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Research Article

SLC2A9 Genotype Distribution and Left Atrium Diameter in Patients with Arterial Hypertension and Atrial Fibrillation

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BACKGROUND: In recent years, asymptomatic hyperuricemia (HU) has been found to have significant adverse effects on the cardiovascular system. Uric acid (UA) accumulation in cardiomyocytes may cause ionic and structural remodeling of the atria. One of the causes of increased UA and a significant risk factor for HU is polymorphism in the *SLC2A9* gene, which encodes the GLUT9 protein, a highly specific urate transporter in proximal renal tubular cells.

AIM: To investigate the frequency of genotypes and alleles of the *SLC2A9* gene rs734553 polymorphism and left atrium (LA) diameter in patients with arterial hypertension (AHT) and atrial fibrillation (AF).

MATERIALS AND METHODS: One hundred four patients, including 94 (90.4%) men and 10 (9.6%) women (aged 55 [45; 61] years old) were enrolled in the study. The patients were divided into the following groups: first — patients with AF (n = 13); second — patients with AHT and AF (n = 68); and third — patients with AHT (n = 23). The LA diameter equal to the LA anterior–posterior dimension on transthoracic echocardiography was taken into account as a characteristic of structural changes of the LA. All patients underwent instrumental, laboratory, and molecular genetic testing, including SLC2A9 gene rs734553 polymorphism using the polymerase chain reaction technique.

The data were presented as median, first and third quartiles, and absolute and relative frequencies. Differences between groups of patients were assessed using the Mann – Whitney U-test and Fisher and Pearson's χ^2 test. The Kruskal–Wallis test was used to compare three independent groups. Differences were considered statistically significant at $p < 0.05$. The relationship between the quantitative and dichotomous variables was described using the rank-biserial correlation coefficient (rrb). The distribution of alleles and genotypes in the studied patient groups was tested for Hardy – Weinberg equilibrium and assessed using the χ^2 test.

RESULTS: There were no significant differences ($p > 0.05$) when comparing the LA diameter and the genotype of the *SLC2A9* gene rs734553 polymorphism in all groups of patients. However, in Group 2, the LA diameter in the CC genotype (43 [42; 44] mm) patients and the AC genotype (40 [49; 43] mm) patients was determined to be larger than in the AA genotype ones (38 [38; 42] mm). In Group 1, the LA diameter in the AC genotype patients (40 [38; 42] mm) was larger than in the AA genotype ones (38 [34; 38] mm).

When studying the distribution frequency of genotypes and alleles of the *SLC2A9* gene rs734553 polymorphism in patients with LA dilatation, we found that in the second group of patients, the AC genotype was significantly more common than in other groups (23.5%) ($p = 0.004$), and there was also a trend toward a higher incidence of AA (13.2%) and CC (14.7%) genotypes. However, it did not reach the criteria for statistical significance. It should be noted that in patients of the first group, LA dilatation was diagnosed only with the AC genotype (38.5%). Dilatation of the LA in patients of the third group was not detected.

CONCLUSIONS: In Group 1 patients (with AF), LA dilatation was observed only in the AC genotype ones. In Group 2 patients (with AHT and AF), LA dilatation was significantly more frequent ($p = 0.004$) in the AC genotype ones. The AC and CC genotype of the *SLC2A9* gene rs734553 polymorphism was more frequent in Group 2 patients (with AHT and AF).

Keywords: arterial hypertension; atrial fibrillation; hyperuricemia; uric acid; left atrial diameter; left atrial enlargement; *SLC2A9* gene polymorphism.

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Научная статья

Распределение генотипов гена *SLC2A9* и диаметр левого предсердия у пациентов с артериальной гипертензией и фибрилляцией предсердий

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Обоснование. В последние годы установлено, что бессимптомная гиперурикемия (ГУ) оказывает существенное негативное воздействие на сердечно-сосудистую систему. Накопление мочевой кислоты (МК) в кардиомиоцитах может привести к ионному и структурному ремоделированию предсердий. Одной из причин повышения МК и значимым фактором риска возникновения ГУ является наличие полиморфизма гена *SLC2A9*, кодирующего белок GLUT9 — высокоспецифического транспортера уратов в клетках проксимальных почечных канальцев.

Цель. Изучить частоту встречаемости генотипов и аллелей полиморфизма rs734553 гена *SLC2A9* и диаметр левого предсердия (ЛП) у пациентов с артериальной гипертензией (АГ) и фибрилляцией предсердий (ФП).

