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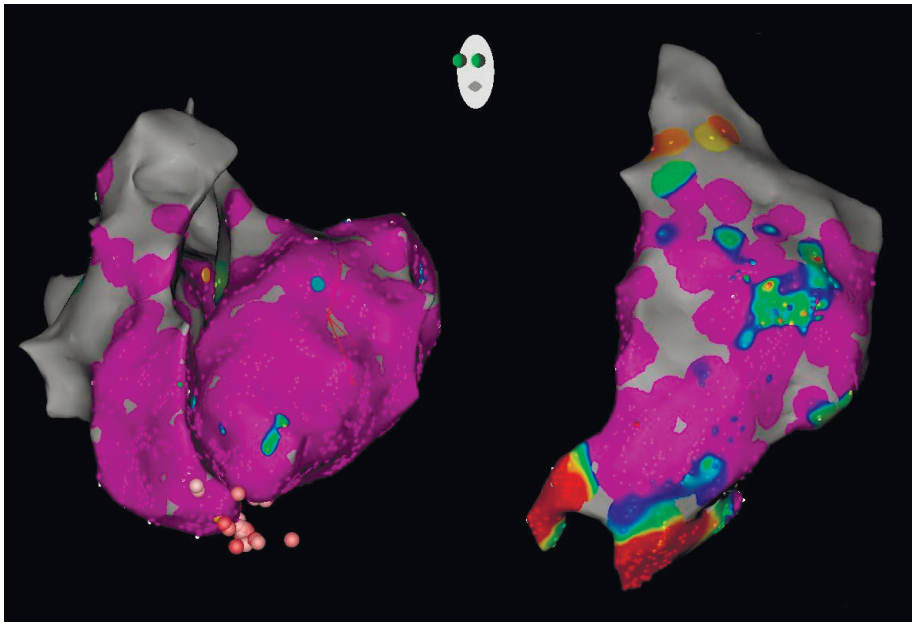

Figure from the article by K.A.Simonova, M.A.Naymushin, A.V.Kamenev et al.

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CONTENT

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GENETICS OF THE LONG QT SYNDROME

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This editorial refers to a paper Komissarova SM, Chakova NN, Rebeko ES, Dolmatovish TV, Niyazova SS. Clinical characteristics of patients with various genetic types of long QT syndrome. Journal of Arrhythmology. 2022;29(1): 7-16.

Keywords: long QT syndrome; channelopathies; genetic testing

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Long QT syndrome (LQTS) is one of the first cardiovascular diseases that has been recognized as a primarily inherited disease and quickly got a broad spectrum of causative genes [1]. LQTS's relatively high population prevalence (approximately 1:2500), well-recognized ECG pattern, and clear genotype-phenotype correlations were the impetus for the introduction of genetic testing for LQTS into clinical practice. Being one of the first genetic syndromes in the cardiovascular field, LQTS continues to prove its pioneering role in cardiogenetics, bringing on the stage the problem of "variants of unknown clinical significance" and focusing the attention on the growing number of new LQTS susceptibility genes only occasionally described in connection with the disease without segregation analysis and functional studies though [2]. As a result, LQTS first underwent an evolution which later was repeated by many other genetic cardiovascular disorders, such as Brugada syndrome, arrhythmogenic cardiomyopathy, and dilated cardiomyopathy. This evolution included the quick identification of the broad spectrum of disease-associated genes using NGS technologies, defining the genotype-phenotype correlations, recognition of the polygenic impact on the disease phenotype, the renaissance of single nucleotide polymorphisms (SNPs), and analysis of their role in modifying the disease manifestation. The recent achievements of structural biology, molecular electrophysiology, and pharmacogenetics are exploited to narrow the spectrum of all found causative genes to the functionally proven for further safe usage in clinical genetics.

Apart from the most frequent forms of LQTS - LQTS types 1, 2, 3 together with recessive and rare malignant conditions such as Jervell and Lange-Nielsen syndrome, Timothy syndrome, and Andersen-Tawil syndrome, a vast majority of genes associated with LQTS often had very scarce evidence and only single case reports. For many of these genes, e.g., *AKAP9*, *ANK2*, *CAV3*, *KCNE1*, *KCNE2*, *SCN4B*, *SNTA1*, later on, the doubts have been raised, leading to the reappraisal of defined causative genes for LQTS [3]. Currently, only *KCNQ1*, *KCNH2*, *SCN5A* are considered as causal genes for typical LQTS, and another four genes (*CALM1*, *CALM2*, *CALM3*, *TRDN*) were reported as definitive for LQTS with atypical features, including neonatal atrioventricular block. While for *CACNA1C*, the level of evidence is moderate, other genes are considered as having limited evidence as causative for LQTS. In parallel, growing evidence appeared regarding the role of common genetic variants (SNPs) in LQTS-associated genes as important modulators of disease phenotypic variability. Thus, previously reported LQTS-associated genes *KCNE1* and *KCNE2* were recognized as the significant contributors of acquired LQTS, and the role of common genetic determinants of *NOS1AP*, *KCNQ1*, and *KLF12* genes in the development of acquired LQTS prolongation is confirmed now [4].

Since LQTS mainly manifests in childhood, most of the patients reported with genetic testing are children. In our country, inherited LQTS in adult patients was unrecognized for a long time, and LQTS diagnosis was not commonly accepted. Therefore, there are only few papers published on the genetic spectrum of adult patients with LQTS. The research paper published in the current Journal issue [5] represents one of them, providing clinical and genetic information on 24 adult patients with LQTS. Overall, this study confirms worldwide data on the approximate rate of positive genotyping around 60-70% and supports the data on the prevalence of *KCNQ1* and *KCNQ2* pathogenic variants among patients with LQTS. Importantly, the authors also demonstrated the low frequency of *CACNA1C* and other variants among patients with LQTS raising criticism regarding including these genes in clinical testing [6]. Together with recently published papers on the role of rare genetic variants in LQTS, this study can lead to the reappraisal of the clinical inter-

pretations of the earlier reported genes and their use in target panels for genetic testing.

Currently, our knowledge on LQTS genetics, electrophysiology, and structural biology, together with data on SNPs impact, demand new clinical concepts regarding diagnostic and treatment approaches in patients with inherited and acquired disease. Therefore, the paper presented in this issue is well in line with the most contemporary view of LQTS genetics and supports modern trends in the cardiovascular genetic field.

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CLINICAL CHARACTERISTICS OF PATIENTS WITH VARIOUS GENETIC TYPES OF LONG QT SYNDROME

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The aim of the study is to evaluate clinical characteristics, including adverse events and outcomes, in patients with various genetic types of long QT syndrome (LQTS).

Material and methods. We examined 24 patients with a clinical diagnosis of LQTS, observed in the for 5 years. The clinical and instrumental study included registration of electrocardiography (ECG), Holter monitoring, collection of a genealogical history with an ECG assessment of all family members and identification of cases of sudden cardiac death (SCD) in the family or the presence of a family form of the disease, echocardiography and cardiac magnetic resonance imaging to exclude structural changes in the myocardium. The search for mutations in the coding sequences of genes associated with the development of channelopathy and other hereditary heart rhythm disorders was carried out by next generation sequencing (NGS).

