ISSN 2782-4284 (Print)
ISSN 2782-4233 (Online)

eura
EurAsian Arrhythmology Association

VOLUME 3 | ISSUE 1 | 2023

Cardiac Arrhythmias

INTERNATIONAL PEER-REVIEW MEDICAL JOURNAL

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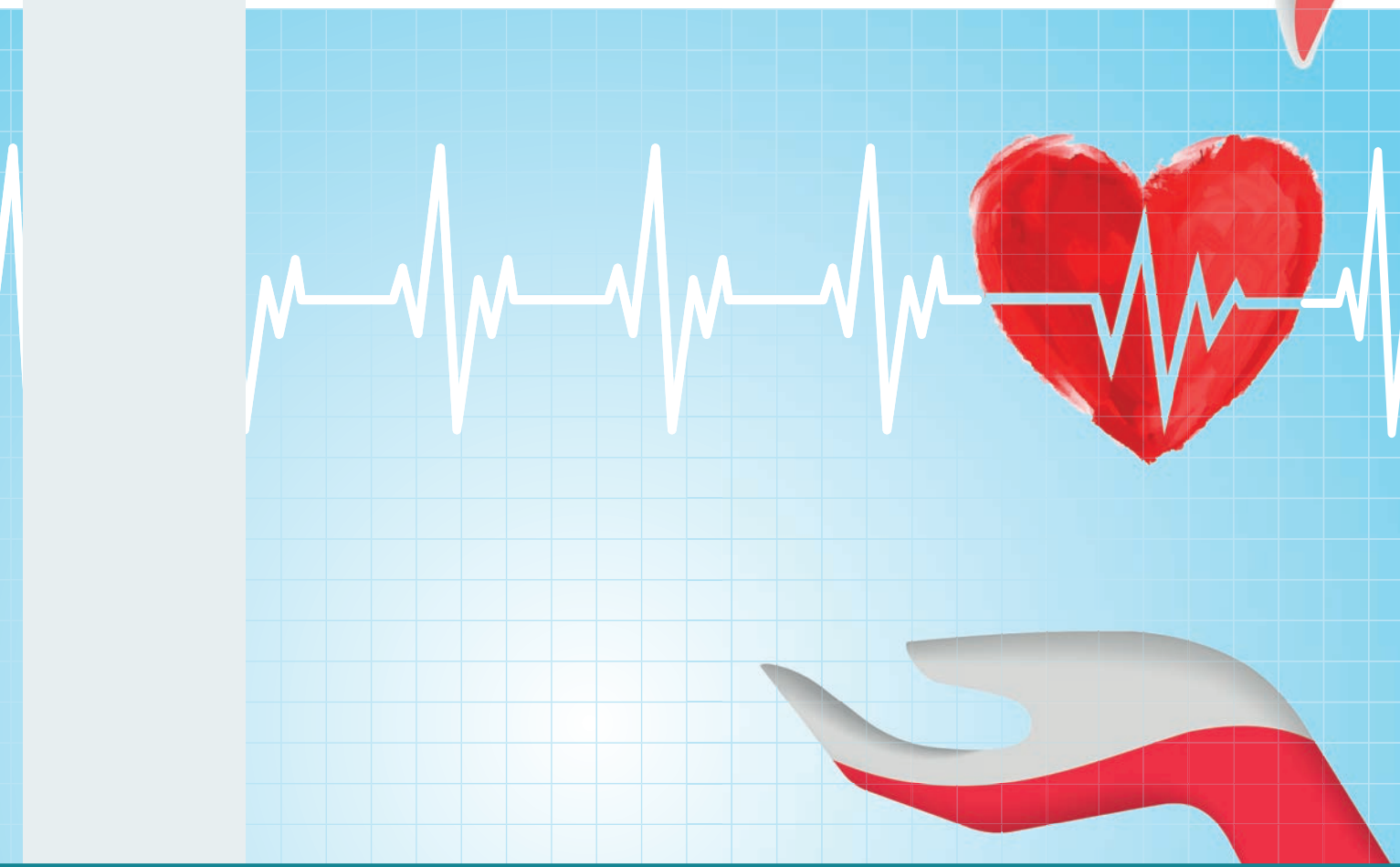

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Address:
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Federal Supervisory Service on Mass Media, Information Technologies and Mass Communication (Roskomnadzor)
ПИ № ФС77-79865

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ISSN 2782-4284 (Print)
ISSN 2782-4233 (Online)

CARDIAC ARRHYTHMIAS

Volume 3 | Issue 1 | 2023

INTERNATIONAL PEER-REVIEW MEDICAL JOURNAL

Published under the supervision of Eurasian Arrhythmology Association

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Журнал зарегистрирован Федеральной службой по надзору в сфере массовых коммуникаций, связи и охраны культурного наследия, свидетельство о регистрации СМИ ПИ № ФС77-79865 от 18.12.2020

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На печатную версию журнала: Объединенный каталог «Пресса России» https://www.pressa-rf.ru.
Подписной индекс на полугодие — 85697, на год — 85698.
На электронную версию журнала: https://journals.eco-vector.com; eLibrary.ru

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Тел.: +7 (495) 308 83 89
E-mail: adv@eco-vector.com

Оригинал-макет изготовлен ООО «Эко-Вектор».
Редактор: *И.Л. Уразовская*
Редактор переводческих проектов: *А.А. Богачев*

Формат 60 × 90$^{1}/_{8}$. Печать офсетная.
Усл. печ. л. 6. Тираж 200 экз. Цена свободная

Отпечатано в ООО «Типография Экспресс В2В». 191180, Санкт-Петербург, наб. реки Фонтанки, д. 104, лит. А, пом. 3Н, оф. 1.
Тел.: +7(812)646-33-77.
Подписано в печать 31.03.2023.
Заказ 3-3484-lv.
Выход в свет 24.04.2023.

16+

ISSN 2782-4284 (Print)
ISSN 2782-4233 (Online)

CARDIAC ARRHYTHMIAS

Том 3 | Выпуск 1 | 2023

МЕЖДУНАРОДНЫЙ МЕДИЦИНСКИЙ РЕЦЕНЗИРУЕМЫЙ ЖУРНАЛ

Издается под эгидой Евразийской аритмологической ассоциации врачей кардиологов и терапевтов

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DOI https://doi.org/10.17816/cardar164429

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.

To cite this article:
Snezhitskiy VA, Kopytsky AV, Barysenka TL. *SLC2A9* genotype distribution and left atrium diameter in patients with arterial hypertension and atrial fibrillation. *Cardiac Arrhythmias*. 2023;3(1):5–15. DOI: https://doi.org/10.17816/cardar164429

Received: 01.02.2023 **Accepted:** 05.03.2023 **Published:** 31.03.2023

УДК 616.125.2:575.22:616.12-008.331.1-008.313.2

DOI https://doi.org/10.17816/cardar164429

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*.

Как цитировать:
Снежицкий В.А., Копыцкий А.В., Борисенко Т.Л. Распределение генотипов гена *SLC2A9* и диаметр левого предсердия у пациентов с артериальной гипертензией и фибрилляцией предсердий // Cardiac Arrhythmias. 2023. Т. 3, № 1. С. 5–15. DOI: https://doi.org/10.17816/cardar164429

Рукопись получена: 01.02.2023 **Рукопись одобрена:** 05.03.2023 **Опубликована:** 31.03.2023

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

Funding. The study was conducted on an initiative basis.

Conflicts of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

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DOI: https://doi.org/10.17816/cardar233537

Research article

Diagnostic Value of Slow Conduction Index in Differential Diagnosis of Wide *QRS* Complex Arrhythmias with Left Bundle Branch Block Morphology

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BACKGROUND: Differential diagnosis of arrhythmias with wide *QRS* complexes remains an unresolved problem in clinical practice. After decades of careful research, many different criteria and algorithms have been proposed, but many of them are not quite accurate and effective in real clinical conditions. One of the approaches is to use ECG to estimate the speed of propagation of excitation through the ventricular myocardium. The estimation is based on the ratio of the amplitudes of the initial and final parts of the *QRS* complex, in particular, using the slow conduction index.

AIM: To study the possibility of using the slow conduction index in the differential diagnosis of arrhythmias with wide *QRS* complexes and to carry out a detailed comparative analysis of the diagnostic value of this criterion in all 12 ECG leads with evaluation and comparison of the obtained values of diagnostic accuracy.

MATERIALS AND METHODS: The study included 280 single wide *QRS* complexes with a form of left bundle branch block (LBBB) detected during one-day and multi-day ECG monitoring in randomly selected 28 patients. For a detailed analysis, a comparison of the original 12-lead ECG and individual scalable ECG graphs for selected leads was carried out, followed by measurement of the absolute values of the total amplitudes during the initial and final 40 ms wide *QRS* complexes. For a qualitative and quantitative assessment of diagnostic significance, ROC analysis was used to determine the informative value of a diagnostic test based on sensitivity (Sn), specificity (Sp) and diagnostic accuracy (Acc).

RESULTS: According to the obtained values of Sn, Sp and Acc, all 12 leads were arranged in the following order as the diagnostic value of the slow conduction index decreased: aVL, V2, aVF, V5, III, V1, V4, II, aVR, V6, V3 and I. In the first six ECG leads, Acc was consistently above 90%, gradually decreasing in the next six leads from 89% to 67%, respectively ($p < 0.001$ for all leads).

CONCLUSIONS: The results of this study showed that the slow conduction index can be used in any ECG leads as a criterion for the differential diagnosis of arrhythmias with wide *QRS* complexes with a form of LBBB. The study also demonstrated the importance of a comprehensive approach to the analysis of the form of the *QRS* complex and the need for a consistent detailed analysis of the existing criteria for the differential diagnosis of arrhythmias with wide *QRS* complexes in different clinical groups of patients.

Keywords: differential diagnosis; wide *QRS* complex; left bundle branch block.

To cite this article:
Chmelevsky MP, Budanova MA, Stepanov DA, Zhabina ES, Tulintseva TE. Diagnostic value of Slow Conduction Index in differential diagnosis of wide *QRS* complex arrhythmias with left bundle branch block morphology. *Cardiac Arrhythmias*. 2023;3(1):17–30. DOI: https://doi.org/10.17816/cardar233537

Received: 15.02.2023 **Accepted:** 07.03.2023 **Published:** 31.03.2023

УДК 616.12

DOI: https://doi.org/10.17816/cardar233537

Научная статья

Диагностическая ценность индекса медленного проведения в 12 отведениях ЭКГ при дифференциальной диагностике аритмий с широкими комплексами *QRS* и формой блокады левой ножки пучка Гиса

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Обоснование. Дифференциальная диагностика аритмий с широкими комплексами *QRS* остается сложной и до конца не решенной проблемой в клинической практике. После десятилетий тщательных исследований было предложено множество различных критериев и алгоритмов, но многие из них являются недостаточно точными и эффективными в реальных клинических условиях. Один из подходов дифференциальной диагностики таких аритмий — оценка на ЭКГ скоростей распространения возбуждения по миокарду желудочков на основе соотношения амплитуд начальной и конечной части комплекса *QRS*, в частности с помощью использования индекса медленного проведения.

Цель. Изучение возможности использования индекса медленного проведения в дифференциальной диагностике аритмий с широкими комплексами *QRS* с последующим детальным сравнительным анализом диагностической ценности этого критерия во всех 12 отведениях ЭКГ и сопоставлением полученных значений диагностической точности с электрофизиологической точки зрения.

Материалы и методы. В исследование было включено 280 одиночных широких комплексов *QRS* с формой блокады левой ножки пучка Гиса), выявленных при односуточном и многосуточном мониторировании ЭКГ у случайно выбранных 28 пациентов. Для детального анализа проводилось сопоставление исходной 12-канальной ЭКГ и отдельных масштабируемых графиков ЭКГ для выбранных отведений с последующим измерением абсолютных значений суммарных амплитуд в течение начальных (V_i) и конечных (V_t) 40 мс широких *QRS* комплексов. Для качественной и количественной оценки диагностической значимости использовался ROC-анализ с определением информативности диагностического теста на основании чувствительности, специфичности и диагностической точности. При сравнении площадей ROC-кривых статистически значимыми принимались значения $p < 0{,}001$.

Результаты. Согласно полученным значениям чувствительности, специфичности и диагностической точности все 12 отведений расположились в следующим порядке по мере уменьшения диагностической ценности индекса медленного проведения: aVL, V2, aVF, V5, III, V1, V4, II, aVR, V6, V3 и I. При этом в первых шести ЭКГ-отведениях диагностическая точность была стабильно выше 90 %, постепенно уменьшаясь в последующих шести отведениях с 89 до 67 % соответственно ($p < 0{,}001$ для всех отведений).

Заключение. Результаты данного исследования показали, что индекс медленного проведения может использоваться в любых отведениях ЭКГ как критерий дифференциальной диагностики аритмий с широкими комплексами *QRS* и формой блокады левой ножки пучка Гиса. Также проведенное исследование продемонстрировало важность всестороннего подхода к анализу формы комплекса *QRS* и необходимость последовательного детального анализа существующих критериев дифференциальной диагностики аритмий с широкими комплексами *QRS* в разных клинических группах пациентов.