Материалы и методы. В исследование включены 104 пациента, из них 94 (90,4 %) мужчин и 10 (9,6 %) женщин, в возрасте 55 [45; 61] лет. Пациенты были разделены на следующие группы: 1-я — пациенты с ФП (n = 13); 2-я — пациенты с АГ и ФП (n = 68); 3-я — пациенты с АГ (n = 23). В качестве характеристики структурных изменений ЛП учитывался диаметр ЛП, равный передне-заднему размеру ЛП, при выполнении трансторакальной эхокардиографии. Всем пациентам проводились инструментальные, лабораторные и молекулярно-генетические исследования, в том числе определение полиморфизма rs734553 гена *SLC2A9* с помощью методики полимеразной цепной реакции.

Данные представлены в виде медианы, 1-го и 3-го квартилей, абсолютной и относительной частот. Различия между группами пациентов оценивали с помощью *U*-критерия Манна — Уитни, Фишера и критерия χ^2 Пирсона; при сравнении 3 независимых групп использован критерий Краскела — Уоллиса. Различия считались статистически значимыми при значении $p < 0,05$. Связь между количественной и дихотомической переменными описывалась при помощи рангово-бисериальногго коэффициента rrb. Распределение аллелей и генотипов в исследуемых группах пациентов проверяли на соответствие равновесию Харди — Вайнберга и оценивали с помощью критерия χ^2.

Результаты. При сравнении диаметра ЛП и генотипа полиморфизма rs734553 гена *SLC2A9* среди всех групп пациентов достоверных различий получено не было ($p > 0,05$). Однако диаметр ЛП у пациентов 2-й группы с генотипом CC (43 [42; 44] мм) и генотипом AC (40 [49; 43] мм) определялся больший, чем с генотипом AA (38 [38; 42] мм). Диаметр ЛП у пациентов 1-й группы с генотипом AC (40 [38; 42] мм) был больше, чем у лиц с генотипом AA (38 [34; 38] мм).

При изучении частоты распределения генотипов и аллелей полиморфизма rs734553 гена *SLC2A9* у пациентов с дилатацией ЛП нами было установлено, что во 2-й группе пациентов достоверно чаще по сравнению с другими группами встречался генотип AC (23,5 %) (p = 0,004), а также наблюдалась тенденция к более высокой встречаемости генотипов AA (13,2 %) и CC (14,7 %), однако она не достигла критериев статистической значимости. Следует отметить, что у пациентов 1-й группы дилатация ЛП была диагностирована только с генотипом AC (38,5 %). Дилатация ЛП у пациентов 3-й группы не выявлена.

Заключение. У пациентов 1-й группы (с ФП) дилатация ЛП наблюдалась только при генотипе AC. Во 2-й группе пациентов (с АГ и ФП) дилатация ЛП встречалась достоверно чаще (p = 0,004) при генотипе AC. У пациентов 2-й группы (с АГ и ФП) чаще встречался генотип AC и CC полиморфизма rs734553 гена *SLC2A9*.

Ключевые слова: артериальная гипертензия; фибрилляция предсердий; гиперурикемия; мочевая кислота; диаметр левого предсердия; дилатация левого предсердия; полиморфизм гена *SLC2A9*.

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Increased uric acid (UA) blood levels, along with gout progression, are associated with cardiovascular system (CVS) diseases [1]. Atrial fibrillation (AF) and arterial hypertension (AHT) are the two most common, often combined CVS pathologies. The incidence of these diseases increases with age, leading to numerous complications and a high mortality rate [2].

Due to the high prevalence of AHT in the population, it is associated with more cases of AF than any other risk factor. The risk of AF incidence in patients with hypertension is 1.9-fold higher compared with patients with normal blood pressure (BP) [3].

There is no single explanation for the relationship between HU and cardiovascular disease (CVD). There are several concepts that interpret the possible influence of UA on the incidence and progression of a number of CVDs, as proved by the results of some clinical and experimental studies [4].

UA itself has several adverse effects and may be directly involved in the pathogenesis of CVDs. In general, prooxidant activity, nitric oxide deficiency and endothelial dysfunction, stimulation of inflammation, and potentiation of vasoconstrictor responses and proliferative vascular stimuli can be considered as the most obvious mechanisms of UA involvement in the pathogenesis of circulatory system diseases [5].

