Original Article

# Gut Microbiota Metabolites As A New Therapeutic Target In Patients With Coronary Artery Disease And Atrial Fibrillation

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## Abstract

The aim: To reveal new peculiarities of gut microbiota metabolites in CAD patients with or without AF and to detect special connections toward ones with clinical and laboratory features of investigated groups.

Materials and methods: 300 patients were investigated. They were divided into 3 groups: control group – 28 patients without CAD and arrhythmias; main group – 149 patients with CAD but without arrhythmias; comparable group – 123 patients with CAD and AF paroxysm. Plasma TMAO, TMA, fecal SCFA levels was determined by gas chromatography with mass electron detection.

Results: Metabolomic analysis of the gut microbiota metabolites (plasma TMA, TMAO, fecal SCFA) and clinic-laboratory factors in patients with CAD and AF paroxysm was done in our study. We checked gut microbiota metabolites changes that are common for patients with CAD and AF comparable with CAD patients: increasing of TMA, TMAO plasma levels, fecal valeric acid level (13,88%, 36,52% and 1128,43% respectively, $p<0,05$) and decreasing total amount of fecal SCFA, USFA, MCFA, butyric, isovaleric, caprylic acids levels (17,09%, 38,16%, 95,54%, 78,75%, 56,29% and 99,21% respectively, $p<0,05$). Reliable correlations between CAD and AF with TMA, TMAO plasma and fecal SCFA levels were revealed by them and age, BMI, GFR, total cholesterol, TG, LDL, HDL, ApoB levels ($|r|>0,3$, $p<0,05$) were revealed that are known risk factors of CAD and AF. Moreover, TMAO, TMA, butyrate, total SCFA, USFA, MCFA levels are closely connected with IL-6 and CRP levels ($|r|>0,3$, $p<0,05$).

Conclusions: Gut microbiota metabolites (TMA, TMAO, SCFA, MCFA, USFA, butyric acid) are the new promising therapeutic targets for pathogenetic treatment and prevention AF paroxysm in CAD patients.

**Keywords:** coronary artery disease (CAD), atrial fibrillation (AF), gut microbiota composition, trimethylamine-N-oxide (TMAO), trimethylamine (TMA), short chain fatty acids (SCFA)

## Introduction

Coronary artery disease (CAD) is the most common cardiovascular disorder while atrial fibrillation (AF) is the most common cardiac arrhythmia. Number of patients with CAD and AF increasing every year: presence of CAD increased risk of AF development and vice versa.

This can be explained by the similarity in etiology and pathogenesis of CAD and AF. Both diseases share associated risk factors – arterial hypertension, diabetes mellitus, chronic kidney diseases, obesity, heart failure and inflammatory diseases.

Dyslipidemia and chronic inflammation play the main pathogenetic role in CAD and AF development, but their real connections are still uninvestigated [1, 2, 3].

Gut microbiota – the complex of gut microorganisms. Today its role in cardiovascular diseases development was estimated: its impact on metabolic disorders as obesity, diabetes mellitus, atherosclerosis has been already approved, but anti- and proarrhythmic properties are still unknown. Gut microbiota changes are pathogenetically connected with arterial hypertension, chronic kidney diseases, inflammatory diseases and heart failure, which are an important etiological factors of AF and CAD [4].

Gut microbiota can cause direct and indirect (through its metabolites) impact on lipid exchange and inflammatory processes. Its metabolites include trimethylamine (TMA)/ trimethylamine-N-oxide (TMAO)/ choline, short chain fatty acids (SCFA), lipopolisacharide (endotoxine)/ bacterial wall products, bile acids, phenilacetylglutamine and uremic toxins (p-cresol/ indoxyl) [4, 5]. Plasma amino acids composition can be also included in gut microbiota metabolites [6].