Results. Mutations in 4 genes associated with LQTS (*KCNQ1*, *KCNH2*, *CACNA1C*, *ANK2*) were detected in 18 out of 24 (75.0%) patients. Mutations in the *KCNQ1, KCNH2* and *CACNA1C* genes were detected in 14 (58.0%) patients. In 4 out of 24 (17%) patients, two or more variants of clinical significance (VUS) were detected in the genes associated with LQTS and hereditary arrhythmias, 6 patients had no genetic changes. The most severe form of the disease with pronounced clinical manifestations and episodes of clinical death with subsequent resuscitation measures, as well as a significant increase in the QTc interval exceeding 500 ms, was observed in patients with LQT2 and multiple mutations. Implantation of a cardioverter-defibrillator (CD) was required in 14 (58.3%) patients, including 11 (78.56%) - for secondary prevention of SCD and 3 (21.4%) - for primary prevention.

Conclusion. A comparative analysis between different genetic types of LQTS (LQT1; LQT2; patients with multiple VUS) showed that in patients with LQT1 syndrome, despite the early manifestation of the disease and the presence of syncopal conditions, life-threatening arrhythmias, SCD and the frequency of CD implantation were significantly less often recorded than in other LQTS. The most severe form of the disease with pronounced clinical manifestations, episodes of clinical death with subsequent resuscitation and CD implantation was observed both in the group of probands with LQT2 and in patients with several nucleotide variants (VUS), one of which was in the *CACNA1C* or *ANK2* genes.

Keywords: long QT syndrome; genetic testing; genetic types; life-threatening arrhythmias

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Congenital long QT syndrome (LQTS) is a life-threatening arrhythmia syndrome, a major cause of sudden cardiac death (SCD) in young adults. It is characterized by the long QT interval on the electrocardiogram (ECG), the occurrence of syncope or cardiac arrest, mainly triggered by emotional or physical overexertion [1]. The incidence of the disease is now generally estimated to be about 1:2000-2500 [2].

LQTS is caused by functional changes in ion channels, mostly caused by defects in the genes encoding the pore-forming α-subunits (*KCNQ1*, *KCNH2*, *SCN5A*, *KCNJ2* and *CACNA1C*) or the regulatory β-subunits (*KCNE1*, *KCNE2* and *SCN4B*) of ion channels. 75% of mutations are concentrated in one of the three genes: about 35% in *KCNQ1*, about 30% in *KCNH2*, and about 10% in *SCN5A*. Another 5-10% of mutations can cause multisystem syndromes, including long QT interval and the occurrence of malignant ventricular arrhythmias: Timothy syndrome (mutations in the *CACNA1C* gene), Andersen-Tawil syndrome (mutations in the *KCNJ2* gene), and Ankyrin B syndrome (mutations in the *ANK2* gene). The list of genes causing LQTS has now been expanded to 17 genes [3].

The clinical features are best studied in the first three genetic types of LQTS. Each type has a characteristic ST-T ECG pattern, a typical trigger for arrhythmias, and a different response to treatment with beta-blockers [4, 5].

The duration of the QTc interval is a significant risk factor for cardiac arrhythmias. According to the recommendations of the Heart Rhythm Society/European Heart Rhythm Association experts (HRS /EHRA, 2011), the values of the 99th percentile of the QTc duration should be considered abnormally prolonged depending on sex [6]. This corresponds to a QTc > 460 ms for male and female patients in the prepubertal phase, a QTc > 470 ms for males, and a QTc > 480 ms for females in the postpubertal phase. A QTc duration ≥ 500 ms is considered extremely unfavorable in both males and females and is associated with the risk of ventricular torsades de pointes (TdP) [6]. However, prolongation of the QTc interval on ECG does not always occur. For example, in a study by Silvia G. Priori et al. [7] QT interval values within normal limits were found in 36% of patients with LQT1, in 19% of patients with LQT2, and in 10% of patients with LQT3.

A QTc duration is modulated by LQTS genotype and sex. Female patients with LQTS2 and male patients with LQT3 with a QTc ≥500 ms are at greatest risk for arrhythmic events between birth and 40 years of age in the absence of therapy [8].

The association between genotype and trigger of arrhythmias is well known [9]. Thus, most events in patients with LQT1 occurred during physical exertion or stress, with swimming being a very specific trigger. Patients with LQT2 are extremely sensitive to stress and sudden auditory stimuli such as an unexpected loud noise or phone call. Most LQT3 events occurred when patients were sleeping or resting. The inability of the QTc interval to adapt to a higher heart rate leads to a high risk of postdepolarization, which can lead to the development of TdP [10]. This can be very dangerous for patients with LQT1, in whom a sudden increase in heart rate with impaired QTc shortening contributes to the R-on-T phenomenon and the occurrence of ventricular tachycardia (VT)/ventricular fibrillation (VF).

There is clear evidence of the efficacy of treatment with beta-blockers depending on the LQTS genotype. Thus, patients with LQT1 respond well to treatment with beta-blockers [1]. At the same time, noncompliance with the treatment regimen is the most important cause of arrhythmic events occurring during treatment [11]. Compared with LQT1, patients with LQT2 are more likely to experience life-threatening events (6-7%) despite treatment with beta-blockers [12], yet they remain the first-line agent for this type of LQTS. Arrhythmias have been reported to occur more frequently (10-15%) in patients with LQT3 treated with beta-blockers [12], as bradycardia-dependent arrhythmias are more common in this type of LQTS. Therapy with a sodium channel blocker such as mexiletine shortens the QTc interval more effectively and improves prognosis in patients with LQT3 [1].

Overall, integration of LQTS genotype information with clinical features improves risk stratification for life-threatening arrhythmias and is an example of successful genotype-specific treatment of patients with LQTS. However, the relationship between genotype and phenotype in rare genetic variants of this disease is poorly understood.

The aim of this study was to evaluate clinical characteristics, including adverse events and outcomes, in patients with different genetic types of LQTS.

MATERIALS AND METHODS

The study included 24 patients with a primary diagnosis of LQTS. The clinical and instrumental study included ECG registration in 12 leads, daily ECG monitoring, endocardial electrophysiological study when indicated, taking a genealogical history with ECG evaluation of all family members to identify cases of SCD in the family or the presence of a family form of the disease.

The following parameters were assessed by ECG: heart rate, corrected QT interval (QTc), morphology, and T-wave change. The QT interval and the preceding RR interval were measured manually in at least three consecutive cardiac cycles, and mean values were calculated. The end of the T wave was defined as the intersection of the tangent line drawn along the maximum slope of the descending T wave with the isoelectric T-P line; the U waves were not included if they were different from the T [13]. QTc was

Table 1.

Genotypes and phenotypes of LQTS

Genotype	ECG pattern	Frequency of asymptomatic carriers	Risk factors for arrhythmic events	Beta-blocker therapy efficacy
LQT1	Prolongation of the QT interval with a high shaped T wave [4]; impaired adaptation of the QTc interval to tachycardia [5].	30% [6].	Physical activity or stress, swimming [7].	High
LQT2	Prolongation of the QT interval with a clear and typical notch on the T wave. Normal adaptation of the QTc interval to tachycardia.	19%.	Stress, auditory stimuli (sudden noise, phone call, sudden awakening) at rest; female.	Decreased*.
LQT3	Horizontally elongated ST segment with a biphasic T wave with a late onset.	10%.	During sleep or at rest; male.	Low*.

Note: * - in comparision with LQT1 [8].

calculated according to the formula of Bazett. LQTS diagnostic criteria were evaluated using the modified scale of R.J.Schwartz et al. (2011) [14].

To exclude structural myocardial abnormalities, echocardiographic examination was performed according to current recommendations at PHILIPS IE -33.