Ключевые слова: дифференциальная диагностика; широкие комплексы *QRS*; блокада левой ножки пучка Гиса.

Как цитировать:
Чмелевский М.П., Буданова М.А., Степанов Д.А., Жабина Е.С., Тулинцева Т.Э. Диагностическая ценность индекса медленного проведения в 12 отведениях ЭКГ при дифференциальной диагностике аритмий с широкими комплексами *QRS* и формой блокады левой ножки пучка Гиса // Cardiac Arrhythmias. 2023. Т. 3, № 1. С. 17–30. DOI: https://doi.org/10.17816/cardar233537

Рукопись получена: 15.02.2023 **Рукопись одобрена:** 07.03.2023 **Опубликована:** 31.03.2023

ЭКО•ВЕКТОР

BACKGROUND

Differential diagnosis of arrhythmias with wide *QRS* complexes remains an unresolved problem in clinical practice [1, 2]. Electrocardiography (ECG) and ECG Holter monitoring are key data interpretation tools in the differential diagnosis of these arrhythmias. After decades of careful research, many different criteria and algorithms have been proposed, but many of them are not sufficiently accurate and effective in real clinical conditions [3, 4]. This is confirmed by many scientific publications and individual clinical observations that demonstrate the insufficient effectiveness of most of these algorithms [5, 6].

The main problem in the differential diagnosis of arrhythmias with wide complexes is the need to analyze the relationship between atrial and ventricular rhythms to search for signs of atrio-ventricular (AV) dissociation and other criteria for ventricular tachycardia (VT), when high-quality visualization of atrial activity waves renders difficult. In this regard, it is often impossible to use this approach and it becomes necessary to assess the shape of wide *QRS* complexes (the so-called morphological features) characteristic of VT or aberrant ventricular conduction. Despite the ever-increasing number of algorithms for assessing the shape of *QRS* complexes, most of these criteria show low diagnostic accuracy in repeated studies on different groups of patients [5]. The reasons for this are, firstly, the high degree of subjectivity in the assessment of amplitude-time characteristics by different researchers, and secondly, the inability to take into account the individual characteristics of the propagation of the excitation wave through the myocardium using these criteria in arrhythmias with wide *QRS* complexes.

In fact, all amplitude-time criteria can be divided into three groups. The first group includes signs that characterize the shape of individual deflections of the *QRS* complexes. The second group includes features that determine the duration of the individual components of the *QRS* complexes. The third one includes characteristics aimed at determining the rate of change in the amplitude of the initial and final parts of the *QRS* complexes and their ratio. At the same time, almost all amplitude-time criteria included in the first two groups show relatively low diagnostic accuracy in repeated studies on clinically different groups of patients [5]. Apparently, one of the reasons leading to such results is the presence of structural changes in the myocardium and a significant difference in the individual ratios of the shape of the chest and the location of the heart, which largely affect the amplitude characteristics of individual elements of the *QRS* complex and their duration.

As we pointed out in our previous publication [7], one of the approaches designed to solve these problems is the ECG assessment of the propagation velocities of excitation through the ventricular myocardium based on the ratio of the amplitudes of the initial and final parts of the *QRS* complex. The most well-known criterion for assessing the amplitude ratio is the slow conduction index proposed by A. Vereckei et al. [8]. This criterion allows for differential diagnosis of arrhythmias with wide *QRS* complexes based on the analysis of the ratio of the absolute values of the total amplitude of the *QRS* complex over the first and last 40 ms, which is calculated in each individual ECG lead. This approach greatly reduces the subjectivity of wide *QRS* morphology assessment by different specialists, especially in complex cases of arrhythmias with the form of a complex in the form of a left bundle branch block (LBBB).

One of the features of using the slow conduction index is the need to select an ECG lead with a wide RS-type complex according to the original concept of the authors of the proposed criterion [8]. However, the choice of an ECG lead is largely arbitrary, especially in the presence of several similar leads, which can show conflicting results. At the same time, in a number of other cases, the absence of an RS-type form of the complex leads to the formal impossibility of using the slow conduction index in practical work. Such features of the use of this criterion, in our opinion, are significant limitations. In this regard, in our previous publication, we presented the results of a study that showed the fundamental possibility of using the slow conduction index in the differential diagnosis of arrhythmias with wide *QRS* complexes in any ECG lead without the need to search for a biphasic wide complex with an RS-type shape [7]. In addition, it was shown that the diagnostic value of the slow conduction index was quite high in leads II, III, aVL, aVF, V1, V2, V4, V5 (8 out of 12). At the same time, upon careful study of the obtained results, it becomes obvious that a detailed comparison of the diagnostic value of this criterion in 12 ECG leads, as well as a detailed analysis of the obtained incorrect values, is necessary. It is also necessary to evaluate the results of the study in terms of analyzing the relationship between the obtained diagnostic characteristics and the electrophysiological features of the propagation of the excitation wave through the myocardium.

In this regard, this work continues the previous study on the possibility of using the slow conduction index in the differential diagnosis of arrhythmias with wide *QRS* complexes. It is also devoted to a detailed comparative analysis of the diagnostic value of this criterion in all 12 ECG leads with evaluation and comparison of the obtained values of diagnostic accuracy, as well as analysis of the obtained results from the electrophysiological point of view.

MATERIALS AND METHODS

Data processing and recording

The layout for recording and processing ECG data for subsequent analysis was described in detail in a previous publication [7]. In this work, a detailed analysis of the morphological characteristics of *QRS* and a consistent comparison of the total amplitude during the initial and final 40 ms wide

ventricular complexes were additionally carried out in those cases and ECG leads, when the use of the slow conduction index led to erroneous results. To do this, a comparison of the original 12-channel ECG and individual scalable ECG graphs for the selected leads was carried out, followed by the measurement of the absolute values of the total amplitudes during the initial and final 40 ms wide *QRS* complexes.

Building scalable ECG graphs

To build separate scalable graphs, ECG data was exported from the PhysioNet in the text format, which were then imported into Microsoft Excel spreadsheets (Microsoft Corporation, 2016). The amplitude-time values of the ECG were synchronized in 12 leads according to the sampling frequency of the original signal. After finding the boundaries of the *QRS* before its beginning and after its end, the values of 100–120 ms were plotted, which were used as points between which the ECG was visualized in a separately selected lead using the built-in tools for creating graphs in Microsoft Excel. As a result, for each separately selected ECG lead, two-dimensional diagrams were constructed, on which the time scale was plotted along the abscissa axis (*X*) with a scale corresponding to the minimum value of the sampling frequency of the original recording. The amplitude scale was plotted along the ordinate axis (*Y*) with automatic scaling according to the initial values of the potentials of the *QRS* complex. After that, on each ECG graph, 40 ms from the beginning and end of the wide *QRS* complex were plotted on the time scale, and the absolute values of the total amplitudes at these points were measured, followed by a comparison of the results obtained.

STATISTICAL ANALYSIS

The technique of statistical analysis is also described in detail in our previous publication [7].

In this work, a detailed study of the diagnostic value of the slow conduction index was carried out based on a comparison of the results of ROC analysis. To assess and compare the areas of ROC curves (AUC — Area Under Curve) in all 12 leads, a nonparametric approach was used according to the DeLonghi-Clark-Pearson method [9]. Further comparison of the areas under the curves was carried out based on the values of the standard error calculation method of Hanley and McNeil [10; 11], and an exact 95% confidence interval (CI) based on the binomial distribution [12]. To compare the results, baseline p values < 0.05 were assumed to be statistically significant. Diagrams of ROC curves were visualized using a color scale for each ECG lead (6 out of 12) on one graph.

For additional analysis of the results, a plot of the area difference (AUC difference) of the ROC curves and the corresponding significance level p was plotted by analogy with the method of constructing correlograms [13]. To visualize the change in the absolute values of the difference in the areas of the ROC curves and the corresponding significance levels, a color palette in the RYG (Red-Yellow-Green) format was used.

The calculated values of sensitivity (Sn), specificity (Sp) and diagnostic accuracy (Acc) for all 12 ECG leads were compared with each other and visualized in the form of color grouped bar graphs for clarity.

After analyzing the number of comparisons made with the p-level estimate and calculating the probability of an incorrect conclusion regarding at least one of the hypotheses that significantly exceeds the initial significance level (p < 0.05), it was decided to correct the obtained values for multiple testing using the Bonferroni corrections [14]. As a result, p values < 0.001 were finally considered statistically significant. The resulting AUC difference plots of the ROC curves were adjusted according to this final accepted level of statistical significance.

Complete statistical analysis was performed using Statistica v.12 (Statsoft Inc., USA), SPSS v.23 (IBM Corp., USA), and MedCalc Statistical Software v.20.115 (MedCalc Software Ltd, Ostend, Belgium).

RESULTS

Diagnostic value of slow conduction index in 12-lead ECG

According to the obtained values of Sn, Sp and Acc, all 12 leads were arranged in the following order as the diagnostic value of the slow conduction index decreased: aVL, V2, aVF, V5, III, V1, V4, II, aVR, V6, V3 and I. In the first six ECG leads, Acc was consistently above 90%, gradually decreasing in the next six leads from 89% to 67%, respectively (Fig. 1). All obtained values were statistically significant (p < 0.001).

Comparison of the Obtained Values of the Diagnostics of the Slow Conduction Index in 12 ECG Leads

Comparison of the ROC curves showed that the diagnostic value of the slow conduction index does not differ significantly in leads aVL, V2, aVF, V5, III, V1, while in leads V4, II, aVR, V6, V3, and I it clearly decreases (Fig. 2).

According to the ROC area difference chart, there were no significant differences in the diagnostic value of the slow conduction index for the first 8 leads (aVL, V2, aVF, V5, III, V1, V4 and II), while the remaining leads (aVR, V6, V3 and I) were statistically significantly different from them (Fig. 3).

Evaluation of the obtained incorrect values of the slow conduction index in individual ECG leads

A detailed examination of the results obtained revealed that in some cases the use of the slow conduction index led to errors in the differential diagnosis of wide *QRS* complexes. These cases were singled out and selected for further analysis. So, as a result of reviewing some ECGs with

Fig. 1. Histogram of slow conduction index Sensitivity (Sn), Specificity (Sp) and diagnostic Accuracy (Acc) for 12 lead ECG

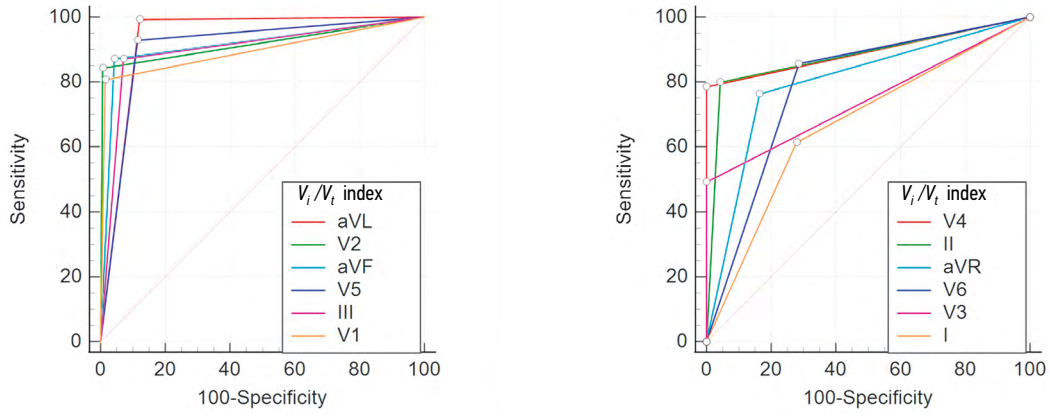

Fig. 2. ROC curves comparison charts as an illustration of slow conduction index diagnostic value difference for 12 lead ECG. Cut-off values are marked as red marker on each of ROC curves

premature atrial contractions (PAC) and aberrant conduction by the type of LBB block, it turned out that in one of the leads (aVL) the use of the obtained values of the slow conduction index $V_i / V_t < 1$) led to an erroneous diagnosis of premature ventricular contractions (PVC), while in in all other leads, the use of this criterion showed correct results (Fig. 4). Analysis of the scaled ECG plot in lead aVL showed that the absolute values of the amplitudes of the initial (V_i) and final (V_t) 40 ms of the *QRS* complex were 94 μV and 316 μV, respectively (Fig. 5). Similarly, reviewing some PVC ECGs with a form of LBBB, it was found that in some leads (aVR) the use of the obtained slow conduction index values ($V_i / V_t > 1$) led to an erroneous diagnosis of PAC, while in all other leads the use of this criterion showed correct results (Fig. 6). Analysis of the scaled ECG plot in lead aVL showed that the absolute values of the amplitudes of the initial (V_i)