TMA is a product of gut microbiota which is produced from dietary choline, betaine or carnitine. TMAO is a product of TMA

oxidation by liver flavinmonooxygenase. Different authors detected the significant correlation between levels of TMAO and AF phenotypes and its progression. In neonatal rats TMAO injections increase inflammasomes activity and fibrosis in cardiomyocytes [7]. On the other hand, SHFA decreased inflammasome activity and atrial remodeling by GPR43/NLRP3 signaling and vice versa. SCFA composition also revealed an important role: acetic, propionic and butyric acid concentrations decreased gradually with AF occurrence and progression [8]. According to animal trials and in vitro, butyrate has an anti-inflammatory effect due to suppression of tumor-necrosis factor-α, interleukin-12 and interferon-γ (IF-γ) production [14, 15]. Also, butyrate provides an antiatherogenic effect

by inhibition of histone deacetylase in vascular endothelium [16, 17]. SCFA are able for parasympathetic nervous system activation through gut-brain communication, on the other hand their abundance lead to high sympathetic activity [9].

Thus, gut microbiota metabolites play an important pathogenetic role in pathogenesis of AF paroxysm in CAD patients, therefore it can be a promising new target for prevention and studying arrhythmias in investigated groups.

### The Aim

To reveal new peculiarities of gut microbiota metabolites in coronary artery disease patients with or without atrial fibrillation and to detect special connections toward ones with clinical and laboratory features of investigated groups.

## Materials And Methods

300 patients were investigated during study. They were divided into 3 groups: control group – 28 patients without CAD and arrhythmias; main group – 149 patients with CAD but without arrhythmias; comparable group – 123 patients with CAD and AF paroxysm. The diagnosis was performed according the latest ESC guidelines [2, 3]. We excluded patients with valvular atrial fibrillation, heart failure from Class III to IV (by New York Heart Association), reported malignancies, chronic kidney disease (Glomerular Filtration Rate, GFR <60 mL/min), thyroid pathology, inflammatory bowel disease, irritable bowel syndrome, pregnancy, taking probiotics and antibiotics for at least one month before the study. There were no vegetarians or vegans among the investigated persons. Informed consent was obtained from all subjects in accordance with the Declaration of Helsinki. The study was conducted at the base and was approved by the ethical commission of the Kiev City Clinical Hospital No. 12.

The main clinical and laboratory characteristics of all groups were comparable and estimated in table 1.

**Table I.** Clinical and laboratory characteristics of investigated groups, mean ± standard error

| *Characteristic /group* | *CAD* | *CAD+AF* | *CG* | *P1-2* | *P2-3* | *P1-3* |
|---|---|---|---|---|---|---|
| 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 |
| BMI (kg/m2) | 27,02±0,33 | 26,93±0,43 | 28,12±2,10 | 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 |
| 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 |
| 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 |
| GFR (ml/min) | 62,03±2,31 | 67,73±1,98 | 84,01±5,48 | P>0,05 | P<0,05 | P<0,05 |
| Total cholesterol (mmol/l) | 5,73±0,37 | 6,18±0,31 | 4,32±0,21 | P>0,05 | P<0,05 | P<0,05 |
| Triglycerides (mmol/l) | 2,02±0,18 | 1,74±0,14 | 1,12±0,09 | P>0,05 | P<0,05 | P<0,05 |
| LDL (mmol/l) | 2,63±0,29 | 2,66±0,24 | 1,54±0,11 | P>0,05 | P<0,05 | P<0,05 |
| HDL | 1,46±0,13 | 1,23±0,14 | 1,74±0,12 | P>0,05 | P<0,05 | P<0,05 |

| | | | | | | |
|---|---|---|---|---|---|---|
| (mmol/l) | | | | | | |
| Lpα (mg/dl) | 22,53±1,26 | 24,73±1,48 | 15,96±1,23 | P>0,05 | P<0,05 | P<0,05 |
| Apo A1 (g/l) | 2,02±0,16 | 2,34±0,27 | 1,62±0,09 | P>0,05 | P<0,05 | P<0,05 |
| Apo B (g/l) | 2,24±0,19 | 2,91±0,13 | 1,21±0,18 | P<0,05 | P<0,05 | P<0,05 |
| CRP, mg/l | 2,15±0,20 | 3,03±0,19 | 0,91±0,12 | P<0,05 | P<0,05 | P<0,05 |
| IL-6, pg/ml | 2,66±0,16 | 3,27±0,16 | 1,61±0,09 | P<0,05 | P<0,05 | P<0,05 |

CAD was defined by the presence of typical clinical (symptoms of angina pectoris) and electrocardiogram pattern, at least 50% stenosis in one or more of the major coronary arteries. AF was diagnosed by electrocardiogram pattern and Holter ECG monitoring: Cardiosens K Holter monitor was used during 24 hours. The level of TMAO, TMA plasma was determined by gas chromatography with mass electron detection. They were extracted from blood plasma into acid by adding internal standards (2,2,2-Trichloroethyl chloroformate for TMA and titanium(III) chloride for TMAO). Blood sampling from patients 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. 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 regions by the type of distribution and Spearman's rank correlation coefficient (by EPSS).