Daily ECG was used to evaluate the mean heart rate per day, the value of the averaged, maximum, and minimum QT intervals, the presence/absence of an alternate T wave, and concomitant arrhythmias. The ventricular genesis of the arrhythmia was confirmed by daily ECG data, ECG registration during an attack, and in some cases by endocardial electrophysiological study.

A physical stress test on a Shiller ERGOLIM/LODE ergometer with ECG monitoring in 12 leads was performed when QTc values at rest were uncertain to clarify the diagnosis [14]. The test was performed according to the standard protocol until the heart rate reached 170 beats per minute or fatigue occurred. The ECG was recorded for 5 minutes after the end of exercise, and the QTc value was determined after 4 minutes of the recovery period.

The search for mutations in the coding sequences of genes associated with the development of channelopathies and other inherited cardiac arrhythmias was performed by high-throughput sequencing (NGS) on a MiSeq Gene Analyzer (Illumina). Samples were prepared using the TruSight Cardio Sequencing Kit (Illumina). Annotation of sequencing results was performed using ANNOVAR software [15]. Interpretation of pathogenicity of new and previously described genetic variants was performed according to the 2015 American Society for Medical Genetics recommendations [16]. Pathogenic (class V) and probably pathogenic (class IV) genetic variants were considered diagnostically significant. Variants of uncertain clinical significance (VUS, pathogenicity class III) in genes associated with inherited arrhythmias were included separately in the data analysis.

Statistical analysis. Two unrelated groups were compared for quantitative characteristics using the nonparametric Mann-Whitney U test. Differences at $p<0.05$ were considered statistically significant.

RESULTS

In 18 of 24 (75%) patients, nucleotide sequence variants of pathogenicity classes III-V were identified according to ACMG2015 criteria in 4 genes directly associated with LQTS (*KCNQ1*; *KCNH2*; *CACNA1C*; *ANK2*). Of these, 14 variants were diagnostically significant mutations in classes IV and V: (*KCNQ1*, 8 mutations; *KCNH2*, 4 mutations; *CACNA1C*, 2 mutations). 4 Nucleotide substitutions in the *CACNA1C* and *ANK2* genes were variants of uncertain significance (VUS, grade III) and were found in combination with other rare variants in genes associated with inherited arrhythmias: 1) *ANK2* и *KCNE1*; 2) *ANK2* и *SNTA1*; 3) *CACNA1C* и *KCNH2*; 4) *CACNA1C*, *SCN3B* и *DSG2*. Six (25.0%) patients with a clinical diagnosis of LQTS lacked any genetic alterations (Table 1).

Table 1 shows the clinical characteristics of the three groups of patients: Group 1, with diagnostically significant pathogenicity mutations of class IV-V (n=14), including subgroups with different genetic types of LQTS (subgroup 1, LQT1; subgroup 2, LQT2; subgroup 3, LQT8); group 2, patients with multiple VUS in genes (n=4) associated with arrhythmias); and group 3, genotype-negative patients (n=6). The median age at diagnosis was 26.4 [12;43] years in the 14 patients with genetically confirmed LQTS, compared with 37.5 [33;45] years in patients with two VUS (p=0.04, compared with group 1) and 35.5 [22;46] years in patients without mutations (p=0.04, compared with group 1). Comparative analysis of sex in these groups showed that in LQT1, LQT2 and LQT8 patients with a single pathogenic mutation, the female sex predominated (85.7%), while in the group with multiple VUS, three out of four were male, and in the genotype-negative patients the sex ratio was 1:1. QTc interval duration exceeded 500 ms in 50% of patients with LQT1 and multiple VUS and in 100% of patients with LQT2. A QTc interval duration ≤460 ms was observed in 12.4% of patients with LQT1, in 25% of patients with multiple VUS, and in 17% of genotype-negative patients. Syncopal episodes were observed in 87.5% (21 of 24) of patients, and 29.2% (7 of 24) had a family history of SCD. Information about SCD with successful resuscitation or cardiac arrest with implantation of a cardioverter-defibrillator (ICD) was documented in 13 of 24 (54.2%) patients observed, and in 2 (8.3%) cases, the ICD was used for primary prevention of SCD. In LQT2, there was a family history of SCD in 50.0% of cases, which was 4 times higher than in LQT1 (12.4%) and twice higher than in the multiple VUS group (25%). It is noteworthy that in the group of genotype-negative patients, the incidence of SCD in the family history was also quite high, reaching 50.0%. In the same group, all subjects developed SCD followed by successful resuscitation and ICD implantation for secondary prevention of SCD. Life-threatening arrhythmic events (SCD with successful resuscitation, sustained VT, cardiac arrest) occurred 3 times less frequently in subjects with LQT1 compared with other groups.

When comparing the clinical manifestations of the disease in the subgroup of patients with LQT1, only 2 (25%) patients (no. 1 and 7) with pathogenic mutations in exons 5 (p.Val127Met) and 6 (p.Gly179Arg) of the *KCNQ1* gene showed severe disease (Table 2). In both patients, the disease manifested with cardiac arrest due to the development of VT/VF during physical activity. The patients were successfully resuscitated and subsequently received an ICD. Both patients had a history of syncope at 24 and 12 years of age; patient 1 had a family history of SCD in a close relative. Resting ECG showed QTc prolongation up to 520 ms and 620 ms, respectively. Three patients (Nos. 3, 4, and 5) with probable pathogenic mutations (class IV according to ACMG2015 criteria) in the *KCNQ1* gene had a more favorable disease course, without development of hemodynamically significant ventricular arrhythmias with mild prolongation of the QTc interval (450 ms; 465 ms and 480 ms, respectively) according to resting ECG. The diagnosis of LQTS was made on the basis of the results of the exercise test (QTc prolongation at the peak of exercise and in the 4th minute of the recovery phase was recorded up to 485 ms; 500 ms and 516 ms, respectively) and the LQTS probability score according to the score of R.J.Schwartz et al, which was 4.5; 5 and 5 total scores, respectively. Patient

Table 2.

Phenotypic manifestations of genotype in patients with LQTS, n (%)

Patient groups		Sex m/f	Age at diagnosis	SCD history	Family form	Syncope	QTc <460 ms	QTc 460-499 ms	QTc ≥500 ms	SCD / CA	ICD	Associated diseases
Group 1. DS IV-V classes	*KCNQ1,* n=8	2/6	23.5[12; 35]	1 (12,4)	4 (50)	6 (75)	1 (12,4)	3 (37,5)	4 (50)	2 (25)	2 (25)	LQTS1
	KCNH2, n=4	0/4	34.0[24;43]	2 (50,0)	4 (100)	4 (100)	-	-	4 (100)	1 (25)	3 (75)	LQTS2
	CACNA1C, n=2	0/2	22.5[14; 31]	-	1 (50)	2 (100)	-	1 (50)	1 (50)	1 (50)	1 (50)	LQTS8
Group 2. Few VUS, n=4		3/1	37.5[33;45]	1 (25)	1 (25)	3 (75)	1 (25)	2 (50)	1 (25)	3 (75)	3 (75)	LQTS
Group 3. Genetically negative, n=6		3/3	35.5[22; 46]	3 (50)	3 (50)	6 (100)	1 (17)	5 (83)	-	6 (100)	6 (100)	-

Note: hereinafter SCD - sudden cardiac death; CA - cardiac arrest; ICD - implantable cardioverter-defibrillator; DS - diagnostically significant.

Table 3.