Area under curve (AUC)		0.94	0.92	0.91	0.91	0.90	0.90	0.89	0.88	0.80	0.79	0.75	0.67
		AUC difference											
max	Lead	aVL	V2	aVF	V5	III	VI	V4	II	aVR	V6	V3	1
0.94	aVL		0.018	0.021	0.029	0.036	0.039	0.043	0.057	0.136	0.150	0.189	0.268
0.92	V2	0.407		0.004	0.011	0.018	0.021	0.025	0.018	0.096	0.111	0.150	0.229
0.91	aVF	0.268	0.884		0.007	0.014	0.018	0.021	0.036	0.114	0.129	0.168	0.246
0.91	V5	0.226	0.620	0.776		0.007	0.011	0.014	0.029	0.107	0.121	0.161	0.239
0.90	III	0.049	0.482	0.100	0.785		0.004	0.007	0.021	0.100	0.114	0.154	0.232
0.90	VI	0.078	0.239	0.312	0.671	0.671		0.004	0.018	0.096	0.111	0.150	0.229
0.89	V4	0.059	0.336	0.310	0.545	0.754	0.873		0.014	0.093	0.107	0.146	0.225
0.88	II	0.012	0.385	0.011	0.190	0.194	0.385	0.516		0.079	0.093	0.132	0.211
0.80	aVR	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001		0.014	0.054	0.132
0.79	V6	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.576		0.039	0.118
0.75	V3	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.076	0.218		0.079
0.67	1	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.002	0.023	
min		min	*p*-value										max

Fig. 3. Diagram of AUC difference between ROC curves (right upper triangle) and corresponding p-value (left bottom triangle) illustrating a difference of slow conduction index diagnostic value in 12 lead ECG. Leads are sorted towards a decrease of their diagnostic value from up to down (left column) and from left to the right (upper row) according to the calculated absolute value. A color palette of diagram shows changing of AUC difference absolute values from min (green) to max (red) and *p*-values from max (green) to min (red). AUC difference with corresponding $p < 0.001$ are marked with red font on white background

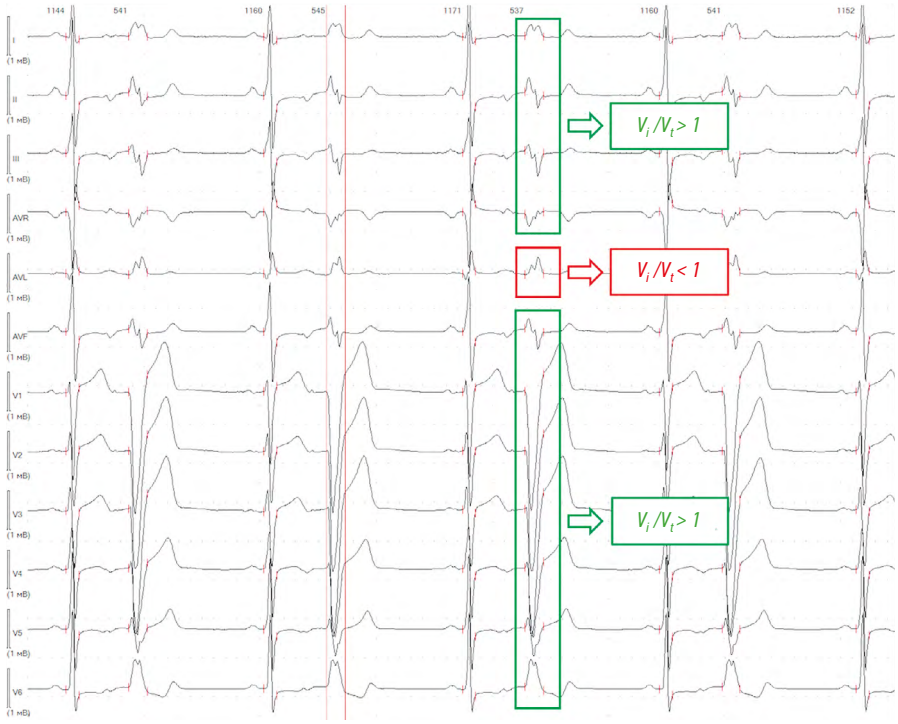

Fig. 4. ECG example of supraventricular extrasystoles with LBBB aberration. Borders of all *QRS* complex are marked with small red vertical lines. Borders of selected for analysis wide QRS complex are marked with solid red vertical lines in all 12 ECG leads. Leads with correct results ($V_i / V_t > 1$) of slow conduction index calculations in differential diagnosis are marked with green color while leads with wrong results ($V_i / V_t < 1$) for this case are marked with red color

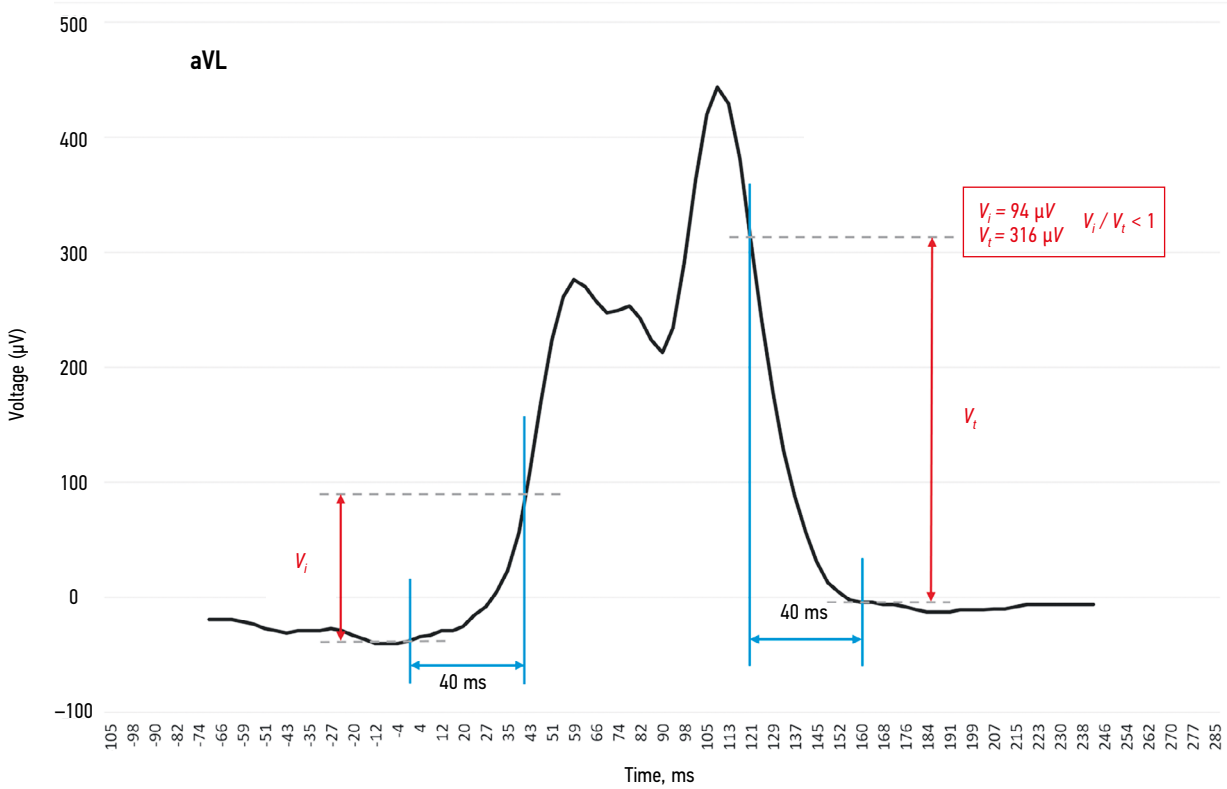

Fig. 5. ECG plot in aVL lead and determination of an absolute values of initial (V_i) and terminal (V_t) 40 ms of wide *QRS* complex for the case of supraventricular extrasystoles with LBBB aberration where calculation of slow conduction index (V_i / V_t) shows wrong results (V_i / V_t < 1) in differential diagnosis. Voltage (μV) — ECG amplitude (microVolts), time in ms

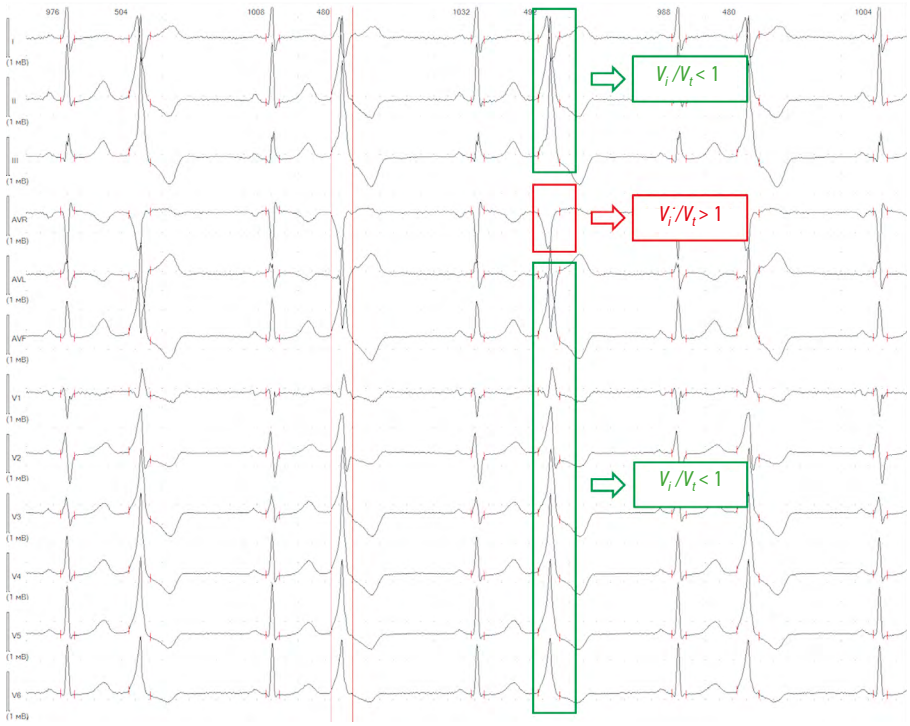

Fig. 6. ECG example of ventricular extrasystoles with LBBB type morphology. Borders of all *QRS* complex are marked with small red vertical lines. Borders of selected for analysis wide QRS complex are marked with solid red vertical lines in all 12 ECG leads. Leads with correct results (V_i/ V_t < 1) of slow conduction index calculations in differential diagnosis are marked with green color while leads with wrong results (V_i/ V_t> 1) for this case are marked with red color

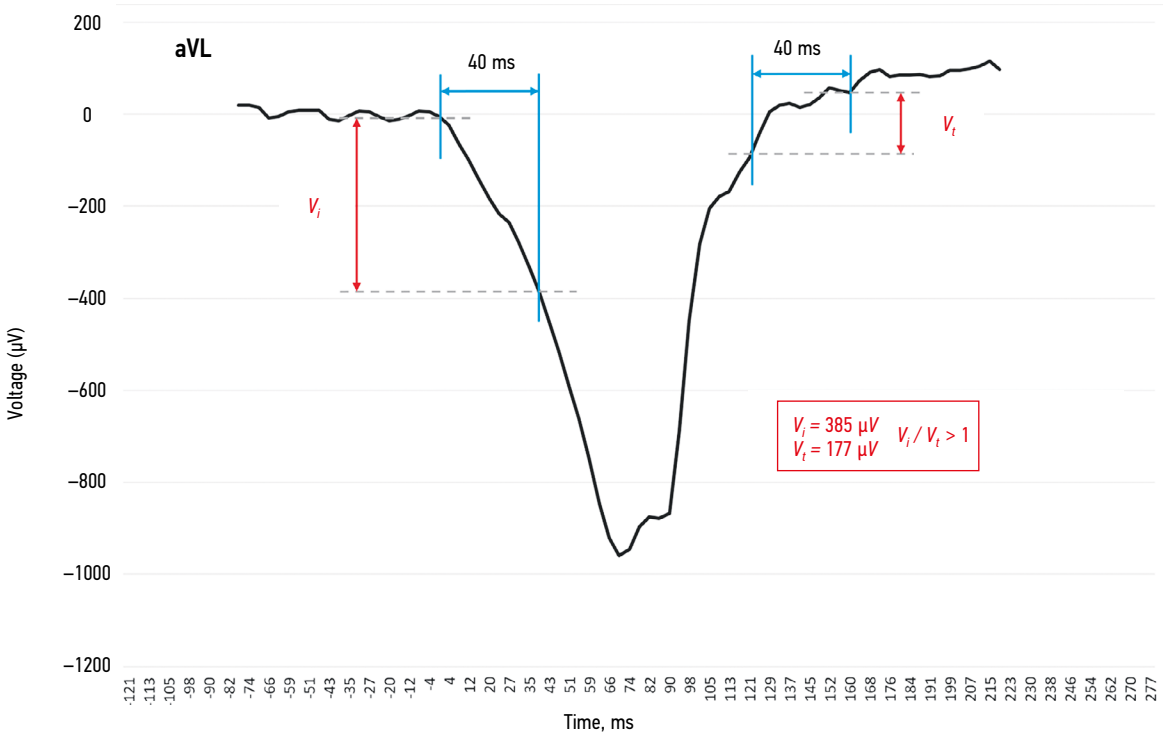

Fig. 7. ECG plot in aVR lead and determination of an absolute values of initial (V_i) and terminal (V_t) 40 ms of wide *QRS* complex for the case of ventricular extrasystoles with LBBB type morphology where calculation of slow conduction index (V_i / V_t) shows wrong results (V_i / V_t > 1) in differential diagnosis. Voltage (μV) — ECG amplitude (microVolts), time in ms

and final (V_t) 40 ms of the *QRS* complex were 385 μV and 177 μV, respectively (Fig. 7).