## Results

We determined plasma TMA and TMAO levels in CAD patients with AF or without AF and control group. Results are shown in table 2.

**Table II.** TMA and TMAO plasma levels in patients with CAD and patients with CAD and AF compared with control group, mean ± standard error, mmol/l

| *Characteristic /group* | *CAD* | *CAD+AF* | *CG* | *P1-2* | *P2-3* | *P1-3* |
|---|---|---|---|---|---|---|
| TMA | 21,89±0,45 | 25,42±0,37 | 17,87±0,50 | P<0,01 | P<0,01 | P<0,01 |
| TMAO | 2,52±0,11 | 3,97±0,13 | 1,68±0,11 | P<0,01 | P<0,01 | P<0,01 |
| TMA/TMAO | 9,02±0,31 | 6,66±0,27 | 11,08±0,79 | P<0,01 | P<0,01 | P<0,01 |

A significant difference from the serum levels of TMAO and TMA, their ratio was found between all investigated groups. TMA plasma level in comparable group (CAD+AF) was significantly higher by 13,88% (P<0,01) than in main group (CAD) and by 29,70% (P<0,01) than in CG. TMAO plasma level in comparable group (CAD+AF) was significantly higher by 36,52% (P<0,01) than in mean group (CAD) and by 57,68% (P<0,01) than in control group. TMA/TMAO ratio was significantly higher in control group in comparison

with main and comparable groups and vice versa. So, TMA and TMAO plasma levels increased gradually for patients with CAD and for patients with CAD and AF in comparison with CG.

The correlation analysis between TMA and TMAO plasma levels and the clinical and laboratory characteristics of the examined groups was done. Spearman's correlation analysis was used to explore their correlations with species abundance. All correlations are shown in the table 3.

**Table III.** Plasma TMA and TMAO levels correlations with clinical and laboratory changes, P<0.05

| *Clinical and laboratory changes / Gut microbiota metabolites* | *TMA (mmol/l)* | *TMAO (mmol/l)* | *TMA/TMAO* |
|---|---|---|---|
| Age (years) | 0 | + | 0 |
| BMI (kg/m2) | + | + | 0 |

| | | | |
|---|---|---|---|
| GFR (ml/min) | 0 | + | 0 |
| Total cholesterol (mmol/l) | + | 0 | 0 |
| Triglycerides (mmol/l) | 0 | + | - |
| LDL (mmol/l) | - | - | 0 |
| HDL (mmol/l) | + | + | - |
| ApoA1 (g/l) | - | - | 0 |
| ApoB (g/l) | + | ++ | -- |
| Lpα (mg/dl) | + | + | 0 |
| CRP, mg/l | + | ++ | -- |
| IL-6, pg/ml | + | ++ | -- |

+ – moderate positive correlation, 0.3< r<0.7; ++ – strong positive correlation, r>0.7; 0 – no significant correlations; - – moderate negative correlation, -0.3> r>-0.7; -- – strong negative correlation, r<-0.7

Considering the potential interaction between gut microbiota metabolites and CAD with AF development, the correlation between blood lipid profile, inflammatory markers and TMA, TMAO was checked. It was found that plasma TMA and TMAO levels in all investigated groups had significant correlations with clinical and laboratory sings. Positive moderate strength correlations were revealed between plasma TMAO and ApoB, CRP, IL-6 levels. Also, the largest level of correlations was estimated between TMAO level and clinic-laboratory characteristics.

Secondary, fecal SCFA composition was studied in all

investigated groups. 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. Also, the sum of middle chain fatty acids (MCFA) was investigated. MCFA include caproic acid (C6:0), isocaproic acid (C6:1) and caprylic acid (C8:0) [10]. Results are shown in table 4.