Clinical and genetic characteristics of patients with LQTS (continued)

	N	Patient code	AM	Sex	SCD history	Family form	Syncope	QTc_{max}. ms#	Schwartz score	Other arrhythmias	Events / outcomes	Substitution in the DNA (substitution in the protein)	Pathogenicity
LQT1 (мутации в гене *KCNQ1*)	1.	566	24	f	+	+	+	520	6.0	SB. SAB	PM→ICD	c.379G>A (p.Val127Met)	V (PS)
	2.	656	35	f	-	+	-	500	5.5	SVT	-	c.592G>A (p.Gly198Arg)	V (PS)
	3.	640	18	f	-	-	-	480	4.5	SVT	-	c.1621G>A (p.Val541Ile)	IV (PM)
	4.	639	25	f	-	+	+	450	5.0	SVT	-	c.1555C>T (p.Arg519Cys)	IV (PM)
	5.	635	19	m	-	-	+	465	5.0	-	-	c.1999G>A (p.Val667Met)	IV (PM)
	6.	713	21	m	-	-	+	630	5.5	SVT	-	c.641C>T p.Ala214Val	V (PS)
	7.	609	12	f	-	+	+	620	6.0	SVT	VT/VF. CPR. ICD	c.535G>C (p.Gly179Arg)	V (PS)
	8.	666	34	f	-	-	+	440	4.0	SVT	-	c.1233delA (p.Lys411Asnfs*8)	IV* (PV)
LQT2 (мутации в гене *KCNH2*)	9.	564	24	f	-	+	+	594	5.5	SVT	VT/ICD	c.371T>A (p.Met124Lys)	V* (PS)
	10.	720	43	f	+	+	+	513	6.0	PVC. SVT	ICD	c.2775dupG (p.Pro926AlafsX14)	V (PV)
	11	589	35	f	-	+	+	505	4.5	-	-	c.2131A>G (p.Ile711Val)	IV (PS)
	12.	655	34	f	+	+	+	623	5.5	SVT	ICD	c.1424A>G (p.Tyr475Cys)	V (PS)
LQT8 (мутации в гене *CACNA1C*)	13.	628	14	f	-	-	+	440	4.0	PVC. SVT. SVT	-	c.2053C>T (p.Arg685Trp)	IV*(PM)
	14.	610	31	f	-	+	+	580	7.5	SVT	VT/ICD	c.2573G>A (p.Arg858His)	V (PS)

Table 3.

Clinical and genetic characteristics of patients with LQTS (continued)

	N	Patient code	AM	Sex	SCD history	Family form	Syncope	QTc_{max}. ms#	Schwartz score	Other arrhythmias	Events / outcomes	Substitution in the DNA (substitution in the protein)	Pathogenicity
Few VUS	15.	613	39	f	+	+	+	500	6.5	SVT. SAB	VF / CPR. ICD	CACNA1C: c.1186G>A (p.Val396Ile) KCNH2: c.49A>T (p.Arg17Trp)	III III*
	16.	607	33	m	-	-	-	460	4.0	PVC. SVT	VT. RFA	CACNA1C: c.4942G>A (p.Ala1648Thr) SCN3B: c.260C>G (p.Pro87Arg) DSG2: c.1442T>C (p.Ile481Thr)	III III III
	17.	586	33	m	-	-	+	440	5.0	SVT	VT / AF. ICD	ANK2: c.1397C>T (p.Thr466Met) KCNE1: c.253G>A (p.Asp85Asn)	III III
	18.	543	45	m	-	-	+	375	5.5	SVT	VT / VF. ICD. ES	ANK2: c.1397C>T (p.Thr466Met) SNTA1: c.787G>T (p.Ala263Ser)	III III
Genetically negative	19.	574	30	f	+	+	+	500	6.5	PVC. VT	VT. ICD	not found	
	20.	597	22	m	+	+	+	465	6.0	SVT	VT. ICD. ES	not found	
	21.	644	46	f	-	-	+	460	6.5	SVT	VT / VF. CPR. ICD	not found	
	22.	647	46	m	-	-	+	477	5.5	SVT	VT/VF. CPR. ICD	not found	
	23.	629	40	f	+	+	+	478	6.0	SVT	VT. CPR. ICD	not found	
	24.	631	29	m	-	-	+	456	5.5	SVT	VF. CPR. ICD	not found	

Note: AM - age at manufestation; # - on ECG; SB - sinus bradycardia; SAB - sinoatrial block; VT - ventricular tachycardia; NVT - non-sustained ventricular tachycardia; VF - ventricular fibrillation; PVC - premature ventricular complex; SVT - supraventricular tachycardia; ES - electrical storm; CPR - cardiopulmonary resuscitation; V - pathogenic mutation; IV - probably pathogenic mutation, III - variant of uncertain significance (VUS); DNA - deoxyribonucleic acid; PM - pacemaker; ICD - implanted cardioverter-defibrillator; RFA - radiofrequency ablation; AF - atrial fibrillation; * - new mutations.

no. 8 was found to have a new deletion with a frameshift and premature stop c.1233delA/p.Lys411Asnfs*8 in the *KCNQ1* gene. Syncope occurred in the patient at the age of 34 years. On a resting ECG (Fig. 1a), the duration of the QTc interval did not exceed 440 ms. During exercise tests at the peak of exercise and in the 4th minute of the recovery phase, QTc prolongation was recorded up to 475 ms and up to 535 ms, respectively (Fig. 1b). The LQTS probability score according to the score of R.J.Schwartz et al. was 4. Based on the above data, a diagnosis of LQTS was made. The patient was prescribed therapy with a beta-blocker (propranolol 40 mg ½ b.i.d) and syncope did not recur during treatment.

All patients with LQT2 had QTc duration ≥500 ms with syncopal states. Two of them had a family history of SCD in close relatives. In patients no. 9 and 10 with class V mutations in the *KCNH2* gene, the disease manifested with cardiac arrest due to the development of VT / VF with successful resuscitation and subsequent ICD implantation. Patient No. 12 experienced syncope at the age of 34 years against a background of emotional stress triggered by her identical twin sister's SCD during pregnancy. The ECG showed prolongation of the QTc interval up to 623 ms. The LQTS probability score according to score of R.J.Schwartz et al. was 5.5. Considering the SCD in a twin sister of the same age and the prolongation of the QTc interval up to 623 ms, it was decided to implant an ICD in the patient. Genetic testing revealed a pathogenic p.Tyr475Cys (rs199472907) mutation in the *KCNH2* gene. This mutation is represented as VUS in the ClinVar database and is registered as diagnostically significant in other databases (HGMD, LOVD). The results of segregation analysis confirmed the pathogenic significance of this variant: the mutation was found in a sister with SCD and the daughter of a deceased woman with clinical manifestations of LQTS.

Class IV-V mutations in the *CACNA1C* gene were found in two patients (no. 13 and 14). In patient no. 14 with the pathogenic c.2573G > A (p.Arg858His) mutation in exon 8 of the *CACNA1C* gene, a severe clinical picture with recurrent syncope and cardiac arrest requiring resuscitation and subsequent ICD implantation was observed (Table 2). The ECG showed prolongation of the QTc interval up to 550 ms and a negative T wave with a broad base in leads V2-V5 (Fig. 2). Over the course of 8 years, the patient developed spindle-shaped VT (TdP) three times, which was stopped by an ICD; the ICD was replaced twice, and she currently continues to be treated with a beta-blocker (nadolol 80 mg q.d.).