Further consideration of the obtained results showed that the frequency of occurrence of such cases with incorrect values of the slow conduction index, leading to erroneous results in the differential diagnosis of arrhythmias with wide *QRS* complexes, directly corresponds to the values of the diagnostic accuracy of this criterion in each ECG lead shown in Fig. 1.

DISCUSSION

Main results

The study showed that the diagnostic value of the slow conduction index does not differ significantly in leads aVL, V2, aVF, V5, III, V1, V4, and II, while for the remaining leads aVR, V6, V3, and I, it clearly decreases (Figures 1 and 3). These facts once again confirm the results of the previous study [7], which showed the fundamental possibility of using this diagnostic criterion in any ECG leads. In addition, the obtained results show in which leads the use of the slow conduction index leads to the best results in the differential diagnosis of arrhythmias with wide *QRS* complexes with LBBB.

Analysis of the results of comparing the values of the diagnostics of the slow conduction index in 12 ECG leads

A detailed analysis of color grouped bar graphs with the values of diagnostics showed that the spread of Sn and Sp values in leads aVL, V2, aVF, V5 and III does not exceed 10% at the level of Acc from 94% to 90%, respectively (Fig. 1). This fact testifies to the significant robustness of the slow conduction index against changes in the shape of wide *QRS* complexes with the form of LBB blockade as a criterion for the differential diagnosis of such arrhythmias. This is confirmed by a direct comparison of the shape of the ROC curves in these leads (Fig. 2), as well as a sequential pairwise comparison of the difference in their areas (AUC) and the corresponding significance levels p (Fig. 3). For the remaining leads V1, V4, II, aVR, V6, V4 and I, the spread of Sn and Sp values increases significantly, reaching 51% in lead V3, and the values of Acc, respectively, begin to decrease markedly from 89% to 67%. This, in turn, may indicate a significant sensitivity of the slow conduction index to changes in the shape of wide *QRS* complexes in these leads. At the same time, sequential pairwise comparison of the area difference (AUC) and the corresponding significance levels p for these leads in Fig. 3 shows that for leads aVR, V6, V3, and I, the difference in diagnostic values reaches the level of statistical significance adopted in this study ($p < 0.001$). These facts confirm that these leads are not the best choice for using the slow conduction index as a criterion for the differential diagnosis of arrhythmias with wide *QRS* complexes with a form of LBBB.

In general, the analysis of the color palette of the diagram of the difference in the areas of ROC curves shows a gradual significant and pronounced decrease in the diagnostic value of the slow conduction index from its central part towards

the right and lower borders, while there is no such significant difference in the upper-central part of the diagram.

Analysis of cases of incorrect differential diagnosis of wide QRS complexes when calculating the index of slow conduction in some individual ECG leads

According to the results obtained, the use of the slow conduction index in some cases led to erroneous results in the differential diagnosis of wide *QRS* complexes. As the most illustrative cases, ECGs of one of the patients with PAC and aberrant conduction in the form of LBBB were selected and it was shown that in one of the leads (aVL) the calculated index of slow conduction incorrectly indicates the ventricular genesis of these wide *QRS* ($V_i / V_t < 1$) complexes, while in the remaining 11 leads diagnostics is correct (Fig. 4). When considering the scaled ECG graph in lead aVL, it turned out that the absolute value of the amplitude of the initial 40 ms of the *QRS* complex (V_i) is three times less than the corresponding value of the final 40 ms (Fig. 5). The reason for this is, apparently, that the first 20 ms of the *QRS* complex are almost isoelectric and a significant increase in amplitude begins only from the 30th ms. However, this does not mean that during the first 20 ms, excitation spreads slowly through the myocardium. In this case, such individual anatomical features of this patient as the location of the heart in the chest and its shape relative to the recording leads, as well as the electrophysiological features of the course of excitation in the myocardium lead to the fact that the main vector of the first 20 ms of depolarization is directed almost perpendicular to aVL lead, which results into isoelectric form of this section of the ECG.

A similar situation arises when considering another selected case of PVC with LBBB, when in one of the leads (aVR) the calculated slow conduction index also incorrectly indicates the supraventricular genesis of wide *QRS* ($V_i / V_t > 1$), while in the other 11 leads, this criterion correctly diagnoses PAC (Fig. 6). When considering the scaled ECG plot in aVR lead, it turns out that the absolute value of the amplitude of the initial 40 ms of the *QRS* complex (V_i) is more than twice the corresponding value of the final 40 ms (Fig. 7). Similar to the previous case, when analyzing the terminal part of the *QRS* complex, it becomes apparent that the last 30 ms is almost isoelectric. The reasons for this, apparently, are the same as in the situation described above with incorrect diagnosis of PVC in lead aVL in a patient with PAC and aberrant conduction like LBBB.

When analyzing the remaining cases of incorrect results of differential diagnosis, it turned out that in the vast majority of cases the causes are similar to those described above. From our point of view, these facts testify that with an arbitrary choice of one of the 12 ECG leads for calculating the slow conduction index, erroneous results may spontaneously appear. In this regard, to use this criterion in the differential diagnosis of arrhythmias with wide *QRS* complexes, it is necessary to choose ECG leads with the highest diagnostic value.

Evaluation of the results of using the slow conduction index in connection with the electrophysiological features of the propagation of excitation through the myocardium

As shown above, in some cases, the use of the slow conduction index in individual ECG leads may show incorrect results in the differential diagnosis of wide *QRS* complexes. This raises the question: are these erroneous results random or are there any definite patterns? To answer this question, we must first consider more detail the electrophysiological basis for the use of the slow conduction index.

The original algorithm of A. Vereckei is based solely on the hypothesis of differences in the direction and speed of initial and final myocardial activation during ventricular and supraventricular arrhythmias with aberrant conduction [8]. The electrophysiological rationale for the slow conduction index criterion is that during arrhythmias with wide *QRS* due to PAC, the initial activation of the interventricular septum (occurring either from left to right or from right to left, depending on the type of BBB) occurs at a rate slightly slower than during normal conduction of the excitation wave according to the His-Purkinje system, and intraventricular conduction delay, causing a wide *QRS* complex, occurs in its middle and final parts. As a result, the increase in the amplitude of the initial part of the *QRS* complex will occur more rapidly than the final one. Therefore, the slow conduction index is greater than 1 ($V_i / V_t > 1$) during supraventricular tachycardias with aberrant conduction. In arrhythmias with wide *QRS* due to PVC, the slower propagation of the excitation wave through the contractile myocardium occurs until the impulse reaches the His-Purkinje system, after which the rest of the myocardium is activated more rapidly. As a result, the amplitude of the initial part of the *QRS* complex rises much more slowly, so the slow conduction index is less than 1 ($V_i / V_t < 1$) during ventricular tachycardias. According to the authors, this assumption should be true regardless of the mechanism of occurrence of VT, the presence or absence of structural heart disease [3]. At the same time, the authors point to the use, among other things, of another assumption when developing the criterion for the slow conduction index (V_i / V_t) that the steepness of the initial part of the wide *QRS* complex is directly proportional to the conduction velocity of the excitation wave propagating in the ventricles [3].

A critical analysis of the electrophysiological foundations of these hypotheses shows that these assumptions, from our point of view, only partially reflect the real relationship between the shape of the *QRS* complex and the nature of the propagation of the excitation wave through the ventricles of the heart. First, the assumption that the degree of increase in the amplitude of the initial part of the *QRS* complex is directly proportional to the rate of conduction of excitation in the ventricles is based on a simplified idea of the shape and homogeneity of the excitation wave front. In fact, as shown in experimental studies, when various conduction blockades

occur, the excitation waveform can vary significantly and be divided into several fronts [15–18]. Secondly, according to the accepted dipole ECG model, the propagation of excitation can be described by the vector theory in the form of the dependence of the amplitude of the *QRS* complex on the location of the recording electrode on the body surface with respect to the front of the excitation wave in the ventricles of the heart [19]. However, this dependence is not linear and also implies the use of a significantly simplified dipole model, when the ECG is a total reflection of the electrical activity of the heart [20, 21]. Thus, the magnitude of the amplitude of the initial and final parts of the *QRS* complex is not a direct reflection of the nature of the propagation of the excitation wave in the heart.

In addition, it is important to note that the original concept of using the slow conduction index for the differential diagnosis of arrhythmias with wide *QRS* complexes, proposed by the authors, involves only assessing the ratio of the amplitudes of the initial and final parts of the *QRS* complex (V_i / V_t) relative to each other. Moreover, not only the values of the amplitudes themselves, but also the absolute value of this ratio are not used in the analysis, which leads to the loss of a significant part of the information, since these values also register the features of the rate of change in the *QRS* amplitude as an indirect characteristic of the speed and direction of propagation of the excitation wave through the myocardium. It should also be added that the assessment of these parameters in the sections of the initial and final part of the *QRS* complex with a duration of 40 ms poses a significant number of questions without an obvious electrophysiological justification.

Thus, the incorrect results of the differential diagnosis of wide *QRS* complexes when using the slow conduction index are, apparently, a reflection of the limitations of this criterion as a characteristic that actually reflects the course and nature of the propagation of the excitation wave through the ventricles of the heart. These limitations, most likely, are systematic rather than random and lead to an understanding of the need for a deeper and more detailed analysis of the relationship between the surface ECG and the electrophysiological features of the conduction of excitation through the myocardium.

Analysis of the methodology used and evaluation of the results of the study in connection with previously published data

In their original work, the authors of the proposed slow conduction index criterion showed that their algorithm was generally superior to the P.Brugada algorithm in terms of diagnostic accuracy (90.3% vs. 84.8%, respectively) [3]. At the same time, the superiority of the A. Vereckei algorithm was mainly due to the significantly better overall accuracy of testing the V_i / V_t criterion at the 4th step compared to the 4th step of the P. Brugada algorithm (82.2% versus 68%, respectively). Later proposed by A. Vereckei et al. the algorithm for the differential diagnosis of arrhythmias with wide *QRS* complexes based on only one aVR lead showed that the overall accuracy of testing the new criteria was similar to the accuracy of the first A. Vereckei algorithm and exceeded the accuracy of the P. Brugada algorithm (91.5% versus 90.7% and 85, 5%, respectively) [22].

However, when analyzing subsequent publications, it turned out that independent assessments of different research groups did not show such high diagnostic characteristics as described in the original publications by A. Vereckei et al. [23–28]. For example, one of the groups showed that, when independently tested, the A. Vereckei algorithm showed high sensitivity, but very low specificity (29%) [26].

From our point of view, the published results show that the algorithm used has been tested on different groups of patients, as well as by different researchers, without using a common standardized approach. Moreover, the ECG analysis and calculation of the slow conduction index were carried out manually without the use of modern digital information processing methods. In addition, it becomes obvious that the subjective method of selecting different ECG leads was used to calculate the index of slow conduction according to the first original algorithm of A.Vereckei. When using the new aVR algorithm, the degree of subjectivity, apparently, was lower, however, the use of different groups of patients and the lack of digital methods for recording and processing ECG do not allow an objective comparison of previously published research results. Similar conclusions are reached by other scientific groups that have conducted a detailed analysis of the results of using various algorithms for the differential diagnosis of arrhythmias with wide *QRS* complexes [29].

In this regard, it should be noted in general that the method of calculating the slow conduction index is extremely important. Firstly, the ECGs selected for analysis should initially be recorded digitally at a high sampling rate, and not on paper at a speed of 25 mm/s, as is often described in many publications. Secondly, a detailed analysis of the initial and final parts of the *QRS* and an assessment of the characteristics of its shape in different ECG leads is necessary. That is why the ECG analysis technique used by us in this study was initially developed taking into account all the above features. Moreover, this method of analysis of the results was subjected to a thorough retrospective analysis, and the results obtained were analyzed in detail using modern digital information processing methods and the possibility of detailed scaling of the ECG.

