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## ATRIAL FIBRILLATION IN CORONARY ARTERY DISEASE PATIENTS: GUT MICROBIOTA COMPOSITION AND ECHOCARDIOGRAPHY INDEXES

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**The aim:** to find connections between gut microbiota composition and transthoracic echocardiography (TTE) indexes in patients with coronary artery disease (CAD) and atrial fibrillation (AF).

**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. 16-S rRNA sequencing checked gut microbiota composition. TTE was done by ALOKA SSD-5000.

**Results:** The II group patients were characterized by the increase of LAD (10.03 %), LAV (15.40 %) and LAVI (11.48 %) in comparison with the I group,  $P < 0.05$ . The II group patients were characterized by a rise of *Pseudomonadota* in comparison with the I group,  $P < 0.05$ . Also, II group patients were characterized by rise of *Actinobacter Spp.* and decrease of *Blautia Spp.*, *Bacteroides Thetaiotaomicron* in comparison with the I group,  $P < 0.05$ . *Firmicutes* were correlated with AO ( $r = 0.308$ ), LADI ( $r = -0.363$ ), RV ( $r = -0.470$ ), IVS ( $r = -0.381$ ), LVPW ( $r = -0.345$ ), LVM ( $r = -0.476$ ) and EF ( $r = 0.312$ ),  $P < 0.05$ . *Akkermansia Muciniphila* was correlated with LAD ( $r = -0.343$ ), LADI ( $r = -0.308$ ), LAV ( $r = -0.494$ ), LAVI ( $r = -0.488$ ), RAV ( $r = -0.316$ ), RAVI ( $r = -0.397$ ), RV ( $r = -0.383$ ), EF ( $r = 0.332$ ),  $P < 0.05$ . *Bifidobacterium Spp.* were correlated with LAV ( $r = -0.487$ ), LAVI ( $r = -0.327$ ), RV ( $r = -0.341$ ), IVS ( $r = -0.306$ ), RWT ( $r = -0.389$ ), LVM ( $r = -0.369$ ), LVMI ( $r = -0.312$ ), EF ( $r = 0.317$ ),  $P < 0.05$ . *Streptococcus Spp.* were correlated with AO ( $r = 0.329$ ), LVOT ( $r = 0.390$ ), RV ( $r = 0.393$ ), IVS ( $r = 0.648$ ), LVPW ( $r = 0.579$ ), RWT ( $r = 0.356$ ), LVM ( $r = 0.336$ ), LVMI ( $r = 0.376$ ),  $P < 0.05$ . *Ruminococcus Spp.* were correlated with AO ( $r = 0.412$ ), LVOT ( $r = 0.351$ ), LADI ( $r = -0.343$ ), IVS ( $r = -0.316$ ), LVPW ( $r = -0.367$ ), LVM ( $r = -0.302$ ), LVMI ( $r = -0.379$ ),  $P < 0.05$ .

**Conclusion:** Gut microbiota composition and TTE indexes play a significant role in CAD and AF pathogenesis. *Firmicutes*, *Bifidobacterium spp.*, and *Verrucomicrobiota (Akkermansia muciniphila)* were significantly correlated with left atrium size and volume, as well as their ultrasound indexes. *Bifidobacterium spp.*, *Bacteroides Spp.*, *Streptococcus Spp.* and *Ruminococcus Spp.* were significantly correlated with left ventricular sizes and its hypertrophy indexes

**Keywords:** coronary artery disease, atrial fibrillation, echocardiography, gut microbiota composition

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### 1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the world, which affects more than 37 million people. Coronary artery disease (CAD) is the most common cardiovascular disorder, which affects more than 110 million people. CAD and AF are the risk factors of each other, which worsened their course and prognosis. Moreover, CAD and AF have a lot of common risk factors, such as diabetes mellitus, dyslipidemia, arterial hypertension, heart failure, etc. All of them are pathogenetically connected with gut microbiota composition abnormalities [1–3].