In patient no. 13 with a single, previously undescribed c.2053C > T, (p.Arg685Trp) variant pathogenic by predictors in silico and localized in the region of other pathogenic

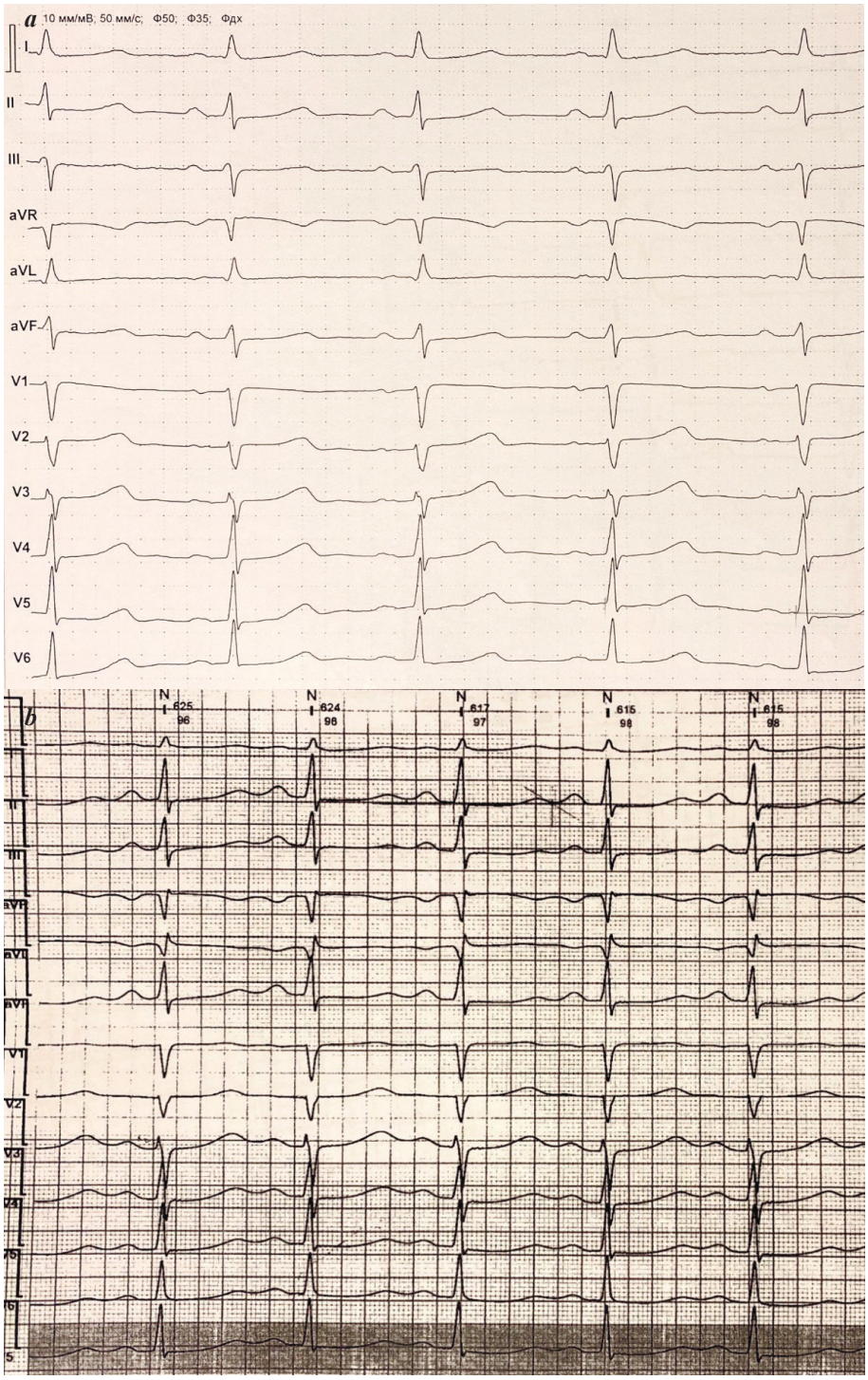

Fig. 1. Resting ECG (a) of patient #8, female 34 years old, recorded QTc 440 ms, ECG during exercise test (b) at the 4th minute of the recovery period recorded QTc 531 ms.

mutations in the *CACNA1C* gene, the disease manifested at age 21 years with a presyncopal state and episodes of unstable monomorphic VT. No changes in T-wave morphology and prolongation of the QTc interval (QTc 420-440 ms) were registered in the ECG series. During cycle ergometry, prolongation of the QTc interval was registered up to 495 ms at the peak of exercise and up to 485 ms in the recovery phase. No sustained VT paroxysms were elicited during diagnostic endocardial electrophysiology study administration. Considering the absence of syncope, paroxysms, or stable VT, it was decided to treat the patient conservatively. Beta-blocker therapy (metoprolol 100 mg/day) was prescribed. No syncopal states were observed during the follow-up examination, and no QTc prolongation was registered in the ECG.

None of the patients with the observed genetic variants, including the pathogenic mutation and the new variant, showed syndactyly, cognitive impairment, facial dysmorphism, or other noncardiac features suggestive of Timothy syndrome.

The combination of multiple VUS nucleotide variants in different genes associated with cardiac arrhythmias was found in 4 (17%) patients, and in 2 subjects one of the replacements was in the *CACNA1C* gene and in 2 subjects - in the *ANK2* gene. All patients with multiple replacements had a severe disease course (Table 2). The most severe clinical picture with prolongation of the QTc interval up to 500 ms, syncopal episodes, development of VT/VF with successful resuscitation and ICD implantation was observed in a patient with VUS in exon 19 of the *CACNA1C* gene in combination with a new c.49A > T (p.Arg17Trp) substitution in the *KCNH2* gene. A patient with VUS in exon 40 of the *CACNA1C* gene in combination with rare substitutions in the SCN3B and DSG2 genes had frequent episodes of unstable VT and malignant ventricular extrasystoles. Radiofrequency ablation of the ectopic foci was performed, and beta-blocker treatment (metoprolol 100 mg/day) was prescribed (Table 2).

In 2 unrelated male subjects, VUS were identified in exons 15 and 38 of the *ANK2* gene, which encodes an ankyrin family adaptor protein previously associated with the development of LQTS type 4, in combination with additional mutations in the *KCNQ1* and *SNTA1* genes [17]. Both patients had no poor family history and QTc interval prolongation in the ECG series (median QTc of 407.5 [375;440] ms). The LQTS probability score according to R.J.Schwartz et al. was 5.0 and 5.5. Patients had recurrent syncopal states, development of VT / VF requiring resuscitative measures and ICD implantation. One 43-year-old proband with substitutions in the *ANK2* and *SNTA1* genes developed polymorphic VT/VF during the 8-year follow-up period, and ICD replacement was performed three times (Table 2). No episodes of syncopal states and repeated ICD storms leading to resuscitation occurred during the last years.

We found that patients with multiple VUS in genes associated with arrhythmias were at high risk for life-threatening arrhythmic events despite a slight prolongation of the QTc interval (460 [440; 460]) ms, which falls in the "gray zone," as were patients with mutations in the *KCNH2* gene (LQT2). Thus, during the follow-up period, 5 of 6 patients (80.0%) with multiple VUS and 3 of 4 (75.0%) patients with LQT2 had VT/VF with ICD implantation, whereas only 25.0% of patients with LQT1 had life-threatening arrhythmic events, as mentioned above.

Unexpectedly severe disease courses with development of VT/VF and ICD implantation were recorded in all 6 genotype-negative patients, despite borderline QTc values (median 471 [462.5;477.5]) ms. The LQTS probability score on the score of R.J.Schwartz et al. was 5.5 to 6.0 total scores. Moreover, half of them had a family history of SCD in their relatives, indicating an apparent heritability of the disease (Table 2). It is possible that the absence of genetic abnormalities in these patients was due to the localization of diagnostically significant mutations in the intron region or in other genes that were not included in the study panel, or that they were extensive deletions that are difficult to detect with NGS. The distinguishing feature of this group, as well as of patients with multiple VUS, was the absence of sex differences, as mentioned previously, whereas the clinical manifestations of LQT1 and LQT2 were mainly observed in female patients.