In recent years, whole-genome studies have demonstrated the important role of genetic predisposition to disorders of purine metabolism. In particular, polymorphisms of genes encoding urate transporters in the kidney and intestine (*SLC2A9*, *SLC22A12*, *ABCG2*, etc.) may cause increased UA levels and a significant risk factor for gout and HU [6].

The *SLC2A9* gene is located on the short arm of chromosome 4 at the 15.3–16 position and encodes a protein known as glucose transporter 9 (GLUT9) or urate efflux transporter (URATv1) [7]. In the proximal renal tubules, *SLC2A9* transports UA through the basolateral membrane into the bloodstream during reabsorption, thereby being critical for UA homeostasis [8].

SLC2A9 has a relatively conserved amino acid sequence in the seventh and eighth helices located around the central channel of the transport protein [9], which makes the polymorphic variant in intron 7 very important. The rs734553 polymorphism in intron 7 (A/C alleles) may alter the polarity of some of these conserved amino acids. Consequently, it can affect the transporter-UA affinity, which causes changes in UA levels in the blood [10].

According to published information, the *SLC2A9* gene rs734553 polymorphism in intron 7 affects UA levels in the blood serum, contributing to predisposition to gout, Parkinson's disease, or chronic kidney disease (CKD) progression [11,12].

Common genetic variants of *SLC2A9* have recently been found to be strongly associated with serum urate levels and gout in Caucasian cohorts from Italy, the United Kingdom, Croatia, the United States, Germany, and Austria [13]. Genetic variants of SLC2A9 affected UA levels in Korean adult patients A number of studies have been described in the foreign literature on the relationship between UA levels in the blood and the left atrium (LA) diameter in patients with and without cardiac pathology. Thus, K.P. Letsas et al. presented the results of a study that included 86 patients with AF and 48 patients without arrhythmia. It was found that the UA level significantly correlated with the LA diameter ($p < 0.001$) [15].

As a result of a retrospective analysis of 3,043 medical records, T.F. Chao et al. showed that HU is associated with a large LA diameter [16]. Similar results were obtained in another study that included patients with AHT. The UA level was also associated with LA diameter and was a risk factor for LA dilatation [17].

The results of a study by Hidru et al. in 2020, which is conducted using data from 9,618 patients with AH from the hospital registry, HU and a larger LA diameter are independently associated with a higher probability of AF [18].

The research objective was to investigate the frequency of genotypes and alleles of the SLC2A9 gene rs734553 polymorphism and left atrium (LA) diameter in patients with AHT and AF.

MATERIALS AND METHODS

One hundred four patients, including 94 (90.4%) men and 10 (9.6%) women (aged 55 [45; 61] years old) were enrolled in the study. The patients were divided into the following groups: first — patients with AF ($n = 13$); second — patients with AHT and AF ($n = 68$), third — patients with AHT ($n = 3$).

The inclusion criteria for Group 1 were the presence of idiopathic AF or AF developed in the setting of coronary heart disease (CHD). The inclusion criteria for Group 2 were the presence of AHT and AF developed in the setting of AHT and/or CHD. The identification of AF forms was carried out according to the 2012 European Society of Cardiology Guidelines [19]. The inclusion criteria for Group 3 were the presence of AHT, as well as negative AF history and other clinically significant cardiac rhythm disturbances.

The exclusion criteria were as follows: acute coronary or cerebrovascular pathology at the time of examination, history of myocardial infarction or cerebrovascular disorders, clinically significant valve pathology of rheumatic or other etiology, H2A circulatory failure or higher, history of cardiac surgery, AF following alcohol drinking, multifocal atherosclerosis, gout, CKD, diabetes mellitus (DM), obesity, thyroid disorders, bronchopulmonary pathology, exacerbation of gastrointestinal diseases, liver dysfunction, and active inflammatory process of any site.

All patients underwent clinical, laboratory, and instrumental examinations, including analysis of complaints, medical history, physical examination, electrocardiogram

(ECG) recording, 24-h ECG monitoring, echocardiography, and general clinical laboratory tests. UA levels were determined using the enzymatic colorimetric method. Increased serum UA levels above 360 μmol/L in women and 400 μmol/L in men and the absence of signs of gouty arthritis were considered to be HU [20]. The determination of xanthine oxidase in blood serum was carried out by a method based on a solid-phase "sandwich" variant of enzyme immunoassay, the determination of purine metabolites using high-performance liquid chromatography.