**Table IV.** Fecal SCFA levels in patients with CAD and patients with CAD and AF compared with control group, mean ± standard error, mg/g

| *Characteristic /group* | *CAD* | *CAD+AF* | *CG* | *P1-2* | *P2-3* | *P1-3* |
|---|---|---|---|---|---|---|
| Total amount | 2089,00±71,34 | 1732,00±24,43 | 2964,00±75,26 | P<0,01 | P<0,01 | P<0,01 |
| C2:0 | 306,0±53,13 | 464,8±93,11 | 286,3±66,7 | P>0,05 | P<0,05 | P>0,05 |
| C3:0 | 594,5±43,37 | 534,3±72,26 | 639,5±76,89 | P>0,05 | P>0,05 | P>0,05 |
| C4:0 | 244,7±76,82 | 52,01±25,18 | 667,9±140,9 | P<0,01 | P<0,05 | P<0,05 |
| C4:1 | 14,77±7,33 | 19,76±7,06 | 0 | P>0,05 | P<0,05 | P<0,05 |
| C5:0 | 10,2±6,68 | 125,3±54,72 | 453,3±95,12 | P<0,05 | P<0,05 | P<0,01 |
| C5:1 | 824,9±80,43 | 464,3±97,35 | 310,6±202,7 | P<0,05 | P>0,05 | P<0,01 |
| C6:0 | 12,94±7,37 | 39,99±16,9 | 195,8±61,11 | P>0,05 | P>0,05 | P<0,01 |
| C6:1 | 0,42±0,33 | 30,44±12,79 | 0 | P>0,05 | P<0,05 | P<0,05 |
| C8:0 | 80,84±30,36 | 0,64±0,64 | 410,3±145,4 | P<0,05 | P<0,01 | P>0,05 |
| SFA | 1249,00±83,48 | 1217,00±99,66 | 1214,00±301,00 | P>0,05 | P>0,05 | P>0,05 |
| USFA | 840,1±78,30 | 514,50±94,14 | 143,50±95,45 | P<0,05 | P<0,05 | P<0,01 |
| MCFA | 94,20±31,08 | 4,20±1,66 | 277,40±81,19 | P<0,05 | P<0,01 | P<0,05 |

Our results revealed significant decreasing total amount of fecal SCFA in CAD patients with and without AF in comparison with control group (by 71,13% and 41,89% respectively, p<0,05). It was found significant differences of fecal SCFA absolute levels in their content of investigated groups. The significant increasing of absolute acetic (on 62,35%) and decreasing butyric (on 92,21%), valeric (on 72,36%), caprylic (on 99,84%) acids levels in the comparable group (CAD+AF) in comparison with CG was found (P<0.05). The significant increasing of absolute isovaleric (on 62,35%) and decreasing butyric (on 63,36%), valeric (on 97,75%), caproic (on 93,39%) acids levels in the main group (CAD) in comparison with CG was found (P<0.05). The significant increasing of absolute valeric (on 1128,43%) and decreasing butyric (on 78,75%), isovaleric (on 56,29%),

caprylic (on 99,21%) acids levels in the main group (CAD+AF) in comparison with comparable group (CAD) was found (P<0.05). For the CG there was not common presence of isocaproic and isobutyric fecal acids, which occurred in the main (CAD) and comparable (CAD + AF) groups, that is shown in the chart I.