It also becomes apparent that one of the important components of any study in the differential diagnosis of arrhythmias with wide *QRS* complexes is the analysis of the ECG in all 12 leads. From our point of view, the algorithm for using a single lead aVR (proposed by A. Vereckei et al.) has significant drawbacks, since it completely ignores all other information from the remaining 11 ECG leads. In this regard, the obtained high values of the diagnostic accuracy of the algorithm of A. Vereckei et al. in their original study are questionable, despite the relatively

large group of patients used for analysis. Later publications of the results of an independent assessment of various research groups showed a rather low specificity of these criteria. In our work, we also received confirmation of these data, since the results of this study indicate that aVR lead was not the best choice for calculating slow conduction index in the differential diagnosis of wide *QRS* arrhythmias. Moreover, we have shown that in a number of cases, it is in lead aVR that the calculation of the slow conduction index leads to an incorrect result due to the final isoelectric part of the wide *QRS* complex. From our point of view, this is yet another confirmation of the need to analyze all ECG leads in the differential diagnosis of this type of arrhythmias.

Assessment of the representativeness and limitations of the study

The possible limitations of this study were detailed in our previous publication [7]. However, it should be noted that certain limitations may also apply to the limits of applicability of the slow conduction index criterion from an electrophysiological and anatomical point of view. So, the analysis of later publications shows that the authors of various studies also noted certain limitations when using the slow conduction index as a criterion for differential diagnosis [6, 28–30]. In particular, it was pointed out that myocardial diseases with local changes in different segments of the ventricles can lead to changes in the rates of excitation propagation, and, accordingly, incorrect values of the slow conduction index [3]. For example, in the case of local fibrotic changes in the myocardium, the use of this criterion cannot be used in the differential diagnosis of arrhythmias with wide *QRS* complexes. These situations require further research.

CONCLUSION

In the study, the diagnostic value of the slow conduction index in all 12 ECG leads was analyzed, and a detailed analysis of the results obtained from the electrophysiological and clinical points of view was carried out.

The results of this study showed that the slow conduction index can be used in any ECG leads as a criterion for the differential diagnosis of arrhythmias with wide *QRS* complexes with a form of LBBB. According to the obtained values of Sn, Sp and Acc, all 12 leads were sequentially arranged as the diagnostic value of the slow conduction index decreased from 94% to 67% in the following order: aVL, V2, aVF, V5, III, V1, V4, II, aVR, V6 , V3 and I. In these circumstances, in the first 4 leads (aVL, V2, aVF, V5 and III), the level of Acc was from 94% to 90%, respectively.

The study also demonstrated the importance of a comprehensive approach to the analysis of the form of the *QRS* complex and the need for a consistent detailed analysis of the existing criteria for the differential diagnosis of arrhythmias with wide *QRS* complexes in different clinical groups of patients.

ADDITIONAL INFORMATION

Funding. The study was carried out within the framework of the state task of the Ministry of Health of the Russian Federation (No. 123021000126-0) [31].

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

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DOI: https://doi.org/10.17816/cardar305725

Research Article

Atrial Fibrillation Recurrence Rate in Different Clinical Groups: Coronary Artery Disease and Age Matter

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BACKGROUND: Catheter ablation (CA) is an established method for atrial fibrillation (AF) treatment. Up to 20% of patients with AF develop coronary artery disease (CAD) as a secondary diagnosis. The data on whether the CAD affects the efficacy of AF ablation is contrary, while arterial hypertension is a known risk factor for AF as well as for AF recurrence after the CA.

AIM: We conducted this research to assess the AF recurrence rate and its risk factors after the primary catheter AF ablation procedure in the different clinical groups including IdiopathicAF, AF concomitant to arterial hypertension (HTN) and AF concomitant to CAD.

MATERIALS AND METHODS: Patients who underwent 451 PVI procedures performed since January 2016 to December 2017 were screened for AH, CAD and other structural heart disease. Among them 153 pts were selected for the subsequent analysis and divided into 3 groups — IdiopathicAF, AF + AH, AF + CAD.

RESULTS: The presence of CAD ($r = 0.313$, $p < 0.001$), age ($r = 0.224$, $p = 0.008$), CHA2DS2-VASc score ($r = 0.279$, $p = 0.001$), history of MI ($r = 0.240$, $p = 0.004$), LA size ($r = 0.204$, $p = 0.018$) were correlated with the recurrence rate. In the AF + CAD group patients older than 65 years demonstrated dramatically lower AF-free survival rate (37.5%) in comparison to younger CAD population (75%, log-rank $p < 0.001$) as well as to younger and older non-CAD patients.

CONCLUSIONS: The presence of CAD should always attract the attention of physicians before considering the AF ablation as an option to treatment. Elderly CAD patients have the lowest ablation efficacy and the best strategy for this group (more extensive primary ablation or conversion to the permanent AF) needs to be studied.

Keywords: atrial fibrillation; catheter ablation; pulmonary vein isolation; arterial hypertension; coronary artery disease.

To cite this article:
Gorev MV, Urazovskaya IL. Atrial fibrillation recurrence rate in different clinical groups: coronary artery disease and age matter. *Cardiac Arrhythmias*. 2023;3(1):31–40. DOI: https://doi.org/10.17816/cardar305725

Received: 02.03.2023 **Accepted:** 02.04.2023 **Published:** 31.03.2023

УДК 616.12

DOI: https://doi.org/10.17816/cardar305725

Научная статья

Эффективность катетерной аблации фибрилляции предсердий в различных клинических группах: влияние ишемической болезни сердца и возраста

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Обоснование. Катетерная аблация (КА) — распространенный метод лечения фибрилляции предсердий (ФП). До 20 % пациентов с ФП в качестве сопутствующего диагноза имеют ишемическую болезнь сердца (ИБС). Данные о влиянии ИБС на эффективность КА при ФП противоречивы. В то же время артериальная гипертензия (АГ) является известным фактором риска ФП и рецидива ФП после КА.

Цель — оценка вероятности рецидива ФП после первичной КА в разных клинических группах пациентов, включая идиопатическую ФП, ФП на фоне АГ и ФП, сочетающуюся с ИБС.

Материалы и методы. Среди пациентов, которым с января 2016 г. по декабрь 2017 г. были выполнены КА по поводу ФП, был проведен скрининг на предмет АГ, ИБС и другой структурной патологии сердца. Пациенты с ГКМП и клапанной патологией, а также пациенты с повторными КА были исключены. Для последующего анализа были отобраны 153 пациента и разделены на 3 группы — идиопатическая ФП, ФП + АГ, ФП + ИБС.

Результаты. Наличие ИБС (r = 0,313, p < 0,001), возраст (r = 0,224, p = 0,008), риск по CHA2DS2-VASc (r = 0,279, p = 0,001), постинфарктный кардиосклероз (r = 0,240, p = 0,004) и передне-задний размер ЛП (r = 0,204, p = 0,018) коррелировали с риском рецидива ФП. В группе ФП + ИБС пациенты старше 65 лет имели значительно меньшую эффективность КА (37,5 %), чем более молодые пациенты с ИБС (75 %, логарифмический ранг p < 0,001) и пациенты без ИБС.

Заключение. Наличие у пациента ИБС должно учитываться при принятии решения о выполнении КА по поводу ФП. Возрастные пациенты с ИБС имеют наиболее низкую эффективность КА и предпочтительная тактика лечения (более агрессивная КА или перевод в постоянную форму ФП) требует изучения.

Ключевые слова: фибрилляция предсердий; катетерная аблация; изоляция легочных вен; артериальная гипертензия; ишемическая болезнь сердца.

Как цитировать:
Горев М.В., Уразовская И.Л. Эффективность катетерной аблации фибрилляции предсердий в различных клинических группах: влияние ишемической болезни сердца и возраста // Cardiac Arrhythmias. 2023. Т. 3, № 1. С. 31–40. DOI: https://doi.org/10.17816/cardar305725

Received: 02.03.2023 **Accepted:** 02.04.2023 **Published:** 31.03.2023

BACKGROUND

Catheter ablation is an established method for atrial fibrillation (AF) treatment [1]. Despite the fact that it is the most effective approach to maintain sinus rhythm [2, 3], the postprocedural recurrence rate remains high. Better patient selection is one of several directions (as well as durable pulmonary vein isolation (PVI) and looking for additional AF triggers) to improve the AF-free survival after ablation. Up to 20% of patients with AF develop coronary artery disease (CAD) as a secondary diagnosis [4]. The data on whether the CAD affects the efficacy of AF ablation is contrary [6, 7] probably due to the heterogeneity of CAD group (individual coronary anatomy, revascularization status, signs of ischemia, heart failure and other comorbidities, etc.) as well as the number of concomitant risk factors affecting the risk of AF recurrence. We believe that the separation of AF patients into several clinical groups could help describe their profiles better and assess the complex interactions between the AF and CAD in the real-world population.

AIM

This study was aimed to assess the AF recurrence rate and its risk factors after the primary catheter AF ablation procedure in the different clinical groups including IdiopathicAF, AF concomitant to arterial hypertension (HTN) and AF concomitant to CAD.

METHODS

Study design

This study was performed as a single-center retrospective comparison.

Population

Of 451 PVI procedures performed since January 2016 to December 2017, 396 were primary. Two-hundred and forty patients with known coronary anatomy (Coronary angiography (CAG) or computed tomography-angiography (CTA)) were selected for the subsequent analysis. Patients with hypertrophic cardiomyopathy, mitral stenosis (valvular AF) were not included in the study.

After exclusion of the nonqualifying patients, remaining patients (n = 153) were retrospectively enrolled into this study and divided into three groups based on the medical history and CTA data: IdiopathicAF group, AF + HTN group and AF + CAD group (Fig. 1).

IdiopathicAF group (n = 32)

Diagnosis of idiopathicAF was established in AF patients without history of arterial hypertension and coronary atherosclerosis (CCSi = 0).

AF+HTN group (n = 73)

HTN was diagnosed according to guidelines [8]. In all patients' medications were titrated to keep blood pressure at the target level less than 139/89 mmHg.

All patients in this group had no signs of coronary atherosclerosis by CAG or CT-CAG (no stenoses and CCSi = 0).

AF+CAD group (n = 48)

CAD was diagnosed in patients with at least one of the following:

- significant (> 50%) coronary artery stenosis revealed by the CAG or CTA,
- history of percutaneous coronary intervention or coronary bypass surgery before primary ablation.

All patients signed informed consent for the personal data processing during their hospitalization for primary ablation procedure.

Clinical and demographic data are presented in Table 1.

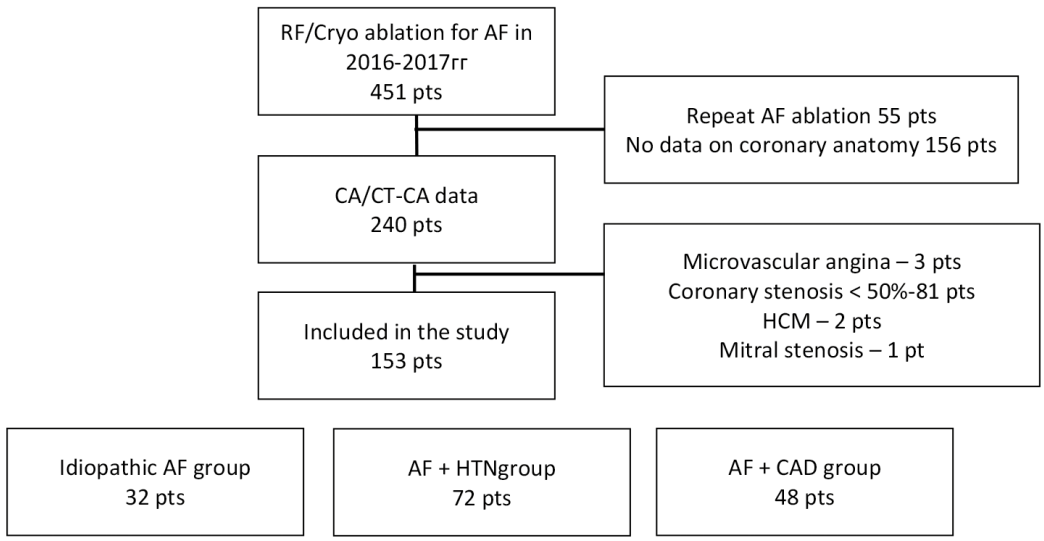


Fig. 1. Study groups selection work-flow

Table 1. Demographic, echocardiography and intraprocedural data

Parameter		IdiopathicAF (*n* = 32)	AF + HTN (*n* = 72)	AF + CAD (*n* = 48)	*p*
Male sex, *n* (%)		22 (68.8)	28 (38.4)	30 (62.5)	1–2 – 0.004 2–3 – 0.009
Age, yrs		48.6 ± 11.9	59.6 ± 9.2	66 ± 6.9	< 0.001
HTN, *n* (%)		0	72 (100%)	48 (100%)	-
DM, *n* (%)		1 (3.1)	5 (6.8)	11 (22.9)	1–3 – 0.005 2–3 – 0.021
MI, *n* (%)		-	-	19 (39.6)	-
Revascularization, *n* (%)		-	-	20 (42)	-
CHA2DS2-VASc score		0.3 ± 0.7	2.3 ± 1.2	3.7 ± 1.3	< 0.001
Anticoagulation	Rivaroxaban, *n* (%)	9(45)	26(60)	18(69)	
	Apixaban, *n* (%)	3(15)	7(16)	0(0)	
	Dabigatran, *n* (%)	6(30)	10(23)	5(19)	
	Warfarin, *n* (%)	2(10)	0(0)	3(12)	
History of stroke, *n* (%)		0	4 (7.1)	9 (22.5)	0.044
Paroxysmal AF, *n* (%)		25 (78.1)	62 (84.9)	44 (91.7)	ns
LV EF, %		64.4 ± 2.3	62.3 ± 4.5	61.2 ± 7.4	1–2 – 0.002 1–3 – 0.008
LA diameter, mm		39.4 ± 4.0	42 ± 4.4	44.3 ± 4.8	1–2 – 0.004 1–3 < 0.001 2-3 – 0.011
Degree of MR		0.8 ± 0.6	1.1 ± 0.6	1.2 ± 0.6	1–2 – 0.013 1–3 – 0.003
CTI ablation, *n* (%)		6 (18.8)	18 (25)	23 (47.9)	1–3 – 0.005 2–3 – 0.01
Energy used for PVI, *n* (%) CBA	RFA	19 (59.4)	55 (76.4)	38 (79.2)	ns
	CBA	13 (40.6)	17 (23.6)	10 (20.8)	

Note: AF — atrial fibrillation, HTN — arterial hypertension, CAD — coronary artery disease, MI — myocardial infarction, LV EF — left ventricular ejection fraction, LA — left atrium, MR — mitral regurgitation, CTI — cava-tricuspid isthmus, RFA — radiofrequency ablation, CBA — cryo-balloon ablation.