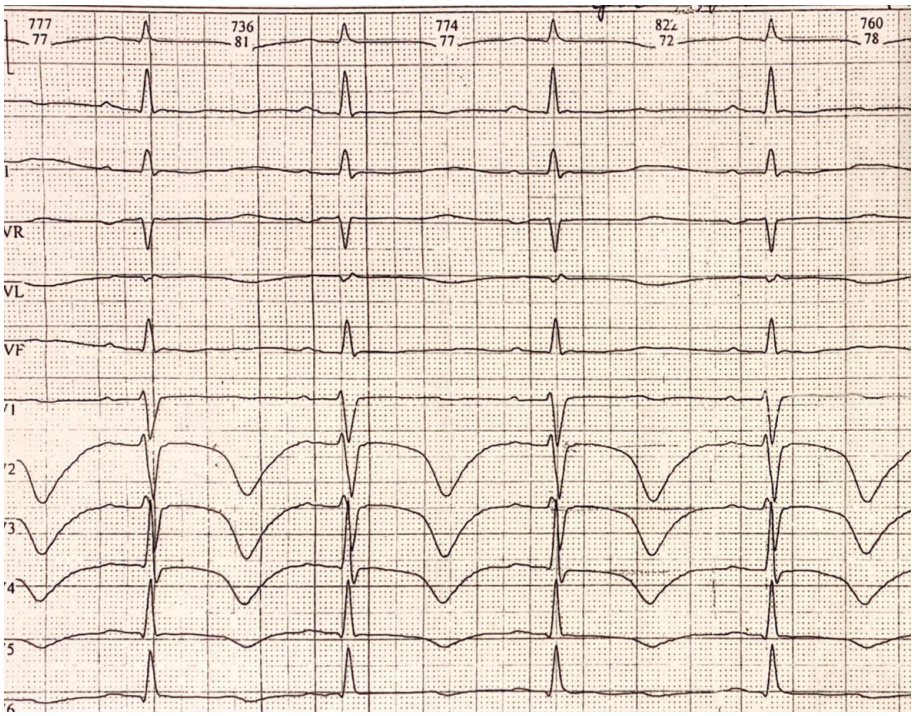

Fig. 2. ECG of patient #14 after cardiac arrest: QTc 550 ms and wide negative T waves in V2-V5 leads were recorded.

DISCUSSION

In the present study, the clinical diagnosis of LQTS was confirmed by genetic testing in 14 of 24 (58.0%) patients in whom mutations in 4 genes

directly associated with LQTS (*KCNQ1*, *KCNH2*, *CACNA1C*) were identified. Six patients with a preliminary diagnosis of LQTS had no genetic alterations. This study presents the results of sequencing 15 genes directly associated with LQTS and genes responsible for the development of other hereditary, life-threatening cardiac arrhythmias. Most previous studies have been limited to the investigation of mutations in 3 genes (*KCNQ1*, *KCNH2*, *SCN5A*) [8]. For each of these genes, genetic evidence is based on linkage analysis in more than one family and is supported by a wealth of genetic and experimental data collected over decades of research and clinical observation [8, 9]. Mutations in both *KCNQ1* and *KCNH2* genes were detected in 50.0% of Belarusian patients in the studied cohort, while no mutations were detected in the *SCN5A* gene. Pathogenic mutations in the *CACNA1C* gene without other noncardiac manifestations indicative of Timothy syndrome were found in 2 patients.

Four of 24 (17%) patients had multiple VUS nucleotide variants, one of which was in the *CACNA1C* or *ANK2* genes. Additional replacements in these subjects were in genes associated with LQTS or other inherited arrhythmias. Syncopal states and prolongation of the QTc interval > 480 ms on ECG series were recorded in the clinical picture of patients with a history of multiple VUS (except for two patients with a mutation in the *ANK2* gene, in whom the QTc did not exceed 440 ms). Three (75%) patients had a documented SCD with successful resuscitation and ICD implantation, and one of them had a family history of SCD.

The presence of multiple mutations in patients with monogenic myocardial disease is increasingly discussed in the literature. A large study by D. Mullally et al [18] in a large cohort of 403 patients with LQTS also identified patients with multiple mutations (14.1%), in whom the phenotypic manifestations and risk of life-threatening events were assessed compared with the group of patients with a single mutation in one of the genes associated with LQTS. Patients with multiple mutations had a longer QTc interval compared to patients with a single mutation (506±72 ms vs 480±56 ms, p=0.003) and had a higher rate of life-threatening events during follow-up (23% vs 11%, $p < 0.001$). Multivariate analysis showed that patients with multiple mutations had a 2.3-fold (p=0.015) higher risk of life-threatening events than patients with a single mutation. The results of our study indicate that the combination of multiple VUS, similar to the effect of multiple mutations, may have a cumulative effect that significantly affects the clinical phenotype. However, this observation requires further research, including clustering of similar cases and segregation analysis.

A comparative analysis between 3 groups (group 1-diagnostically significant mutations of pathogenicity classes IV-V (n=14) with different genetic type of LQTS (LQT1; LQT2; LQT8); group 2-patients with multiple VUS; group 3-genotype-negative patients) revealed a difference in adverse outcomes and events between patients depending on the genetic type of LQTS. The lowest incidence of SCD was observed in patients with LQT1, although this group did not differ from other LQTS in terms of frequency of syncope, and the age of manifestation was earliest in all groups. A severe form of the disease with pronounced clinical manifestations, episodes of clinical death followed by resuscitation, and ICD implantation were observed in the group of subjects with LQT2, as well as in patients with multiple VUS.

It should be noted that all genotype-negative subjects also had a severe clinical picture, including syncopal states and SCD followed by resuscitation and ICD implantation. However, the duration of the QTc interval (471 [462.5;477.5] ms) was shorter compared with patients with LQT1 (513.1 [440;630] ms) and LQT2 (553.5 [509;608.5] ms). In genotype-negative patients, disease manifested before beta-blocker therapy, whereas in genotype-positive patients, life-threatening events occurred during beta-blocker treatment, which should be considered when stratifying the risk of adverse events. ICD implantation was required in 14 of 24 (58.3%) patients, including all six genotype-negative patients.

CONCLUSION

The present study investigated the spectrum of clinical manifestations in patients with different genetic types of LQTS (LQT1; LQT2; patients with multiple VUS). Comparative analysis between these groups showed that patients with LQT1 syndrome were significantly less likely to have life-threatening arrhythmias, SCD, and ICD implantation than other LQTS patients, despite early manifestation of the disease and the presence of syncopal states. The most severe form of the disease with pronounced clinical manifestations, clinical deaths followed by resuscitation, and ICD implantation was observed both in the group of subjects with LQT2 and in patients with multiple nucleotide VUS, one of which was in the *CACNA1C* or *ANK2* genes.

The results confirm the importance of genetic testing of patients with LQTS for disease prognosis and stratification of SCD risk.

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LONG-TERM RESULTS OF CARDIAC CONTRACTILITY MODULATION IN PATIENTS WITH CHRONIC HEART FAILURE

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Aim. Evaluate the overall effectiveness of cardiac contractility modulation (CCM) therapy in patients with chronic heart failure of various etiology.