Molecular genetic testing methods included the determination of the *SLC2A9* gene rs734553 polymorphism using the polymerase chain reaction technique. Whole venous blood was used as a test material for the study of polymorphism. Isolation of human genomic DNA was carried out using the "DNA-Extran-1" reagent kit ("Syntol", Russian Federation). The identification of each polymorphic variant rs734553 of the *SLC2A9* gene was carried out using the corresponding set of reagents manufactured by "Litech" (Russian Federation). DNA amplification was carried out on a Rotor Gene-Q amplifier ("Qiagen," Germany).

As a characteristic of structural changes in the LA, the LA diameter was taken into account, equal to the LA anterior–posterior dimension when performing transthoracic echocardiography on the Philips ultrasound system, IE-33, using a broadband phased probe S5-1 with Pure Wave Crystal technology (single crystal) and an extended frequency band from 1 to 5 MHz using standard positions (in M, B, and Doppler mode). The LA diameter over than 38 mm in women and 40 mm in men was considered to be LA dilatation [21].

During hospital stay, treatment of patients with paroxysmal and persistent forms of AF was consistent with a rhythm control strategy with class III antiarrhythmic drugs (amiodarone or sotalol). All patients with persistent AF also underwent electrical cardioversion to restore sinus rhythm. Treatment of patients with permanent AF was consistent with a strategy to control heart rate, which was achieved by prescribing a β-blocker (metoprolol, bisoprolol, or carvedilol). The treatment of patients of the third group corresponded to the algorithms for managing patients with AHT, with the purpose to achieve the target level of BP. All patients also received one of the angiotensin-converting enzyme inhibitors — perindopril, ramipril, lisinopril, or combination therapy in accordance with the recommendations of the European Society of Cardiology 2018 [22].

The data obtained were processed using STATISTICA 10.0 for Windows (StatSoft, Inc., USA). Descriptive statistics were presented as *Me* [Q1; Q3] where Me is the median and Q1 and Q3 are the first and third quartiles. The categorical data were presented as absolute and relative frequencies. Since the quantitative characters did not conform to the concepts of normal distribution, nonparametric statistical methods were used on comparison. The Mann – Whitney *U*-test was used to compare differences in quantitative characteristics between two independent groups. The Kruskal — Wallis test was used to compare three independent groups. If necessary, posteriori pairwise comparisons were made using the Dwass — Stee — Critchlow — Fligner test. When comparing categorical variables between groups, Fisher's exact two-sided test and Pearson's chi-squared (χ^2) test of homogeneity were used (in case of comparison of dichotomous traits between two groups, Yates' correction was used for the latter). The relationship between the quantitative and dichotomous variables was described using the rank-biserial correlation coefficient (rrb).

For pairwise comparisons of qualitative trait distributions, Holm correction was applied to *p*-values. Differences were considered statistically significant at $p < 0.05$. The distribution of alleles and genotypes in the studied patient groups was tested for Hardy — Weinberg equilibrium and assessed using the χ^2 test.

The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to enrollment.

RESULTS

The study included 104 patients (median age: 55 [45; 61] years). The proportion of men in the total sample was 90.4%. All three groups were dominated by men (85%, 93%, and 87%, respectively), which is consistent with published statistics on the prevalence of AHT and AF [23, 24].

The characteristics of the patient groups enrolled in the study are shown in Table 1.

SBP, systolic blood pressure; DBP, diastolic blood pressure; AF, atrial fibrillation; LA, left atrium; LV EF, left ventricular ejection fraction; LV, left ventricle; IVS, interventricular septum; LV PW, posterior wall of the left ventricle; LV RWT, relative wall thickness of the left ventricle.

UA levels were 310 [273; 370] μmol/L in patients with AF (Group 1), 335 [284; 413] μmol/L in patients with AHT and AF (Group 2), 330 [281; 390] μmol/L in patients with AHT (Group 3) ($p < 0.001$), (Table 1).

HU was detected in 33 (31.7%) patients, of whom 4 (3.8%) patients were in Group 1, 24 (23.1%) patients in Group 2, and 5 (4.8%) patients in Group 3. 71 (68.3%) patients had a normal UA level.

