недостатність.

Стаття надійшла в редакцію 02.02.2024 р.
Стаття прийнята до друку 26.03.2024 р.