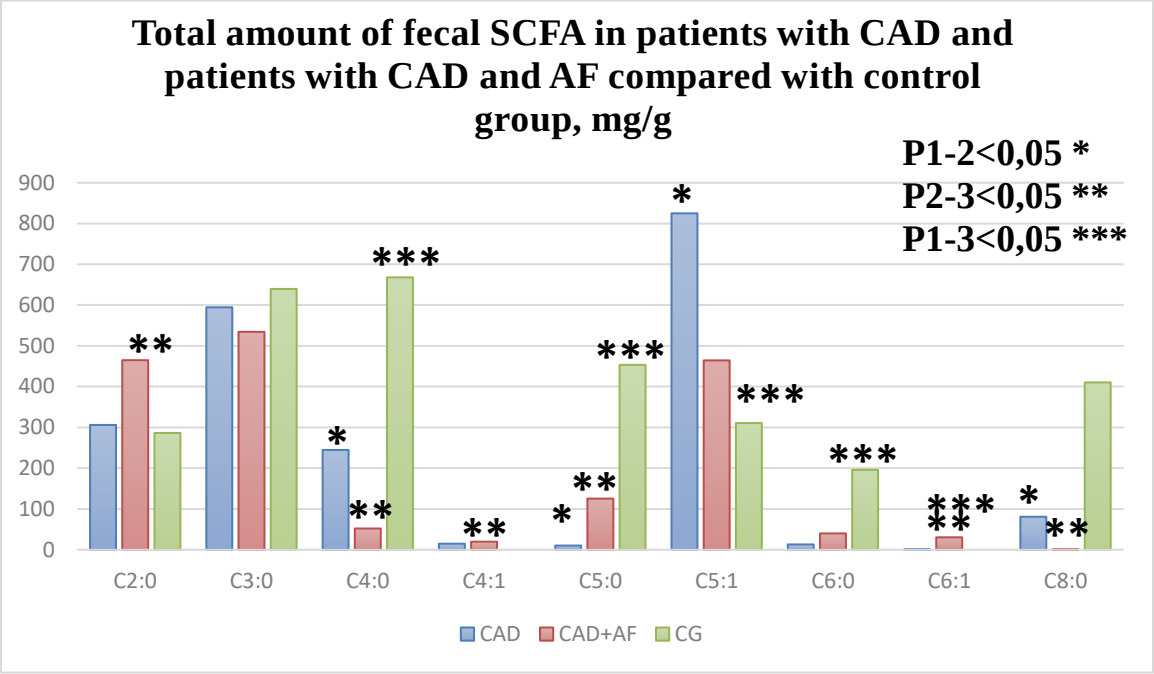


**Chart I.** Total amount of fecal SCFA in patients with CAD and patients with CAD and AF compared with CG, mg/g

Also, in comparable group (CAD+AF) in comparison with CG was found significant increasing level of USFA (on 485,44%) and decreasing of MCFA (on 66,04%). In main group (CAD) in comparison with CG was found significant increasing level of USFA (on 258,54%) and decreasing of MCFA (on 98,49%). In comparable group (CAD+AF) in comparison with main group (CAD) was found significant

decreasing MCFA (on 95,54%) and USFA (on 38,76%) levels; (P<0.05).

The correlation analysis between fecal SCFA and the clinical and laboratory characteristics of the examined groups was done. Spearman's correlation analysis was used to explore their correlations with species abundance. All correlations are shown in the table 5.

**Table V.** Fecal SCFA levels correlations with clinical and laboratory changes, P<0.05

| *Clinical and laboratory changes / Gut microbiota metabolites* | *Total amount* | *C2:0* | *C3:0* | *C4:0* | *C4:1* | *C5:0* | *C5:1* | *C6:0* | *C6:1* | *C8:0* | *SFA* | *USFA* | *MCFA* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age (years) | - | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| BMI (kg/m2) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | - |
| GFR (ml/min) | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total cholesterol (mmol/l) | 0 | 0 | 0 | - | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Triglycerides (mmol/l) | - | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | - |
| LDL | -- | 0 | - | - | 0 | 0 | 0 | 0 | 0 | 0 | - | 0 | - |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (mmol/l) | | | | | | | | | | | | | |
| HDL (mmol/l) | -- | 0 | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| ApoA1 (g/l) | + | 0 | 0 | 0 | 0 | 0 | + | - | 0 | 0 | 0 | + | 0 |
| ApoB (g/l) | -- | 0 | 0 | -- | + | 0 | 0 | 0 | 0 | - | 0 | 0 | - |
| Lpα (mg/dl) | 0 | 0 | 0 | 0 | 0 | - | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| CRP, mg/l | -- | 0 | - | 0 | 0 | 0 | 0 | 0 | 0 | - | -0 | 0 | - |
| IL-6, pg/ml | -- | 0 | 0 | - | 0 | 0 | 0 | 0 | 0 | - | - | 0 | -- |
| TMA (mmol/l) | ++ | 0 | 0 | -- | + | - | 0 | 0 | + | - | - | 0 | - |
| TMAO (mmol/l) | ++ | 0 | 0 | -- | + | 0 | 0 | 0 | + | -- | - | 0 | - |
| TMA/TMAO | -- | 0 | 0 | + | - | 0 | 0 | 0 | 0 | + | 0 | 0 | + |