The LA diameter was 39 [38; 42] mm in patients with AF (Group 1), 41 [38; 43] mm in patients with AHT and AF (Group 2), and 35 [34; 38] mm in patients with AHT (Group 3) ($p < 0.001$), (Table 1).

LA dilatation was detected in 40 (38.5%) patients in all groups cumulatively, including 35 (51.5%) patients in Group 2 and 5 (38.5%) patients in Group 1. LA dilatation was not detected in Group 3 patients. 64 (61.5%) patients had a normal LA diameter.

Groups 1, 2, and 3 were combined for further analysis of patients. The subgroups of patients with hyperuricemia (HU "+") and without hyperuricemia (HU "–") were identified (Table 2).

Table 1. Characteristics of the patient groups enrolled in the study

Parameters	Group 1 (*n* = 13)	Group 2 (*n* = 68)	Group 3 (*n* = 23)	*p*
Men, *n* (%)	11 (85%)	63 (93%)	20 (87%)	< 0.001
Age, years	47 [42; 58]	57 [51; 62]	45 [38; 50]	< 0.001
SBP, mmHg	110 [110; 120]	140 [130; 155]	150 [140; 160]	< 0.001
DBP, mmHg	70 [70; 80]	90 [87.5; 100]	90 [90; 100]	< 0.001
AF experience, months	16 [5; 36]	22 [3; 96]	-	< 0.001
Body mass index, kg/m^2	26.8 [25.7; 28.6]	26.8 [25.7; 28.3]	26.8 [25.6; 27.5]	> 0.05
Uric acid, μmol/l	310 [273; 370]	335 [284; 413]	330 [281; 390]	< 0.001
Xanthine oxidase, pg/ml	0.66 [0.17; 0.71]	0.51 [0.17; 0.92]	0.58 [0.25; 0.76]	> 0.05
Hypoxanthin, μmol/l	6.47 [3.98; 10.05]	4.9 [2.4; 8.2]	3.9 [1.8; 8.5]	< 0.001
Xanthine, μmol/l	0.73 [0.39; 0.83]	0.7 [0.5; 1]	0.69 [0.4; 0.9]	< 0.001
Adenosine, μmol/l	0.12 [0.08; 0.17]	0.12 [0.08; 0.17]	0.13 [0.09; 0.17]	0.01
LA (anterior–posterior dimension), mm	39 [38; 42]	41 [38; 43]	35 [34; 38]	< 0.001
LV EF, %	62 [60; 64]	63 [58; 66]	65 [63; 70]	0.03
LV hypertrophy, *n* (%)	2 (15.4)	49 (72.1)	11 (47.8)	< 0.001
IVS at end-systole, mm	11 [10; 11]	13 [12; 14]	12 [11; 14]	< 0.001
LV PW at end-systole, mm	11 [10; 11]	12 [11; 13]	11 [11; 12]	< 0.001
LV RWT	0.44 [0.41; 0.48]	0.46 [0.42; 0.50]	0.44 [0.41; 0.51]	> 0.05

Note. Here and in Tables 2 and 3, data are presented as absolute number of patients (%) or median, 25% and 75% quartiles.

Table 2. Characteristics of the hyperuricemic and nonhyperuricemic patient groups in the study

Indicator	HU "+" (*n* = 33)	HU "–" (*n* = 71)	*p*
Age, years	54 [43; 57]	55 [45; 62]	> 0.05
Men, *n* (%)	30 (90.9%)	63 (88.7%)	> 0.05
SBP, mmHg	150 [140; 160]	140 [130; 150]	> 0.05
DBP, mmHg	90 [90; 100]	90 [80; 100]	> 0.05
Body mass index, kg/m^2	26.8 [26.5; 28.2]	26.7 [25.6; 28.3]	> 0.05
Paroxysmal AF, *n* (%)	4 (12.1%)	21 (29.6%)	0.04
Persistent AF, *n* (%)	13 (39.4%)	22 (30.9%)	> 0.05
Permanent AF, *n* (%)	11 (33.3%)	10 (14.1%)	0.004
Creatinine, μmol/L	99.5 [89.6; 108]	98.2 [89; 106]	> 0.05
Glucose, μmol/L	5.6 [5.3; 6.1]	5.5 [5.2; 5.9]	> 0.05
C-reactive protein, mg/L	3.7 [0.7; 4.6]	2 [0.3; 4]	> 0.05
Uric acid, μmol/L	420 [412; 423]	310 [267; 330]	< 0.001
Xanthine oxidase, pg/ml	0.51 [0.17; 0.89]	0.65 [0.23; 0.9]	> 0.05
Hypoxanthin, μmol/L	5.57 [2.38; 7.9]	4.85 [2.16; 8.59]	> 0.05
Xanthine, μmol/L	0.73 [0.52; 1.05]	0.71 [0.49; 1]	> 0.05
Adenosine, μmol/L	0.13 [0.09; 0.16]	0.12 [0.08; 0.17]	> 0.05
LA (anterior–posterior dimension), mm	42 [39; 44]	38 [36; 42]	0.002
LV EF, *n* (%)	60 [57; 65]	64 [61; 67]	0.02
LV hypertrophy, *n* (%)	22 (66.7%)	41 (57.8%)	> 0.05
IVS at end systole, mm	13 [12; 13]	13 [11; 14]	> 0.05
LV PW at end systole, mm	12 [11; 13]	12 [11; 13]	> 0.05
LV RWT	0.45 [0.42; 0.49]	0.45 [0.42; 0.50]	> 0.05