Methods. The study included 61 patients with chronic heart failure (NYHA class II-III), ejection fraction 20-40% and narrow QRS <130 ms, who were implanted the CCM devices. Depending on the etiology of heart failure, ischemic cardiomyopathy prevailed (41 patients). All patients were performed echocardiography, 6-min walk test and Minnesota Living with Heart Failure questionnaire (MHFLQ).

Results. The observation period was 25 months. All 54 patients significantly improved left ventricular ejection fraction from 32.2% to 37.6% (p=0.026) and volume parameters (left ventricle end systolic volume from 150 to 137 ml (p=0.034), left ventricle end diastolic volume from 220 to 201 ml (p=0.044), reduced the heart failure NYHA class ≥1 in 29 (53.7%) patients (p=0.015), increased 6-min walk test from 265 to 343 m (p=0.029), and the MHFLQ improved from 46.1 to 35.8 (p=0.042). Non-ischemic cardiomyopathy was associated with significant improvement in MHFLQ (from 42.7 to 30.3, p=0.029) and lowering the heart failure NYHA class≥1 (83.3%, vs 47.2%, p=0.012) compared to ischemic group.

Conclusion. CCM is safe and effective in patients with chronic heart failure NYHA class II-III, ejection fraction 20-40% and narrow QRS <130 ms. Non-ischemic etiology of cardiomyopathy was associated with significant improvement in MHFLQ and lowering the heart failure class.

Key words: chronic heart failure; ischemic cardiomyopathy; nonischemic cardiomyopathy; cardiac contractility modulation; quality of life

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Chronic heart failure (CHF) remains a major cause of cardiovascular mortality. According to the Fremingham Study [1], the average five-year mortality in the overall population of patients with CHF remains high at 62-65% in men and 45-47% in women. Failure to diagnose in a timely manner, ineffective drug therapy, repeated hospitalizations, and the financial cost of health care determine not only the clinical but also the socioeconomic importance of this disease worldwide.

The prevalence of heart failure is 2-3% of the adult population in developed countries and 6-10% of those over 65 years of age. In Europe and North America, it is the most common cause of hospitalization in this age group [2]. The problem is exacerbated by a general increase in life expectancy and an aging world population. Experts predict that the incidence of heart failure will increase by 40% over the next 15 years [3].

Data from randomized clinical trials have shown that drug therapy with beta-blockers, angiotensin-converting enzyme inhibitors, mineralocorticoid antagonists, renin-angiotensin receptor blockers, and diuretics increases the life expectancy of patients with heart failure [4].

Surgical treatments for heart failure are becoming more common every year. These include implantation of cardiac resynchronization devices, artificial ventricles and, at the beginning of this century, a new treatment, cardiac modulation therapy.

The effect of cardiac modulation therapy has been demonstrated in experimental studies. It is associated with the positive inotropic effect of high amplitude electrical stimuli acting on the myocardium during cardiomyocyte refractoriness. It is achieved by increasing the intracellular supply of calcium ions, which leads to an increase in the contractility of the cell [5, 6]. The practical implementation of the method occurred in 2001, when the same effect was observed in the local application of a large group of cardiomyocytes (endocardial electrical stimulation of the right ventricular myocardium), which prepared the industrial development and appearance of the first prototype of a cardiac contractility modulator

(CCM). At the end of 2001, the first experimental device appeared, implanted for the first time and described by C. Pappone et al. in 2001 [7]. In 2004, the first clinical trial was completed, demonstrating the therapeutic efficacy of the proposed method, with significant improvements in quality of life, 6-minute walk test scores, and left ventricular ejection fraction (LVEF) [8].

Since 2016, CCMs Optimizer IVs and the next generation, Optimizer Smart, without an atrial electrode, have been implanted for the first time in patients with atrial fibrillation (AF) in various centers in the Russian Federation (Impulse Dynamics, Germany). The atrial electrode provides detection of the atrial signal and triggers the atrioventricular delay interval system. The ventricular electrodes are used to apply CCM stimuli and are placed in the interventricular septum between the base and the apical segment. According to the manufacturer's recommendations, the distance between them should be at least 2 cm. The right ventricular electrode picks up the signal first and sets itself higher than the Local Sense (LS) electrode. By default, the device delivers two stimuli from each ventricular electrode with an amplitude of 7.5 V and a pulse duration of 5.14 ms, and the duration of therapy is 7 hours per day (Fig. 1a). The desired percentage of effective stimulation should be at least 90% (Fig. 1b). The device is rechargeable. The manufacturer's stated average battery life for the CCM devices is six years before it needs to be replaced, with a maximum life of 15 years. The latest models (Optimizer Smart) have two configurable operating modes for CCM therapy: ODO-LS-CCM and OVO-LS-CCM. The former is used with an atrial electrode (as with Optimizer IVs) and has some limitations on atrioventricular delay. The patient's baseline interval PQ must be between 25 ms and 398 ms. In addition, this mode blocks CCM therapy when atrial tachysystole occurs (adjustable from 62 to 179 beats per minute, 154 is the default). The second mode (OVO-LS-CCM) is available only on Optimizer Smart models and does not require an implanted atrial electrode. It is independent of atrioventricular latency parameters and can be used in AF (including the persistent form). CCM is blocked in this mode when the ventricular contraction rate exceeds 98 beats per minute, regardless of the baseline heart rate (adjustable between 62 and 110 beats per minute). Optimizer Smart is compatible with standard bipolar electrodes with active fixation and a IS -1 connection. The aim of our study was to evaluate the overall efficacy of cardiac modulation therapy and to compare long-term outcomes in patients with heart failure of different etiologies.

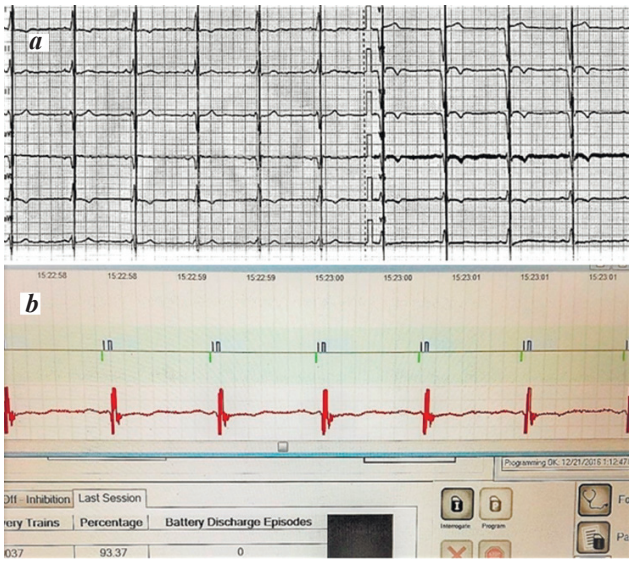

Fig. 1. Modulation of cardiac contractility: ECG shows stimulus artifacts in the refractory part of the QRS complex (a); 93.37% effective therapy (b).

Table 1.