Gut microbiota is a crucial regulator of the host metabolism. It influences lipids, carbohydrates and protein exchange and regulates energy homeostasis [4]. Appropriate development of the human metabolic system is based on the symbiotic relationship between gut microbiota and host [5]. Altered gut microbiota diversity,

composition and function lead to breaks into intestinal barrier integrity through the mucous and lipids metabolites (short chain fatty acids (SCFA)) production changes and gut metabolites expansion. Rise of gut microbiota metabolites in blood flow, such as bile acids (Bas), lipopolysaccharide (LPS), trimethylamine (TMA) and trimethylamine-N-oxyde (TMAO), indoxyl sulphate, choline, have proarrhythmic properties. TMA and TMAO raise sympathetic activity and inflammation fibrosis in the myocardium, which causes structural and autonomic remodelling. LPS increases after depolarisation by activation of L-type  $Ca^{2+}$  channels and decreases conduction velocity by inflammatory fibrosis. Indoxyl sulphate also produces structural remodelling by rising inflammatory cytokines and apoptosis in the myocardium. BAs have proinflammatory and proapoptotic actions but also indirectly affect the  $Na^{+}/Ca^{2+}$  exchanger, which decreases the atrial effective refractory period [3]. So, gut microbi-

ota metabolites affect the myocardium (gut-heart axis), leading to structural remodelling and further AF paroxysm development [3, 6].

Transthoracic echocardiography (TTE) is needed for all AF patients as a treatment guide. Such data as left ventricular (LV) size and function, left atrial (LA) size, valvular disease, right heart size, and systolic function are crucial for further patient management. Impaired LV function and LV hypertrophy are known proarrhythmic markers [1]. Interest in the problem of gut microbiota connections with hemodynamic changes has been increasing during the last 10 years, but the number of studies is still low [7]. Some animal studies describe connections between fecal SCFA and LA indexes in AF models [8] or TMAO and LV mass [9]. Also, other studies found a decrease in intestinal diversity that directly correlates with ejection fraction (EF) [10]. So, to estimate connections between gut microbiota composition, its metabolites and TTE indexes, we consider it will be interesting for a deeper understanding of AF paroxysm pathogenesis in CAD patients.

**The aim:** to find connections between gut microbiota composition and transthoracic echocardiography indexes in patients with coronary artery disease and atrial fibrillation.

## 2. Materials and methods

300 patients were enrolled 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 Kiev 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 [11]. 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 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 in accordance with the Declaration of Helsinki.

Baseline characteristics of 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 # ПТ – 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 is why these baseline characteristics were analyzed and compared; it can help us exclude their influence on the results we obtain.

TTE was done by ALOKA SSD-5000. We analyzed such characteristics: aorta diameter (AO), left ventricular outflow tract (LVOT), left atrium diameter (LAD), left atrium diameter index (LADI), left atrium volume (LAV), left atrium volume index (LAVI), right atrium diameter (RAD), right atrium diameter index (RADI), right atrium volume (RAV), right atrium volume index (RAVI), anterior-posterior size of the right ventricle (RV), interventricular septum (IVS), left ventricle posterior wall (LVPW), relative wall thickness (RWT), left ventricular mass (LVM), left ventricular mass index (LVMI), ejection fraction (EF), left ventricular stroke volume (LVSV), left ventricular stroke volume index (LVSVI), left ventricular end diastolic volume (LVEDV), left ventricular end diastolic volume index (LVEDVI), left ventricular end systolic volume (LVESV), left ventricular end systolic volume index (LVESVI), left ventricular end diastolic diameter (LVEDD), left ventricular end diastolic diameter index (LVEDDI), left ventricular end systolic diameter (LVESD), left ventricular end systolic diameter index (LVESDI) [12].

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.*), Actinomycetota (*Bifidobacterium spp.*), Verrucomicrobiota (*Akkermansia muciniphila*), Pseudomonadota (*Escherichia coli*, *Acinetobacter spp.*) and Archaea (*Methanobrevibacter smithii* and *Methanosphaera stadmanae*). Also, Firmicutes/Bacteroides (F/B) ratio was compared [3, 6, 10].

Results were presented as mean  $\pm$  standard error or [95 % confidence interval (CI)] for continuous variables or as a number for categorical variables. Variable distributions for normality were checked using the Pearson criterion. 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 [13]. All calculations were done in MATLAB R2014a (License number 271828).