Note. SBP — systolic blood pressure; DBP — diastolic blood pressure; AF — atrial fibrillation; LA — left atrium; LV EF — left ventricular ejection fraction; LV — left ventricle; IVS — interventricular septum; LV PW — posterior wall of the left ventricle; LV RWT — relative wall thickness of the left ventricle.

Table 3. Left atrial diameter depending on the genotype of the SLC2A9 gene rs734553 polymorphism in the study subjects

Indicator, group	*SLC2A9* (rs734533) AA	*SLC2A9* (rs734533) AC	*SLC2A9* (rs734533) CC	*p*
LA (anterior–posterior dimension), mm, Group 1 (*n* = 13)	38 [34; 38]	40 [38; 42]	–	0.07
LA (anterior–posterior dimension), mm, Group 2 (*n* = 68)	38 [38; 42]	40 [39; 43]	43 [42; 44]	0.08
LA (anterior–posterior dimension), mm, Group 3 (*n* = 23)	36 [35; 38]	35 [32; 39]	35 [32; 37]	0.6

Note. LA, left atrium.

Table 4. Distribution of genotypes and alleles of the *SLC2A9* gene rs734553 polymorphism in patients with left atrial dilatation

Polymorphism, genotype SLC2A9 (rs734533)	Group 1 (*n* = 13), abs. (%)	Group 2 (*n* = 68), abs. (%)	Group 3 (*n* = 23), abs. (%)	*p*
AA	0 (0)	9 (13.2)	0 (0)	0.09
AC	5 (38.5) *	16 (23.5) #	0 (0) *#	0.004
CC	0 (0)	10 (14.7)	0 (0)	0.06
Allele A	5 (50)	34 (48.6)	0 (0)	1
Allele C	5 (50)	36 (51.4)	0 (0)	1
Corresponded to the Hardy – Weinberg equilibrium	$\chi^2 = 5$, $p = 0.03$	$\chi^2 = 0.25$ $p = 0.62$	–	–

*significant differences between the first and third groups where $p < 0.05$.

#significant differences between the second and third groups where $p < 0.05$.

The findings of an obviously significant relationship between HU and LA diameter ($U = 1{,}616.0$, $p = 0.002$, rrb = –0.379) are of particular interest. The patients with HU had a larger LA diameter compared with those with a normal UA level — 42 [39; 44] mm and 38 [36; 42] mm, respectively ($p = 0.002$) (Table 2) [25]. LA dilatation was more common in patients with HU, with 19 (57.6%) cases, including 16 (48.5%) patients in Group 2 and 3 (9.1%) patients in Group 1. LA dilatation in patients with normal UA levels was detected in 21 (29.6%) patients.

Molecular genetic testing of the *SLC2A9* gene rs734553 polymorphism identified three types of genotypes: AA (homozygous dominant), AC (heterozygous), and CC (homozygous recessive).

There were no significant differences ($p > 0.05$) when comparing the LA diameter and the genotype of the *SLC2A9* gene rs734553 polymorphism in all groups of patients. However, in Group 2, the LA diameter in the CC genotype (43 [42; 44] mm) patients and the AC genotype (40 [49; 43] mm) patients was determined to be larger than in the AA genotype ones (38 [38; 42] mm). In Group 1, the LA diameter in the AC genotype patients (40 [38; 42] mm) was larger than in the AA genotype ones (38 [34; 38] mm) (Table 3).