+ – moderate positive correlation, 0.3< r<0.7; ++ – strong positive correlation, r>0.7; 0 – no significant correlations; - – moderate negative correlation, -0.3> r>-0.7; -- – strong negative correlation, r<-0.7

The largest amount of correlations was checked between fecal SCFA composition and such clinical characteristics as TMAO (total number = 8), TMA (total number = 7) and CRP (total number = 6) levels. At the same time, the highest amount of correlations was between total amount of SCFA (total number = 12), MCFA (total amount = 9), butyric acid (total number = 7) and clinic-laboratory changes.

## Discussion

Human gut microbiota and its metabolites are a new potential interesting target for pathophysiological correction in a lot of metabolic and cardiovascular disorders. It is closely connected with chronic low-grade inflammation and lipid exchange disorders that is known etiological predisposition for AF and CAD. Moreover, according to gut brain axis it can change cardiac innervation that play important role in AF paroxysm pathogenesis [11].

We confirmed the role of plasma TMA/TMAO and total amount of fecal SCFA in AF paroxysm pathogenesis in CAD patients during our study. Strong correlations between TMAO, SCFA levels and IL-6, CRP levels confirms their role in chronic low-grade inflammation on the one hand, while on the other hand, correlations between TMAO, SCFA levels and lipid exchange sings (Lpα, ApoA1, ApoB, total cholesterol, triglycerides, LDL, HDL) confirms their role in lipid metabolism abnormalities, too. This is matched with some authors data [9, 12, 13].

Moreover, we further investigated fecal SCFA content of CAD patients with and without AF. For the first time significant increasing of USFA in CAD patients and decreasing of MCFA in CAD patient with AF was found. Such investigation results have been not estimated previously.

The role of butyric acid decrease in CAD and also in AF paroxysm pathogenesis pay much attention. In some animal studies anti-inflammatory effect of butyric acid was confirmed [9, 14], so this can explain such changes. Butyrate is the major source of energy to the colonic mucosa needed for the maintenance of human gut health and is an important regulator of the bacterial balance, the intestinal barrier function and the expression of various genes, including those encoding lipids and those related to immunity, inflammation, differentiation, apoptosis, phagocytosis and efferocytosis. Butyrate takes part in plasma TMAO level regulation, which could regulate macrophages and provoke atherosclerotic plaque expression [15]. Our work confirmed the connection between TMA, TMAO plasma and fecal butyrate levels, its correlation with IL-6 also proved its anti-inflammatory properties [10]. Butyrate attenuates intestinal cholesterol absorption [16]. Also, in vitro butyrate has been found to lower liver cholesterol biosynthesis. Butyrate promotes lipid oxidation and stimulates all oxidative metabolism. According to some data butyrate prescription can decrease intracellular cholesterol level comparable with atorvastatin permanent usage [14, 17]. So, fecal butyrate correlations with total cholesterol, LDH, HDH and ApoB plasma levels can be estimated: all butyrate properties explained by gut-heart and gut-brain axis [14, 15]. Finally, prescribing butyrate can be a promising way for SCFA composition correction for CAD and AF patients.

## Conclusions

Metabolomic analysis of the gut microbiota metabolites levels (plasma TMA, TMAO, fecal SCFA) and clinic-laboratory factors in patients with CAD and CAD with AF paroxysm was performed in our study. We checked gut microbiota metabolites changes that are common for patients with CAD and AF comparable with CAD patients: increasing of TMA, TMAO plasma levels, fecal USFA, valeric acid level and decreasing TMA/TMAO ratio, fecal total amount of SCFA, MCFA, butyric, isovaleric,

caprylic acids levels. Connections between CAD and AF with TMA, TMAO plasma and fecal SCFA levels are confirmed by reliable correlations between them and age, BMI, GFR, total cholesterol, TG, LDL, HDL, ApoB levels that are known risk factors of CAD and AF. Moreover, TMAO, TMA, butyrate, total SCFA, USFA, MCFA levels are closely connected with IL-6 and CRP levels. The determination of TMA, TMAO, SCFA pathogenetic role will be continued in further studies.

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