## 3. Results

We analyzed the baseline characteristics of the investigated groups. There was no significant difference in age, gender, BMI, total bilirubin and smoking history in the investigated groups.

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 significantly higher, and GFR (by 26.16 % and 19.38 %, respectively) were lower than in CG ( $p < 0.05$ ).

Also, in I and II groups were patients with obesity, diabetes mellitus, stroke or MI history; such cases were absent in CG. Data are shown in Table 1.

Table 1

Baseline characteristics of 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 <sup>2</sup> )	27.02±0.33	26.93±0.43	27.12±2.10	P>0.05	P>0.05	P>0.05
Total bilirubin (mmol/l)	11.3±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

TTE indexes were explored in investigated groups.

In the I group, there were significant increases in IVS (15.15 %), LVPW (17.71 %), RWT (12.35 %), LVM (39.78 %), LVMI (35.87 %), LVEDV (21.42 %) in comparison with CG.

In the II group were significant rise of LVOT (11.47 %), LAD (10.03 %), LAV (15.40 %), LAVI

(11.48 %), RV (11.50 %), IVS (18.18 %), LVPW (20.83 %), LVM (47.93 %), LVMI (46.02 %), LVEDV (27.28 %), LVEDVI (25.88 %) in comparison with CG.

Also, in the II group, significant increases in LAD (10.03 %), LAV (15.40 %) and LAVI (11.48 %) were found in comparison with the I group (p <0.05). Data are presented in Table 2.

Table 2

TTE of investigated groups, mean ± standard error

Characteristic /group	I group	II group	CG	P1-2	P2-CG	P1-CG
AO, cm	3.19±0.04	3.27±0.04	3.06±0.06	P>0.05	P>0.05	P>0.05
LVOT, cm	3.05±0.03	3.11±0.03	2.79±0.09	P>0.05	P<0.05	P>0.05
LAD, cm	4.08±0.04	4.28±0.05	3.89±0.06	P<0.05	P<0.05	P>0.05
LADI, cm/m <sup>2</sup>	2.12±0.04	2.26±0.04	2.08±0.05	P>0.05	P>0.05	P>0.05
LAV, ml	3.95±0.03	4.42±0.05	3.83±0.04	P<0.05	P<0.05	P>0.05
LAVI, ml/m <sup>2</sup>	2.05±0.03	2.33±0.04	2.09±0.03	P<0.05	P<0.05	P>0.05
RAD, cm	3.52±0.04	3.65±0.04	3.48±0.05	P>0.05	P>0.05	P>0.05
RADI, cm/m <sup>2</sup>	1.83±0,03	1.92±0.03	1.87±0.04	P>0.05	P>0.05	P>0.05
RAV, ml	3.85±0.03	3.94±0.03	3.94±0.03	P>0.05	P>0.05	P>0.05
RAVI, ml/m <sup>2</sup>	2.00±0.02	2.11±0.03	2.11±0.03	P>0.05	P>0.05	P>0.05
RV, cm	2.48±0.03	2.52±0.03	2.26±0.02	P>0.05	P<0.05	P>0.05
IVS, cm	1.14±0.01	1.17±0.02	0.99±0.01	P>0.05	P<0.05	P<0.05
LVPW, cm	1.13±0.01	1.16±0.01	0.96±0.02	P>0.05	P<0.05	P<0.05
RWT	0.91±0.02	0.96±0.02	0.81±0.04	P>0.05	P>0.05	P<0.05
LVM, g	188.70±5.60	199.70±7.26	135.00±6.01	P>0.05	P<0.05	P<0.05
LVMI, g/m <sup>2</sup>	98.07±3.26	105.40±3.97	72.18±3.39	P>0.05	P<0.05	P<0.05
EF	0.59±0.01	0.59±0.01	0.59±0.01	P>0.05	P>0.05	P>0.05
LVSV, ml	57.67±1.59	59.93±1.90	48.24±3.61	P>0.05	P>0.05	P>0.05
LVSVI, ml/m <sup>2</sup>	29.83±1.04	31.64±1.24	25.88±2.01	P>0.05	P>0.05	P>0.05
LVEDV, ml	98.64±2.77	103.40±3.73	81.24±4.62	P>0.05	P<0.05	P<0.05
LVEDVI, ml/m <sup>2</sup>	51.37±1.85	54.87±2.34	43.59±2.62	P>0.05	P<0.05	P>0.05
LVESV, ml	40.97±1.60	43.46±2.47	33.00±1.59	P>0.05	P>0.05	P>0.05
LVESVI, ml/m <sup>2</sup>	21.54±1.04	23.24±1.53	17.71±0.92	P>0.05	P>0.05	P>0.05
LVEDD, cm	4.50±0.06	4.61±0.06	4.23±0.09	P>0.05	P>0.05	P>0.05
LVEDDI, cm/m <sup>2</sup>	2.33±0.04	2.40±0.06	2.26±0.06	P>0.05	P>0.05	P>0.05
LVESD, cm	3.05±0.05	3.15±0.06	2.99±0.10	P>0.05	P>0.05	P>0.05
LVESDI, cm/m <sup>2</sup>	1.59±0.03	1.64±0.05	1.60±0.06	P>0.05	P>0.05	P>0.05