When studying the distribution frequency of genotypes and alleles of the *SLC2A9* gene rs734553 polymorphism in patients with LA dilatation, we found that in the second group of patients, the AC genotype was significantly more common than in other groups (23.5%) ($p = 0.004$). There was also a trend toward a higher incidence of AA (13.2%) and CC (14.7%) genotypes. However, it did not reach the criteria for statistical significance. It should be noted that in patients of the first group, LA dilatation was diagnosed only with the AC genotype (38.5%). Dilatation of the LA in patients of the third group was not detected (Table 4).

DISCUSSION

AHT is the most significant risk factor for AF [26]. AF is the most persistent arrhythmia [18] that worsens patients' quality of life and increases the risk of fatal cardiovascular complications [27]. AF is prognostically unfavorable since it is followed by increased overall mortality and, in particular, cardiovascular mortality [28]. Given the continuous growth of life expectancy and the increase in heart disease incidence observed in recent years, the incidence of AF has sharply increased in the last two decades [18].

The RACE and AFFIRM studies have found that the combination of AF and AHT dramatically increases the risk of thromboembolic complications, including stroke, despite anticoagulant therapy [26].

Many epidemiologic studies report that HU is considered among important risk factors for AF [29]. However, there is no well-defined cause of AF in 1.6%–11.4% of cases (according to some authors, up to 30% of cases). In such situations, the role of genetic factors is not excluded for heart rhythm disturbances [30]. Moreover, AF and AHT often coexist in patients with HU [18].

High serum UA levels have been shown to be associated with the development and progression of a number of CVDs, such as CHD, heart failure, AHT, and AF [5]. In patients with

AHT and AF, who made up the second group in our study, serum UA level was significantly higher than in patients from other groups ($p < 0.001$).

Although the exact mechanisms of the relationship between UA and cardiovascular pathology have not yet been identified, some of them are known, suggesting that UA may play a pathogenetic role in the progression of CVDs [31].

First, it is a relationship between HU and classical risk factors for CVDs (in particular, AHT) [32]. Structural changes in the atria are of particular importance for AF [26]. An expectable consequence of AHT is the formation of left ventricular (LV) hypertrophy, which causes increased LV stiffness and diastolic dysfunction. Consequently, there is an increase in the LA pressure and its dilatation shown in the Framing study. Within this study, it was also found out that the LV wall thickening by 4 mm raises the risk of AF by 28%, and the LV diameter increase by 5 mm raises the risk of AF by 39% [33]. It is indicative that in our study, no significant differences in LVH were found when comparing groups of patients with and without HU. However, significant differences in the LA diameter were identified. Thus, in patients with HU, a larger LA diameter was determined than in patients with a normal level of serum UA ($p = 0.002$). LA dilatation was detected in 57.6% of patients with HU, whereas in patients with normal serum UA levels, in 29.6%. These data are consistent with the results of several recent studies, which have shown that the risk of AF and LA dilatation increases significantly in patients with high UA levels [34].

Structural remodeling includes changes in the number and size of cardiomyocytes, hibernation, inflammation, fatty degeneration, accumulation of extracellular matrix, and fibrosis. Fibrosis is one of the main components of structural (and functional) atrial remodeling in AF. Fibrosis is a consequence of the outcome of repair processes and reactive response to inflammation, stress, and recurrent oxidative stress, and can also arise as a consequence of aging and apoptosis. Myocardial fibrosis causes replacement of atrial cardiomyocytes with connective tissue, loss of myofibrils, accumulation of glycogen, and intercellular junction destruction. All of this also contributes to the formation of atrial dilatation. The increased LA size associated with its structural remodeling plays a crucial role in the AF occurrence and maintenance [35].

The association between HU and changes in cardiac structure was investigated in mice. Increased UA level was followed by increased xanthine oxidase activity in cardiac tissue, which caused cardiomyocyte hypertrophy, myocardial oxidative stress, interstitial fibrosis, and diastolic dysfunction due to activation of S6 kinase beta-1, profibrotic TGF-β1/Smad2/3 signaling. These results improved after allopurinol treatment. Xanthine oxidase may facilitate an aggravation of AF, although no prospective clinical studies have yet been performed to test the possibility of xanthine oxidase inhibitor's ability to prevent a genesis of AF [36]. In our study, there were no significant differences obtained in the xanthine oxidase activity index, but in 54% of the subjects, it was above the normal values.