Catheter ablation procedure

Left atrial (LA) and pulmonary venous CTA was performed in all patients to assess the individual anatomy and exclude LA thrombosis. In some patients a transesophageal echocardiography was used to exclude LA thrombi (on condition CTA was performed more than 48 hours earlier than ablation procedure) or to assist transseptal puncture. Right femoral and right jugular (or left subclavian) venous access were used to insert diagnostic and ablation catheters. Transseptal access was performed under the fluoroscopy guidance and the direct LA angiography was done while pacing the ventricles at 200 bpm.

Different energy modalities were used to isolate PVs. Radiofrequency ablation (RFA) was used in 112 pts (73.2%) and cryoballoon ablation (CBA) — in 41 pt (26.8%) (Table 1). During RFA procedures a "single puncture – double access" approach was used. Multipolar circular diagnostic catheter Lasso 2515 (Biosense Webster, USA) was introduced into the LA through the transseptal sheath SR0 or SL0 (Abbott, USA). In the majority of cases RFA was performed under the fluoroscopy guidance using an open-irrigated ablation catheter Thermocool EZsteer (Biosense Webster, USA) consecutively in the RSPV, RIPV, LSPV and LIPV. If non-fluoroscopy mapping system Carto 3 (Biosense Webster, USA) was used, the wide antral isolation of the right and then left PVs was performed by Thermocool SF Nav (Biosense Webster, USA) or Thermocool SmartTouch catheters (Biosense Webster, USA). Contact force technology as well as Ablation index and CLOSE protocol, were not routinely used in patients enrolled in this study. Entrance and exit block were checked and achieved at the end of procedure in all patients.

Cryoballoon ablation was performed using Arctic Front Advance (Medtronic, USA) cryoballoon catheters. Single 240 sec application was performed consecutively in LSPV, LIPV, RIPV and RSPV. Entrance and/or exit block were checked after the cryoapplication in each vein using circular multipolar

diagnostic catheter Achieve 20 mm (Medtronic, USA). Phrenic nerve was paced from the SVC at cycle 1000–2000 ms and voltage of 15 V during right PV cryoablation.

If isthmus-dependent atrial flutter was diagnosed prior to or induced during the procedure, the linear RF ablation in the cava-tricuspid isthmus was performed, and bi-directional conduction block was confirmed at the end of procedure.

Follow up

To collect the data on arrhythmia recurrence, patients on antiarrhythmic therapy were interviewed by phone, the query included the following questions:

1. Do you have episodes of palpitations after the ablation procedure?
2. What time after the ablation were you diagnosed with AF recurrence?
3. Has AF transformed to a permanent form?
4. If AF was paroxysmal, how often did the paroxysms happen?
5. How many AF-related admissions did you have after the ablation procedure?
6. What AAD/dosage are you taking now?

Mean follow up duration at the time of the call was similar in the IdiopathicAF group (27.0 mos) and the AF + HTN group (29.1 mos, $p = 0.47$), while in the AF + CAD group it was significantly shorter (23.5 mos, pAF + CADvsIdiopathicAF — 0.011, pAF + CADvs.AF + HTN < 0.001).

AF recurrence definition

Postablation recurrence was diagnosed if sustained AF episode was registered by the standard surface 12-lead ECG tracing or during ECG monitoring.

Antiarrhythmic therapy after ablation

Antiarrhythmic drugs were prescribed to all patients for at least 3 months post ablation period. The decision whether to continue therapy, to change the drug or to discontinue its use after 3 months was made by primary care physician. As shown at the Table 2, at the moment of the phone call 70.5% in IdiopathicAF group, 42.3% in AF + HTN group and 45.4% in AF + CAD group were off Class 1 and 3 antiarrhythmic drugs ($p > 0.05$).

Statistical analysis

Statistical analysis was performed using licensed SPSS Statistics version 26.0 (IBM, USA) software.

Distribution normality test for continuous and categorical parameters was performed using Kolmogorov-Smirnoff test. Descriptive statistics were presented as a mean value and a standard deviation. Nominal variables were described as a number of cases and a valid percent.

Differences between two groups by quantitative parameters were analyzed using Student's *t*-test or Mann – Whitney test depending on the normality of distribution. Three and more groups were compared using Kruscall – Wallis criterion or ANOVA.

Comparison of categorial data was performed using Fisher's exact test or Chi-square criterion. To compare 3 and more groups we performed Pearson's Chi-square Post-Hoc analysis.

Kaplan – Meier analysis was used to compare the efficacy. The difference was assessed by log rank test.

Correlations between the risk factors and recurrence were assessed using Spearmen method.

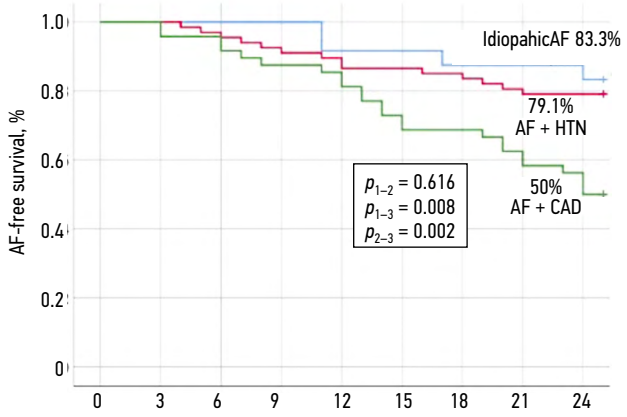
Prognostic model was used to assess the dependence of AF recurrence rate on the studied risk factors. Wald test was used to test the significance of individual coefficients in the model, and the factor with coefficient having the lowest probability of being non-zero is excluded on each step. AF recurrence probability was calculated using formula $p = 1/(1 + e^{-z})$.

The differences in all tests were considered statistically significant when p-value was below 0.05.

Table 2. Antiarrhythmic therapy in 2-years follow up

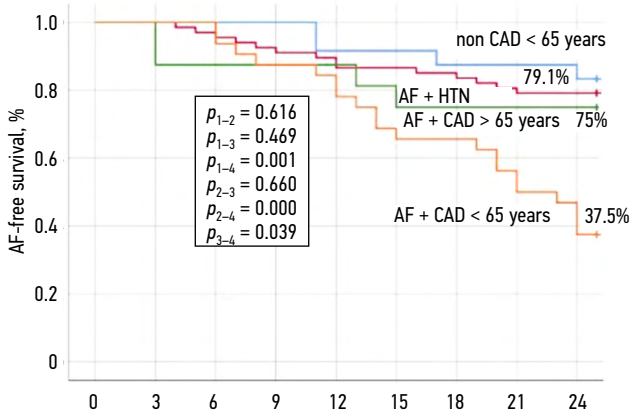
Antiarrhythmic drug	IdiopahicAF	AF + HTN	AF + CAD
Off AAD (none+beta-blocker)	70.5%	42.3%	45.4%
None	47%	23.1%	21.2%
Beta-blocker	23.5%	19.2%	24.2%
Lappaconitine hydrobromide	5.9%	7.7%	9.1%
Propafenone	5.9%	7.7%	0
Flecainide	0	1.9%	0
Sotalol	17.6	32.7%	39.4%
Sotalol + Lappaconitine hydrobromide	0	5.7%	0
Amiodarone	0	1.9%	6.1%

Note: Overall difference between groups was not statistically significant (*p*-value — *ns*)



IdiopahicAF	24	24	24	24	22	22	21	21	21
AF + HTN	67	67	65	62	60	58	57	54	53
AF + CAD	48	48	46	42	41	35	33	30	27

Fig. 2. Caplan – Meyer analysis of the AF recurrence over 2 years after ablation in different clinical groups



IdiopahicAF	24	24	24	24	22	22	21	21	21
AF + HTN	67	67	65	62	60	58	57	54	53
AF + CAD	16	16	14	14	14	13	12	12	12
AF + CAD > 65 years	32	32	32	28	27	22	21	18	15

Fig. 3. Caplan – Meyer analysis of the AF recurrence over 2 years after ablation in different clinical groups depending of age. CAD patients older than 65 years demonstrated worst AF-free survival

RESULTS

Recurrence rate in different clinical groups

As shown at the Figure 2, the patients in AF + CAD group demonstrated significantly lower efficacy than in other clinical groups: 50% vs 83.3% (IdiopathicAF, log-rank p = 0.008) and 79.1% (AF + HTN, log-rank p = 0.002). The recurrence rate in the AF + HTN group did not differ from IdiopathicAF group (log-rank p = 0.616).

Risk factors affecting the recurrence rate

The presence of CAD (r = 0.313, p < 0.001), age (r = 0.224, p = 0.008), CHA2DS2-VASc score (r = 0.279, p = 0.001), history of MI (r = 0.240, p = 0.004), LA size (r = 0.204, p = 0.018) were correlated with the recurrence rate. These weak correlations were confirmed by significant differences which were found during paired comparisons of subgroups of patients with vs without recurrence by these factors.

Table 3. Logistic regression sequence

	Risk factors	*B*-coefficient	*p*-value
Step 1	CAD	0.669	0.234
	Age	0.023	0.442
	CHADS-VASc score	0.184	0.350
	History of MI	0.427	0.500
	LA size	0.057	0.211
	Constant	–5.468	0.037
Step 2	CAD	0.864	0.072
	Age	0.022	0.453
	CHADS-VASc score	0.177	0.368
	LA size	0.054	0.231
	Constant	–5.305	0.042
Step 3	CAD	0.887	0.065
	CHADS-VASc score	0.268	0.087
	LA size	0.051	0.259
	Constant	–4.017	0.034
Step 4	CAD	0.964	0.043
	CHADS-VASc score	0.293	0.059
	Constant	–1.948	0.000

Table 4. Subgroup analysis of AF recurrence risk factors inside the CAD group

Risk factor	Younger 65 years (*n* = 16)	65 years and older (*n* = 32)	*p*-value
Age, years	58.7 ± 4.9	69.7 ± 4.2	< 0.001
Male sex, *n* (%)	14 (87.5)	16 (50)	0.013
LA size, mm	45.6 ± 4.7	43.7 ± 4.7	< 0.001
CHA2DS2-VASc score	2.7 ± 1.1	4.25 ± 1.1	0.01
AF history duration, *Me* (25; 75)	59.4 (14.5; 90)	43.5 (12; 66)	0.001

Note: AF — atrial fibrillation, CAD — coronary artery disease, LA — left atrium

Logistic regression

All factors, correlating with the recurrence rate, showed a low correlation level (less than 0.3) and lost its effects after their inclusion into the regression model. Beta-coefficients and p-values for every separate risk factor at each step of binary regression are presented in the Table 3. At the final step the presence of CAD stayed the only statistically significant risk factor.

The final formula of binary logistic regression model looked like this:

$$p = 1 / (1 + e^{-z}) \cdot 100\%,$$

where $z = -1.948 + 0.964 \cdot \text{CAD}$, p — probability of AF recurrence, CAD — presence of CAD (0 — no CAD, 1 — CAD), were statistically significant (p-0,001) and the model had specificity of 87.1%, sensitivity of 31.7% and diagnostic efficiency of 70.1%.

CAD and age interactions

Then we performed the search on the factors decreasing the AF ablation efficacy in the AF + CAD group. To achieve this goal we consecutively divided AF + CAD group into two subgroups based on different parameters (male *vs* female, paroxysmal AF vs persistent AF, DM vs no DM, LA < 40 mm vs LA > 40 mm, LA < 45 mm vs LA > 45 mm, age < 60 years vs age > 60 years, etc).

The age group over 65 years was the only significant risk factor for AF recurrence.