Further, we checked the gut microbiota composition of the investigated groups. According to our result,

the F/B ratio was not significantly different in the investigated groups (p >0.05). By the taxonomic analysis, in

the I and II groups, there was a significant increase in *Pseudomonadota* and a decrease of *Actinomycetota* and *Verrucomicrobiota* compared with CG; in the II group compared with the I group, there was a significant rise in *Pseudomonadota* ( $p < 0.05$ ).

By the species analysis in the I and II groups comparing with CG were the significant rise of *Bacteroides Spp.*, *Faecalibacterium Prausnitzii*, *Actinobacter Spp.*, *Streptococcus Spp.* and decrease of *Lactobacil-*

*us Spp.*, *Bifidobacterium Spp.*, *Akkermansia Muciniphila*, *Eubacterium Rectale*; in the I group in comparison with CG was the significant rise of *Ruminococcus Spp.*; in the II group in comparison with CG was significant decrease of *Roseburia Inulinivorans*; in the II group in comparison with I group was significant rise of *Actinobacter Spp.* and decrease of *Blautia Spp.*, *Bacteroides Thetaiotaomicron* ( $p < 0.05$ ).

Results are present in the Fig. 1.

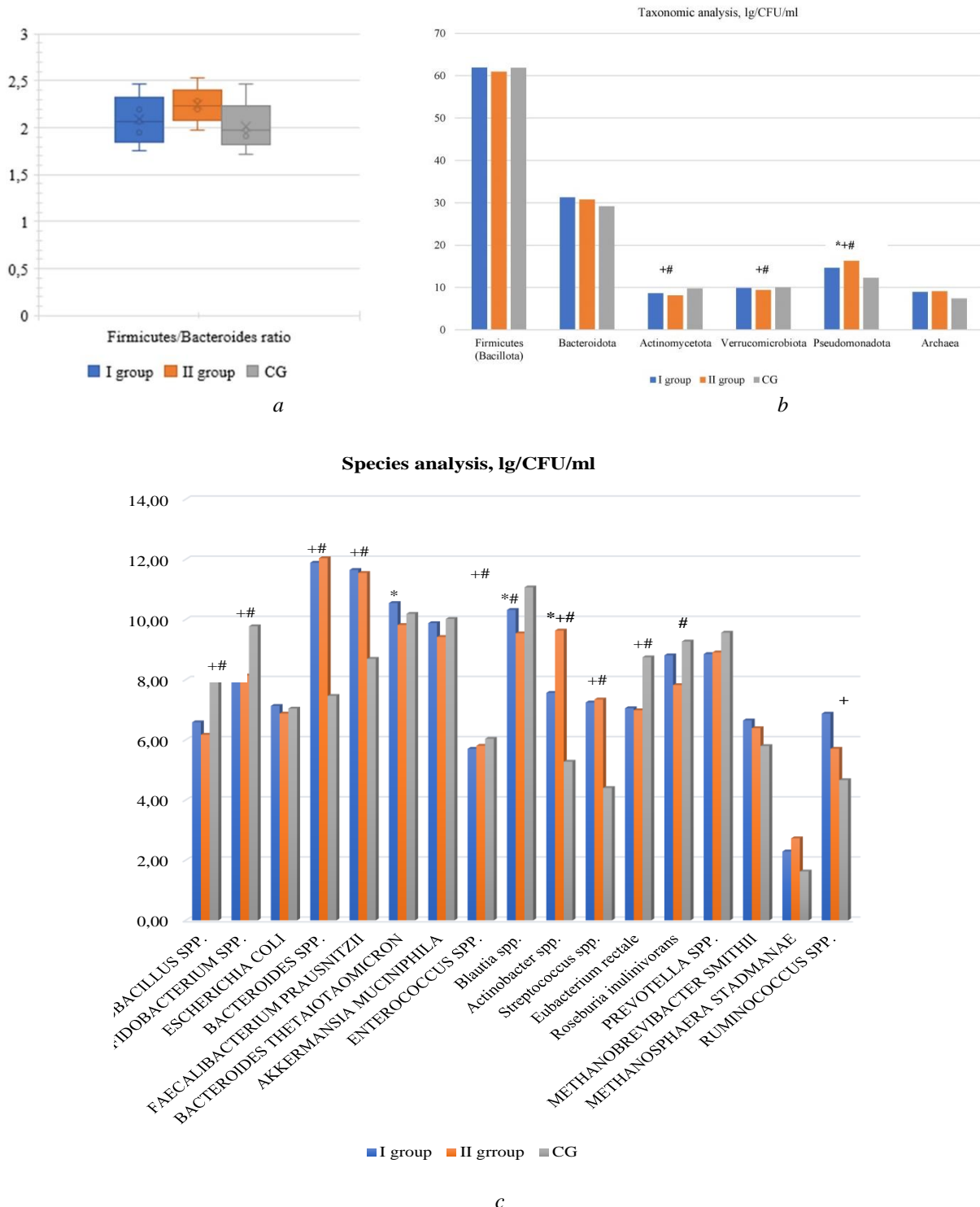


Fig. 1. Gut microbiota composition in investigated groups: *a* – F/B ratio; *b* – taxonomic analysis, mean [95 % CI], lg/CFU/ml; *c* – species analysis, mean [95 % CI], lg/CFU/ml; \*- $P < 0.05$  I-II groups; +- $P < 0.05$  I group – CG; #- $P < 0.05$  II group – CG.

The correlation analysis between gut microbiota phylum and species components and cardiometabolic risk factors was done in the investigated groups. Spearman's correlation analysis was used to explore their correlations with species abundance. All correlations are shown in the Fig. 2 and 3.

The largest amount of correlations was checked between echocardiography indexes and *Verrucomicrobi-*

*ota* (total number=8), *Actinomycetota* (total number=8) and *Firmicutes* (total number=7) phyla. Also, the highest number of correlations were found between IVS (total number=5), EF (total number=4), LAV (total number=4), and gut microbiota phyla. *Firmicutes* were correlated with AO (r=0.308), LADI (r=-0.363), RV (r=-0.470), IVS (r=-0.381), LVPW (r=-0.345), LVM (r=-0.476) and EF (r=0,312), P<0.05.