An electrophysiological hypothesis suggesting that UA may increase atrial cell susceptibility to AF has also been proposed. This hypothesis suggests that UA urate transporters (in particular, URATv1/GLUT9) promote the activation of voltage-dependent K+ channel (Kv1.5) proteins. This results in an inducement of ultrarapid delayed rectifier current (*I*Kur) with decreased atrial action potential, thus influencing the development of arrhythmogenic substrate [37].

UA plays an important role in oxidative stress, which contributes to intracellular calcium overload with decreased density of sodium channels and cell damage aggravation. These pathological processes contribute to LA electrical remodeling [38].

Moreover, UA has proinflammatory effects, contributing to release of proinflammatory factors (e.g., thromboxane A2, platelet growth factor, interleukins, C-reactive protein, tumor necrosis factor-α, and monocyte chemoattractant protein).

The role of neurohumoral systems, in particular, renin-angiotensin system, as well as inflammation, which leads to endothelial activation and damage, tissue factor expression by monocytes, increased platelet activation, and increased fibrinogen level, is known. All of this together leads to remodeling of both the heart and the vascular bed [39].

Taking into account the direct influence of the LA diameter index on the occurrence and persistence of AF, as well as the role of serum UA level and AHT in altering the pathophysiology of AF, we have found it relevant to assess the correlation between the *SLC2A9* gene rs734553 polymorphism and LA diameter in patients with AHT and AF. Thus, in patients with AHT and AF, who made up the second group in our study, there was a tendency to determine a larger LA diameter with the CC and AC genotype, but it did not reach the criteria of statistical significance ($p > 0.05$). In addition, in patients of the same group, with AHT and AF, LA dilatation occurred significantly more often with the AC genotype (23.5%, $p = 0.004$).

In a study by F. Mallamaci et al., a correlation was found between the UA level and the *SLC2A9* gene rs734553 polymorphism (G/T alleles) ($p < 0.001$). An association was also found between this polymorphism and phenotypic markers of atherosclerosis, such as intima-media thickness, internal diameter of the carotid arteries, and arterial stiffness. At the same time, an association between the UA level, the *SLC2A9* gene polymorphism, and BP has been established. The TT genotype individuals had higher systolic BP ($p = 0.02$) [10].

In the study by X.L. Yi et al., the presence of a recessive C allele of the *SLC2A9* gene rs734553 polymorphism in the Chinese population increased the risk of HU and type 2 DM complicated by HU ($p = 0.03$) [8].

It should be noted that the impact of *SLC2A9* genetic variants on serum UA levels varied from country to country: in the Framingham and Rotterdam populations, as well as

on the Croatian Adriatic coast, the c.884 G/A variant was related to high serum UA concentrations (especially in women), but this was not observed in African Americans. Whereas the c.841 G/A variant was obviously related to high serum UA concentrations and gout in the Han, Japanese, and Solomon Islander populations, this was not in the eastern and western Polynesians and Europeans [40]. This may be due to different diet and lifestyle habits, which may also influence serum UA levels. In addition, the regulation of *SLC2A9* gene transcription may be controlled by the combined effect of several polymorphisms. However, the question of whether other polymorphisms are involved in this process requires further investigation [41].

We did not find any studies in the scientific literature on the role of the *SLC2A9* gene rs734553 polymorphism (A/C alleles) in patients with AHT and arrhythmias. Therefore, our study is of particular relevance. We have established, for the first time, a correlation between the identified genotypes of the *SLC2A9* gene rs734553 polymorphism and the LA diameter in patients with AHT and AF.

Our study, however, had some limitations. We studied a small sample of patients, which could have contributed to an overestimation or underestimation of the magnitude of the detected associations, as well as the lack of statistical significance in the obtained intergroup differences. Therefore, the results obtained require clarification and verification on a larger and more heterogeneous group of patients.

CONCLUSION

In Group 1 patients (with AF), LA dilatation was observed only in the AC genotype ones. In Group 2 patients (with AHT and AF), LA dilatation was significantly more frequent ($p = 0.004$) in the AC genotype ones. The AC and CC genotype of the SLC2A9 gene rs734553 polymorphic variant was more frequent in Group 2 patients (with AHT and AF).

ADDITIONAL INFORMATION

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