In the AF + CAD group older patients demonstrated dramatically lower AF-free survival rate (37.5%) in comparison

to younger CAD population (75%, log-rank $p < 0.001$) as well as to younger and older non-CAD patients (Fig. 3).

Risk factors for AF recurrence in CAD patients older than 65 years

Older CAD patients differed from younger CAD population by several significant parameters (Table 4). But none of these factors was an independent predictor of AF recurrence in the regression analysis.

DISCUSSION

Our results support the opinion that in patients with CAD the results of AF ablation are worse than in those without CAD. This could be explained by the effect of CAD itself as well as by the complex action of several risk factors, which are more common in CAD population. All these factors (age, LA size, history of MI, presence of DM and HTN etc.) were found to be insignificant after the adjustment of the presence of CAD.

Data on whether the CAD affects the AF ablation results are contradictory. The retrospective analysis of the Leipzig registry did not find the difference between CAD and non-CAD populations [7]. Similar data are presented by L. Liu at al. in their study [9]. Alternatively in papers by R. Winkle at al. the CAD was described as one of the risk factors for AF recurrence and was used for CAAP-AF score [6; 10]. These discrepancies between studies could be explained by the different inclusion criteria and arrhythmia recurrence definition.

Subsequent analysis of the same risk factors inside the AF + CAD group showed the dramatic decrease in AF-free survival in patients older than 65 years while in IdiopathicAF and AF + HTN groups no correlation between the age and AF recurrence was found.

It is well known that the aging plays an important role in the pathogenesis of AF, as it promotes the atrial fibrosis, dilatation and atrial cardiopathy [11, 12]. In most studies the age serves as a major risk factor for AF development [13] incidence, and morbidity and mortality related to AF (DisModMR software as well as for AF recurrence after ablation [14]. But as these studies were performed on the unselected population it is difficult to understand if worse prognosis in elder patients was affected by age or by higher comorbidity level, including CAD.

LIMITATIONS

Our study presents the retrospective single-center analysis with no investigation of atrial substrate or continuous monitoring of heart rhythm to reveal asymptomatic AF episodes post ablation, however the patients were divided into separate clinical groups and the difference in several demographic and clinical factors was clearly described and accurately analyzed.

Actual recurrence rate (based on the long-term ECG or loop monitoring) would provide more precise results as well as could assess the value of traditional ECG and 24-hour ECG-monitoring in AF detection however, telephone interviews were detailed and all attempts were made to elicit AF recurrence. In the future studies we are going to use subcutaneous loop recorders to assess long term recurrence rate as well as the number of asymptomatic AF paroxysms post catheter ablation in different clinical groups.

CONCLUSION

The presence of CAD should always attract attention of physicians before considering the AF ablation as an option to treat such patient. Elderly CAD patients have the lowest ablation efficacy and the best strategy for this group (more extensive primary ablation or conversion to the permanent AF) needs to be studied

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DOI: https://doi.org/10.17816/cardar321415

Research article

Long *QT* Syndrome in Young Athletes

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Long *QT* syndrome is a disease associated with a high risk of sudden cardiac (arrhythmic) death. The frequency of sudden cardiac death is approximately 1: 100,000 young athletes, while autopsies often do not detect changes, which indicates a primary arrhythmogenic death. The article describes two clinical cases of young athletes with prolongation of the *QT* interval. The possible causes of the long *QT* syndrome and the difficulties of diagnosing this syndrome in children and adolescents involved in sports are discussed. Regardless of the reasons leading to the prolongation of the *QT* interval, there is a risk of arrhythmic events. Timely diagnosis of long *QT* syndrome is the way to the primary prevention of sudden cardiac death in young athletes.

Keywords: sports; young athletes; congenital long *QT* syndrome; secondary causes of *QT* interval prolongation; sudden cardiac death.

To cite this article:
Chuprova SN, Melnikova IYu. Long *QT* syndrome in young athletes. *Cardiac Arrhythmias*. 2023;3(1):41–48. DOI: https://doi.org/10.17816/cardar321415

Received: 16.02.2023 **Accepted:** 19.03.2023 **Published:** 31.03.2022

УДК 616.12-008.318-07-08

DOI: https://doi.org/10.17816/cardar321415

Научная статья

Синдром удлиненного интервала *QT* у юных спортсменов

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Синдром удлиненного интервала *QT* — заболевание, ассоциированное с высоким риском внезапной сердечной (аритмической) смерти. Частота внезапной сердечной смерти составляет примерно 1 : 100 000 юных спортсменов, при этом на вскрытии зачастую не обнаруживают изменений, что указывает на первично аритмогенную смерть. В статье приводится описание двух клинических случаев юных спортсменов с удлинением интервала *QT*. Обсуждаются возможные причины синдрома удлиненного интервала *QT*, трудности диагностики данного синдрома у детей и подростков, занимающихся спортом. Независимо от причин, приводящих к удлинению интервала *QT*, существует риск развития аритмических событий. Своевременная диагностика синдрома удлиненного интервала *QT* — путь к первичной профилактике внезапной сердечной смерти у юных спортсменов.

Ключевые слова: спорт; юные спортсмены; врожденный синдром удлиненного интервала *QT*; вторичные причины удлинения интервала *QT*; внезапная сердечная смерть.

Как цитировать:
Чупрова С.Н., Мельникова И.Ю. Синдром удлиненного интервала *QT* у юных спортсменов // Cardiac Arrhythmias. 2023. Т. 3, № 1. С. 41–48. DOI: https://doi.org/10.17816/cardar321415

Рукопись получена: 16.02.2023 **Рукопись одобрена:** 19.03.2023 **Опубликована:** 31.03.2023

Sudden cardiac death (SCD) is a tragic event, particularly for athletes who undergo routine medical examinations and are considered healthy. The incidence of SCD is approximately 1:100,000 in young athletes, with autopsy often showing no abnormalities indicating primary arrhythmogenic death [1]. The causes of SCD can be acquired or genetic. Acquired causes include myocarditis and coronary artery disease, and genetic causes include genetically determined structural heart diseases and channelopathies [2]. An example of channelopathies is the hereditary (congenital) long *QT* syndrome (LQTS). The prevalence of congenital LQTS is estimated at 1:2000 [3], and for its diagnostics, the criteria developed by Schwartz in 1985 [4] and supplemented by him in 2011 [5, 6] are currently used. Over the past 25 years, 17 genes have been associated with LQTS; however, a recent analysis based on a gene- and disease-specific approach developed by the Clinical Genome Resource classified several of these genes as limited or controversial. This analysis selected seven genes with definitive or conclusive evidence of a causal relationship [7]. All of these remaining genes, i.e., *KCNQ1*, *KCNH2, SCN5A, CALM1, CALM2, CALM3, and TRDN*, encode ion channels involved in cardiac repolarization, their modulating subunits, or proteins that regulate or modulate ion channel function [7]. The LQTS genotype can be identified in 75% of sick people with a clear phenotype, and this is important because it determines the approach to their treatment [8]. In addition to congenital LQTS, various causes (conditions) lead to secondary prolongation of the *QT* interval. One of them is an electrolyte imbalance, such as hypokalemia, hypocalcemia, and hypomagnesemia, which can occur under the influence of many triggers, for example, with long-term intake of diuretics, especially loop diuretics (furosemide).

CLINICAL CASES

Young female athlete A, aged 16 years, was referred for a consultation with a cardiologist because of identified changes in the electrocardiogram (ECG). The history revealed that the patient has been doing rhythmic gymnastics since the age of 3.5 years. At the time of the consultation, the duration of training was 3.5 h a day 5–6 times a week, and she was a sub-master athlete. She coped with exertions, and syncope conditions were not registered. She underwent a planned thorough medical examination (TME). During the regular TME, pathological changes in the ECG, such as prolongation of the *QT* interval, were detected. In the analysis of the family history, cases of SCD and syncope conditions did not occur in the next of kin. The *QT* interval duration in the parents was normal.

On examination, the condition was satisfactory. Her height, weight, and body mass index were 163 cm, 42 kg, and 15.8 kg/m^2, respectively. The skin color was normal. Breath sounds were heard in all lung fields, there were no rales, and the respiratory rate was 20 per min. Visually, the region of the heart was not abnormal. Percussion borders of relative cardiac dullness were within the age norm. The heart sounds were clear, and her heart rate (HR) was 64 per minute and regular in a lying position. Her blood pressure and oxygen saturation were 100/60 mm Hg and 99%, respectively. The abdomen was soft and nontender on palpation. The liver was not enlarged. There was no peripheral edema. The pulse on the femoral arteries was determined on both sides. Bowel and bladder habits were normal.

On a surface 12-channel ECG (computer electrocardiograph CARDI, Medical Computer Systems, Moscow, Zelenograd, Russia), with a recording speed of 50 mm/s (Fig. 1), moderate sinus bradycardia was recorded with an HR of 54–57 beats/min, *QT* interval (V5) of 460 ms, and corrected *QT* (QTc) interval of 438–451 ms.

When taking an ECG in an upright position (Fig. 2) in the presence of an increase in sinus rhythm up to 82 beats/min, the duration of the *QT* interval (V5) was 540 ms and *QT*c was 635 ms (pronounced prolongation of the *QT* interval).

Given the *QT* interval prolongation, Holter ECG monitoring (ECG HM) was performed using the Poly-Spectrum-SM system, Neurosoft, Ivanovo, Russia.

During ECG HM, a prolongation of the *QT* interval up to 680 ms was registered (Fig. 3).

The *QT* interval prolongation persisted regardless of the HR, namely, 680 ms in sinus rhythm with an HR of 53 beats/min, 580 ms with an HR of 85 beats/min (Fig. 4), and with a norm according to ECG HM findings up to 480 ms [9].

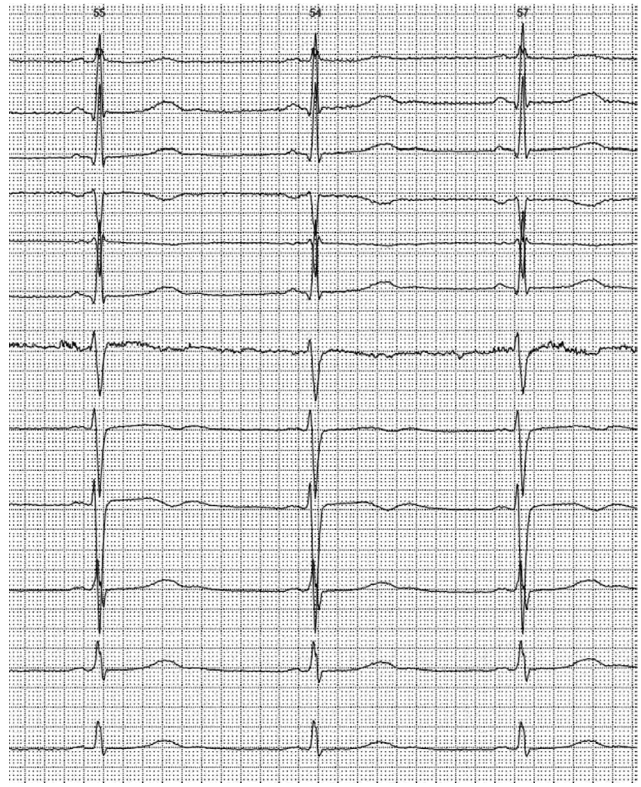

Fig. 1. 12-lead electrocardiogram in young athlete A., 16 years old

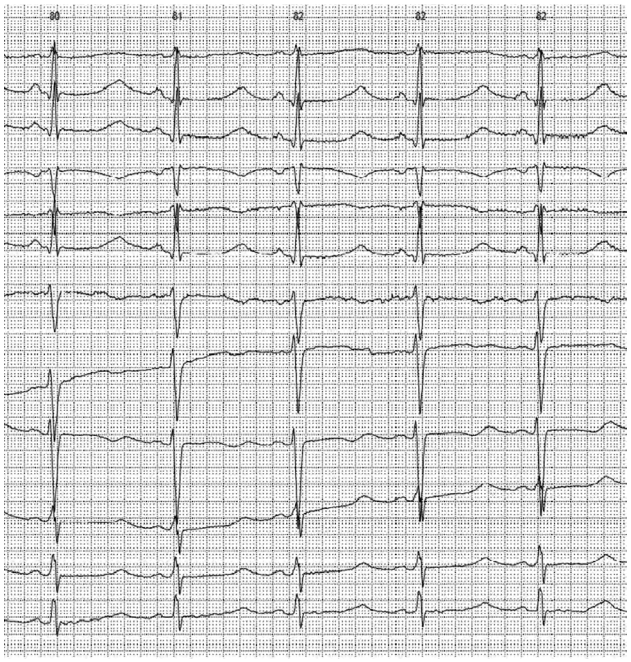

Fig. 2. 12-lead electrocardiogram (standing) in young athlete A., 16 years old

According to the automatic analysis of *QT* (the norms are presented according to the National Russian recommendations for the use of the HM technique in clinical practice), an elongation of this interval was also revealed, where the average *QT* interval was 471 (normal 342–401) ms, *QT*c by Bazett was 500 (normal 396–447) ms, and QTc by Fridericia was 490 (normal 384–421) ms.