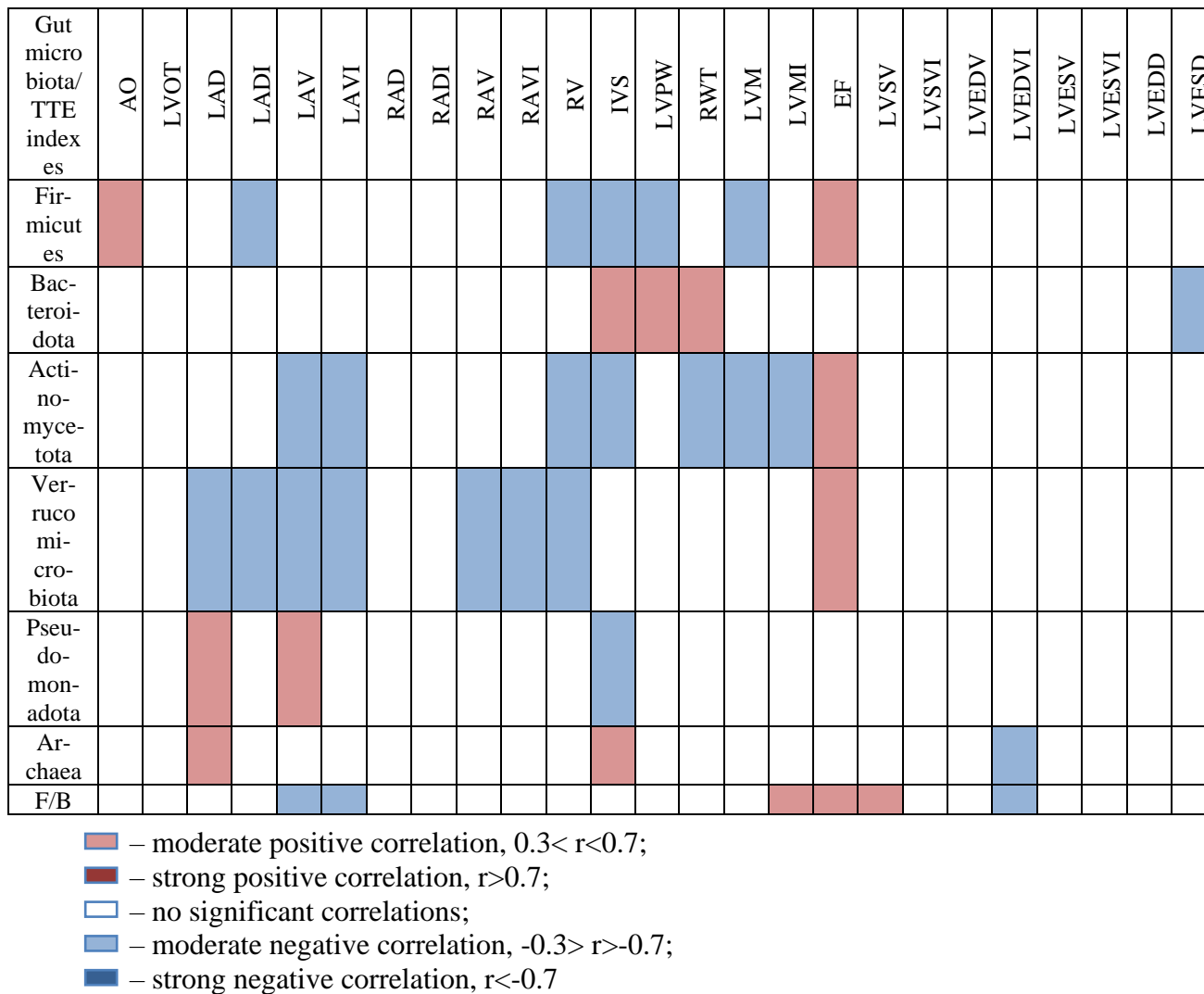


Fig. 2. Heatmap correlation matrices between gut microbiota phylum and echocardiography indexes, P<0.05

The largest amount of correlations was checked between echocardiography indexes and *Akkermansia Muciniphila* (total number=8), *Bifidobacterium Spp.* (total number=8), *Streptococcus Spp.* (total number=8) and *Ruminococcus Spp.* (total number=7) phyla. Also, the highest amount of correlations were found between RWT (total number=8), LAV (total number=5), LAVI (total number=5), IVS (total number=5), LVM (total number=5), LVMI (total number=5) and gut microbiota species. *Akkermansia Muciniphila* was correlated with LAD (r=-0.343), LADI (r=-0.308), LAV (r=-0.494), LAVI (r=-0.488), RAV (r=-0.316), RAVI (r=-0.397), RV

(r=-0.383), EF (r=0.332), P<0.05. *Bifidobacterium spp.* were correlated with LAV (r=-0.487), LAVI (r=-0.327), RV (r=-0.341), IVS (r=-0.306), RWT (r=-0.389), LVM (r=-0.369), LVMI (r=-0.312), EF (r=0.317), P<0.05. *Streptococcus spp.* were correlated with AO (r=0,329), LVOT (r=0,390), RV (r=0,393), IVS (r=0,648), LVPW (r=0,579), RWT (r=0,356), LVM (r=0,336), LVMI (r=0,376), P<0.05.

*Ruminococcus Spp.* were correlated with AO (r=0,412), LVOT (r=0,351), LADI (r=-0.343), IVS (r=-0.316), LVPW (r=-0.367), LVM (r=-0.302), LVMI (r=-0.379), P<0.05.

Gut microbiota/TTE indexes	AO	LVOT	LAD	LADI	LAV	LAVI	RAD	RADI	RAV	RAVI	RV	IVS	LVPW	RWT	LVM	LVMi	EF	LVSv	LVSvI	LVEDv	LVEDvI	LVSv	LVSvI	LVEDD	LVESD
Lactobacillus Spp				Strong negative	Strong negative										Strong negative										
Bifidobacterium Spp					Strong negative	Strong negative					Strong negative	Strong negative		Strong negative	Strong negative	Strong negative	Moderate positive								
Escherichia Coli	Moderate negative	Moderate negative							Moderate positive					Moderate positive											
Bacteroides Spp						Strong negative						Moderate positive	Moderate positive			Moderate positive								Moderate positive	
Faecalibacterium Prausnitzii														Strong negative			Moderate positive						Strong negative	Strong negative	Strong negative
Bacteroides Thetaiotaomicron			Moderate positive	Moderate positive										Moderate positive	Moderate positive					Strong negative	Strong negative			Strong negative	
Akkermansia Muciniphila			Strong negative	Strong negative	Strong negative	Strong negative			Moderate positive	Moderate positive	Strong negative						Moderate positive								
Enterococcus Spp									Strong negative			Moderate positive	Moderate positive	Moderate positive											Strong negative
Blautia Spp					Strong negative	Strong negative								Strong negative											Moderate positive
Actinobacter Spp					Moderate positive									Moderate positive				Strong negative		Moderate positive					Moderate positive
Streptococcus Spp	Moderate positive	Moderate positive									Moderate positive	Moderate positive	Moderate positive	Moderate positive	Moderate positive	Moderate positive									
Eubacterium Rectale																		Strong negative	Strong negative						
Roseburia Inulinivorans													Strong negative			Strong negative								Moderate positive	
Prevotella Spp								Moderate positive												Strong negative				Strong negative	
Methanobrevibacter Smithii						Strong negative											Moderate positive						Strong negative	Strong negative	
Methanospiraeta Stadenae	Strong negative							Strong negative	Strong negative																
Ruminococcus Spp	Moderate positive	Moderate positive		Moderate positive									Strong negative	Strong negative	Strong negative	Strong negative									

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

Fig. 3. Heatmap correlation matrices between gut microbiota species and echocardiography indexes,  $P < 0.05$

#### 4. Discussion

In our study, CAD patients with AF had significantly higher LAD, LAV and LAVI data. Increased LA size is one of the major characteristics of AF onset, development and prognosis. With the latest data, LAVI can predict the risk of AF thromboembolic complications, including stroke. It is well-known that AF is associated with LV hypertrophy, LV systolic (reduced EF <40 %) and diastolic dysfunction (increased E/e' ratio) during TTE [12, 14]. However, in our study, patients with EF more than 40 % were selected, and the I and II groups were comparable by LV hypertrophy presence, also.

The F/B ratio is a widely used and sensitive dysbiosis index, which causes a rise in AF, obesity, dyslipidemia, age, diabetes mellitus, and inflammation [3, 15, 16]. However, in our study, a significant difference in the F/B ratio was not detected, which can be explained by the peculiarities of patients' selection in investigated groups. Also, in both investigated groups, *Pseudomonadota* phylum was increased significantly, especially in the II group patients in comparison with the I group. *Pseudomonadota* rise is associated with dyslipidemia and fatty acid metabolism alterations. Increased *Pseudomonadota* is closely linked with low-density lipoproteins and a rise in uric acid and has proinflammatory opportunities in the intestine [17, 18].