Rare (total 354, extrasystole density 0.4%) single ventricular extrasystoles and episodes (3) of trigeminy (Fig. 5) were registered.

Transthoracic echocardiography (EPIQ 5 Ultrasound Device, Philips, Netherlands) showed normal biventricular systolic function. The valvular apparatus had no pathological abnormalities, and the transvalvular flow was normal. No enlargement/hypertrophy of the heart chambers was detected. To rule out possible secondary causes of *QT* interval prolongation in a young athlete, the level of electrolytes in the blood serum was determined. The analysis revealed hypokalemia (potassium 2.2 mmol/L; normal, 3.6–5.6 mmol/L). During a conversation with the patient, it was established that she had been taking furosemide without control for 1.5 years to reduce weight. After drug correction of the potassium level, the *QT* interval was normalized according to the results of ECG (Fig. 6) and ECG HM, ventricular extrasystoles were not recorded.

Bicycle ergometry (Corival Lode, Netherlands) at all stages of the load, with 4 min of recovery, did not reveal an elongation of the *QT* interval.

During the follow-up period (catamnesis 2 years), the athlete fulfilled the standard of mastery of sports in rhythmic gymnastics, and her blood level of potassium and the duration of the *QT* interval remained within the normal range.

Young female athlete E, aged 10 years, was examined due to acute respiratory disease at the Children's Scientific and Clinical Center for Infectious Diseases of the Federal Medical and Biological Agency. The prolongation of the *QT* interval was revealed by ECG with a recording speed of 50 mm/s. ECG (Fig. 7) recorded sinus arrhythmia, episodes of bradycardia (HR 63–86 bpm), *QT* (V5) of 420 ms, and QTc of 429–506 ms (increase in QTc interval with an increase in HR). The two-humped T wave morphology and notched T wave were revealed in leads V4–V6, which is characteristic

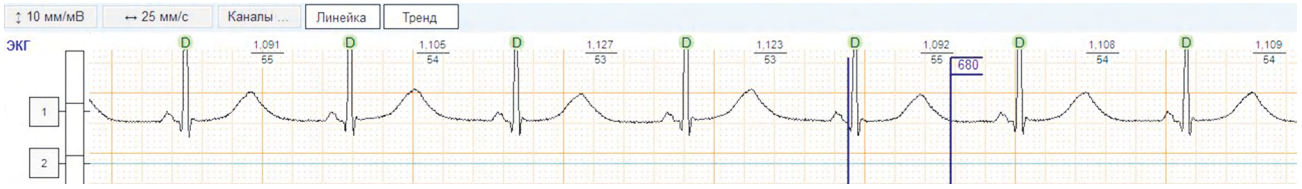

Fig. 3. Fragment of Holter ECG monitoring in young athlete A. The maximum duration of the QT interval

Fig. 4. Fragment of Holter ECG monitoring in young athlete A. Prolongation of the QT interval

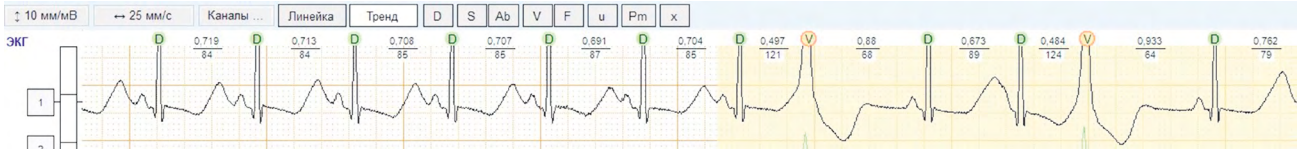

Fig. 5. Fragment of Holter ECG monitoring in young athlete A. Ventricular extrasystoles, trigeminy

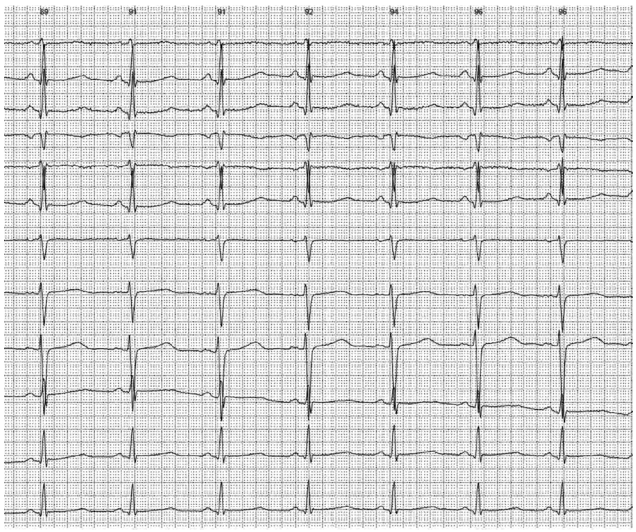

Fig. 6. 12-lead electrocardiogram (standing) in young athlete A., 16 years old, after normalization of potassium concentration in blood serum. *QT* (V5) = 350 ms (A heart rate of 96 beats per min), QTc = 443 ms.

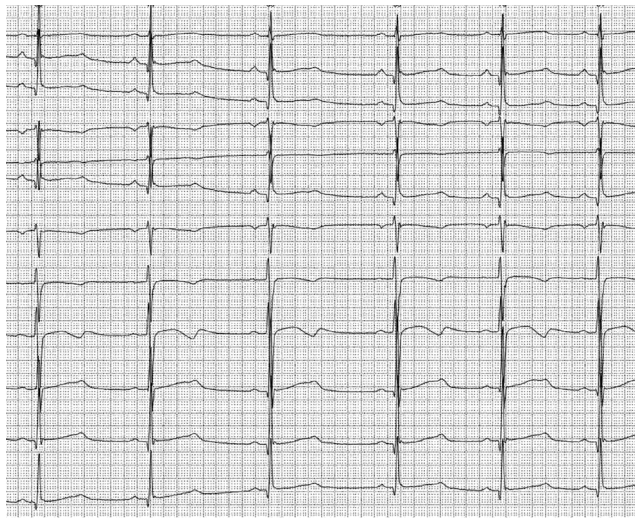

Fig. 7. 12-lead electrocardiogram in young athlete E., 10 years old

of the molecular genetic variant 2 (LQT2) of the hereditary LQTS [10].

During ECG HM (Cardioline System, Italy), the *QT* interval was prolonged up to 540 ms (recording channel 3) at a minimum HR of 46 beats/min (Fig. 8) at a rate of up to 480 ms. Serum electrolytes were normal. Transthoracic echocardiography revealed no pathological changes.

The anamnesis revealed that the patient has been doing rhythmic gymnastics since the age of 4, with training 5–6 times a week for 3 h. No pathological changes in the ECG were detected during the scheduled TME. She had no episodes of loss of consciousness. As regards heredity, the girl's mother had two episodes of loss of consciousness (at the age of 33 and 35 years). The first attack was related to stress, and the other had no apparent cause. The attacks were accompanied by convulsions and involuntary urination. Regarding fainting, the patient was examined in one of the clinics in St. Petersburg and consulted by a neurologist, and a diagnosis of autonomic dysfunction syndrome was made. The ECG of the mother (Fig. 9) revealed sinus rhythm with an HR of 70–80 beats/min and a significant prolongation of the *QT* interval, where the *QT* (V5) at an HR of 76 beats/min was 500 ms and QTc was 562 ms. The T morphology was also characteristic of the molecular genetic variant 2 of the hereditary LQTS.

Based on the generally accepted diagnostic criteria proposed by Schwartz [4, 6], patient E was diagnosed with hereditary LQTS, familial variant (inheritance on the mother's side), and molecular genetic variant 2. Whole-genome DNA sequencing was performed at the EVOGEN Medical Genetic Laboratory (Moscow), which revealed a previously undescribed variant p. Met554ValfsTer100 (leading to the formation of a premature stop codon) in the heterozygous

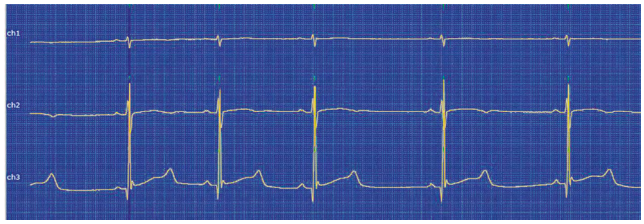

Fig. 8. Fragment of Holter ECG monitoring in young athlete E. Prolongation of the QT interval

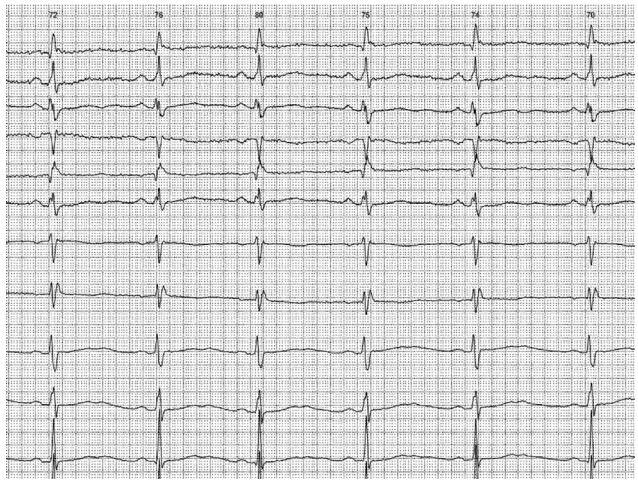

Fig. 9. Prolongation of the *QT* interval in the girl's mother.

state in exon 7 of 15 exons of the KCNH2 gene responsible for the development of the molecular genetic variant 2 of LQTS (LQT2).

Atenolol was recommended at a daily dose of 1 mg/kg. Training at the sports school has been discontinued.

DISCUSSION

LQTS is a disease associated with a high risk of SCD due to the development of torsade de pointes polymorphic ventricular tachycardia [11]. Regardless of the causes of LQTS (such as hypokalemia due to long-term intake of furosemide in clinical case 1 and a mutation in the KCNH2 gene in clinical case 2, which caused the development of LQT2), patients with LQTS are at risk of life-threatening arrhythmic events. In a study conducted in the USA, LQTS causes SCD in 2% of athletes [2], and 0.4% of Olympic athletes may experience ventricular tachyarrhythmias associated with this syndrome [12]. Before diagnosing young athletes with congenital LQTS, acquired causes of *QT* prolongation must be ruled out. The most common causes include medications that prolong *QT*, metabolic changes, and electrolyte disorders. One of the routine methods to detect changes typical for LQTS is a standard 12-lead ECG. The interpretation of the ECG in athletes includes an estimate of the length of the QTc, calculated using the Bazett equation. However, difficulties may be encountered in assessing the *QT* interval in young athletes. Approximately 25%–35% of patients with a genetically confirmed hereditary LQTS may have normal *QT* interval on the ECG at rest [2]. Determining the duration of the *QT* interval associated with sinus bradycardia characteristic of athletes is even more difficult, especially when identifying the prolongation of the *QT* interval associated with an increase in HR (an example of a 10-year-old rhythmic gymnast diagnosed with LQT2). Moreover, when registering severe sinus arrhythmia on the ECG, the response of the *QT* interval to a change in the HR is not instantaneous and complete adaptation takes 1–3 min [13]. Problems can also arise when making a differential diagnosis between the U wave and the two-humped T wave, characteristic of LQT2, on the body-surface ECG.

Until now, there are conflicting opinions on the admission of athletes with a diagnosed congenital LQTS to training and competitions. The 2005 ESC guidelines for participation in sports competitions are the most restrictive [14]. They state that congenital LQTS is a contraindication for any sports, even in the absence of documented serious cardiac arrhythmias. The 2015 European Society of Cardiology guidelines for the treatment of ventricular arrhythmia and the prevention of SCD recommended avoiding intensive swimming, particularly in the case of LQT1; however, no other sports have been mentioned [15]. More recently, the 2015 American eligibility and disqualification guidelines for athletes with channelopathies (including LQTS), who take part in competitions, are less restrictive [16]. According to these guidelines, athletes with symptomatic LQTS (except for competitive swimming with LQT1) may be eligible to compete after the initiation of treatment and appropriate precautions, as long as they have been symptom-free during treatment for at least 3 months and these athletes and their family members received information about potential risks. In the Russian national recommendations on the admission of athletes with abnormalities in the cardiovascular system to training and competitions, for athletes with a history of an episode of cardiac arrest or syncope conditions, presumably associated with LQTS, regardless of the QTc interval or genotype, all sports are contraindicated, except for class IA [17].

Thus, these cases clearly demonstrate the existing difficulties in diagnosing LQTS in young athletes and the need for a comprehensive analysis of possible causes of LQTS, which, in some cases, will help preserve the possibility of continued involvement in the chosen sport and reduce the risk of SCD in other cases. To detect *QT* prolongation in young athletes, further studies including stress tests and molecular genetic testing are needed to search for gene mutations responsible for the development of this syndrome.

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