In our study *Firmicutes*, *Actinomycetota* (*Bifidobacterium spp.*) and *Verrucomicrobiota* (*Akkermansia muciniphila*) were significantly correlated with LA indexes, as LAD, LADI, LAV, LAVI. *Bifidobacterium spp.* and *Akkermansia muciniphila* are butyrate-producing species. Their decrease correlated with HF development. Butyrate has anti-inflammatory, sympatholytic, and antihypertensive properties by activating free fatty acid receptors and suppressing histone deacetylases [19]. Also, decreased *Akkermansia muciniphila* is associated with lipids exchange violations and hyperglycemia, which are known risk factors of CAD and AF [20]. Moreover, in animal studies, *Akkermansia muciniphila* administration decreases TMAO levels and prevents AF paroxysm formation [21]. Furthermore, the F/B ratio was significantly correlated with LAV and LAVI by our data; such results were obtained in patients with diabetes mellitus study also [20].

According to our results, *Firmicutes*, *Bacteroidota* and *Actinomycetota* (*Bifidobacterium spp.*) were significantly correlated with such LV indexes as IVS, LWPV, RWT, LVM, LVMI. By the species analysis, *Bifidobacterium spp.*, *Bacteroides Spp.*, *Streptococcus Spp.* and *Ruminococcus Spp.* were significantly correlated with these LV hypertrophy indexes. Based on the animal models, *Ruminococcus Spp.* rise can prevent left ventricular hypertrophy development by influencing the gut-brain axis and decreasing neuroinflammation [22]. *Streptococcus spp.* are LPS-produced, which leads to proinflammatory changes, the rise of TNF- $\alpha$ , IL-6, IL-18 and toll-like receptor 4, which is crucial in LV hypertrophy pathogenesis [23]. In some studies, *Bacteroidota* and *Bacteroides Spp.* are associated with LV hypertrophy [20].

Nowadays, a lot of data about the influence of central hemodynamic gut microbiota and its metabolites.

But most of them are controversial and based on animal studies [3, 7, 8, 19, 20–23]. So, analysis of connections between TTE indexes and gut microbiota composition, especially in coronary artery disease patients with atrial fibrillation, is an up-to-date medical topic. Obtained data is mostly based on animal studies or little population investigations, and some of them are controversial. Investigations of gut microbiota metabolites and TTE index connections will be interesting for further scientific research.

**Limitations of the study.** The mean study limitation is a strict list of investigated gut microbiota phylum, order and species. A wider amount of bacterial species can be investigated. Also, the lack of prior research studies on the topic is an important study limitation.

**Perspectives of subsequent scientific research:** Investigations of gut microbiota metabolites and TTE index connections will be interesting for further scientific research.

#### 5. Conclusions

Undoubtedly, gut microbiota composition and transthoracic echocardiography indexes play a crucial role in coronary artery disease and atrial fibrillation pathogenesis. Using different types of analysis, we established some special features of gut microbiome compositions with positive and negative correlations in CAD patients with AF hemodynamic characteristics. Also, their links are important as current topics for further investigations in medical science.

1. By transthoracic echocardiography we confirmed that patients with coronary artery disease and atrial fibrillation are characterized by the increase of LAD (10.03 %), LAV (15.40 %) and LAVI (11.48 %) in comparison with coronary artery disease patients without arrhythmia,  $P < 0.05$ ;

2. Patients with coronary artery disease and atrial fibrillation are characterized by a rise of *Pseudomonadota* (by taxonomic analysis), *Actinobacter Spp.* and a decrease of *Blautia Spp.*, *Bacteroides Thetaiotaomicron* in comparison with coronary artery disease patients without arrhythmia,  $P < 0.05$ ;

3. *Firmicutes*, *Bifidobacterium spp.* and *Verrucomicrobiota* (*Akkermansia muciniphila*) were significantly correlated with left atrium size and volume, their indexes;

4. *Bifidobacterium spp.*, *Bacteroides spp.*, *Streptococcus spp.* and *Ruminococcus spp.* were significantly correlated with this left ventricular sizes and hypertrophy indexes.

#### Conflicts of interest

The authors declare that they have 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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**Data availability**

Data will be made available on reasonable request.

**Use of artificial intelligence**

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

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