Patient clinical characteristics

Characteristics	All patients (n=61)	ICM (n=41)	NICM (n=20)
Age, years	60.39±12.81	68.32±14.61	55.23±10.21
Men, n (%)	47 (77)	30 (73.2)	17 (85)
Patients with an ICD, n (%)	23 (37.7)	16 (39)	7 (35)
Paroxysmal AF, n (%)	25 (41)	21 (51.2)	4 (20)
Permanent AF, n (%)	8 (13.1)	3 (7.3)	5 (25)
Diabetes mellitus type 2, n (%)	17 (27.9)	12 (29.3)	5 (25)
LV EF, %, M±SD	31.3±7.8	30.8±7.1	33.1±6.9
LV ESV, ml, M±S	152.4±62.8	148.4±53.1	165.4±61.4
LV EDV, ml, M±SD	219.6±81.1	212.5±69.4	244.2±90.2
HF FC (NYHA), Me [Q1; Q3]	2 [2; 3]	2 [2; 3]	2 [2; 3]
QRS, ms, M±SD	117±27.2	121.5±31.6	106±23.7
6MWT, m, M±SD	259±109.6	253.7±99.6	280.4±112.7
MHFLQ score, M±SD	47.3±9.5	48.9±11.4	43.6±8.2
Drug therapy			
ACE inhibitors, n (%)	61 (100)	41 (100)	20 (100)
Beta-blockers, n (%)	60 (98)	40 (97.6)	20 (100)
MCR antagonists, n (%)	55 (90.2)	37 (90.2)	18 (90)
Diuretics, n (%)	57 (93.4)	38 (92.7)	19 (95)
Amiodarone, n (%)	8 (13.1)	6 (14.6)	2 (10)

Note: hereinafter n is the absolute number; Me [Q1; Q3] - median and quartiles; M±SD - mean ± standard deviation; ICM - ischemic cardiomyopathy; NICM - non-ischemic cardiomyopathy; ICD - implantable cardioverter defibrillator; AF - atrial fibrillation; LVEF - left ventricular ejection fraction; LV ESV - end-systolic volume of the left ventricle; LV EDV - end diastolic volume of the left ventricle; HF FC - heart failure functional class; 6MWT - six-minute walk test; MHFLQ - Minnesota quality of life questionnaire in patients with HF; ACE - angiotensin-converting enzyme; MCR - mineralocorticoid receptors.

MATERIALS AND METHODS

Retrospective evaluation of outcomes of 61 CCM devices implanted in patients with heart failure was performed: Optimizer IVs - 27 and Optimizer Smart - 34. The indications for implantation of the cardiac modulation devices were compensated heart failure class II-III according to NYHA, LVEF 20-40%, QRS complex width < 130 ms. In earlier models (Optimizer IVs), the PQ interval (not exceeding 400 ms) was also considered with sinus rhythm being a prerequisite. Patients with documented AF were implanted with Optimizer Smart models.

The mean age of the patients was 60.39±12.81 years, 47 men and 14 women. Thirty-three patients had various forms of AF (25 with paroxysmal and 8 with persistent). All patients received beta-blockers, angiotensin-converting enzyme inhibitors, diuretics, and anticoagulants (patients with AF). No other change in drug therapy was made. Ischemic cardiomyopathy (ICMP) was the predominant etiology of CHF in 41 patients (67.2%). Postinfarction cardiosclerosis was detected in 37 patients (60.6%). Myocardial revascularization had been previously performed in 29 patients (47.5%) (in 11 patients, mammaro-, aortocoronary bypass surgery; in 18 patients, coronary stenting). Twenty patients (32.8%) were diagnosed with nonischemic cardiomyopathy (NCMP). Most patients with NCMP had dilated cardiomyopathy - 15(75%), 3 had postmyocardial cardiosclerosis, and 2 had other idiopathic cardiomyopathies. Twenty-three patients (37.7%) had previously received implantable cardioverter-defibrillators (ICD). Seventeen patients had type 2 diabetes mellitus (28%). The clinical findings of the patients at enrollment are shown in Table 1.

According to the study protocol, the following tests were performed in all patients at enrollment: 12-lead electrocardiography, transthoracic echocardiography (Echo), 6-minute walk test, and the Minnesota Chronic Heart Failure Quality of Life Questionnaire (MHFLQ). The study was approved by the local ethics committee. All patients signed an informed consent form before being enrolled in the study.

Surgical technique

Depending on the number of leads to be implanted, the left subclavian vein was first punctured two or three times and then a pocket was formed for the device under local anesthesia. Next, the endocardial leads were inserted into the right atrial cavity via 7-Fr introducers. The atrial electrode was placed at the atrium of the right atrium by default, and the ventricular electrode was placed in the projection of the midventricular septum. In patients with the dual-electrode system, no atrial electrode was implanted. All electrodes were tested intraoperatively with an ERA 3000 analyzer (Biotronik, Germany). During surgery, standard parameters were measured: sensitivity (P- and R-waves), stimulation thresholds, and electrode resistance. After satisfactory parameters were determined, the device was tested with an Omni programmer (Impulse Dynamics, Germany) via an adapter connected to each electrode. The intervals and accuracy of stimulus application and the sensitivity of individual patients to CCM therapy were selected and evaluated.

In patients with an existing ICD, the optimizer was implanted on the right side. A mandatory test of the interaction of the ICD with the CCM system was performed to exclude cross-perception of the electrical stimuli. The intraoperative electrode parameters and the CCM therapy parameters are listed in Table 2.

All patients were telemetrically monitored with the Optimizer system on day 2 or 3 after surgery. Each patient received a dedicated charger before discharge. Outpatient follow-up of the devices was performed at 3, 6, and 12 months after implantation (further every 6 months), during which the dynamics of the Echo and 6-minute walk test were assessed, as well as the patient's quality of life and the degree of individual sensitivity to CCM therapy.

Statistical analysis

Statistical processing of the data was performed using Statistica 10 software (StatSoft). Qualitative variables were described by absolute and relative frequencies (percentages). Quantitative measures were tested for normality using the Kolmogorov-Smirnov criterion. Data are presented as mean ± standard deviation (M±SD). Some of the data are presented as medians and quartiles. The U-Mann-Whitney test was used for nonparametric data. Qualitative indicators were compared with Pearson's $\chi 2$ test and Fisher's test. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Between 2016 and November 2019, 61 CCM devices (27-Opimizer IVs and 34-Optimizer Smart) were implanted in patients with heart failure. The final follow-up period for the entire group was 25 months. During this time, the cardiovascular mortality rate in the group was 11.5% (7 patients). All patients who died had an ICD. The cause of death was decompensation of heart failure. Significant improvement in LVEF by Simpson's method from 32.2% to 37.6% (p=0.026), decrease in LV end-systolic volume (ESV) from 150 to 137 ml (p=0.034), LV end-diastolic volume (EDV) from 220 to 201 ml (p=0.044), decrease in chronic heart failure class by NYHA by > 1 in 29 (53.7%) patients (p=0.015). 015), increase in 6-minute walk test from 265 to 343 m (p=0.029) and improvement in quality of life

Table 2.

Intraprocedural lead parameters, CCM therapy settings

P-wave, mV, M±SD	2.4±0.9
RV signal amplitude, mV, M±SD	18.6±5.4
LS signal amplitude, mV, M±SD	15.7±5.9
RV capture threshold, V, M±SD	1.1±0.3
LS capture threshold, V, M±SD	1.2±0.4
Comfortable for patients CCM stimuli amplitude, V, M±SD	6.5±1.0
Discomfort during CCM stimulation - change of parameters, n (%)	32 (52.4)
Discomfort during CCM stimulation - lead repositioning, n (%)	16 (26.2)

Note: CCM - cardiac contractility modulation.

according to the MHFLQ questionnaire from 46.1 to 35.8 points (p=0.042) were observed. The mean percentage of therapeutic stimulation was 92.6±9.2% over the entire follow-up period.

Data were then analyzed in subgroups of patients, according to the etiology of heart failure. The 25-month follow-up was 12.2% (5 patients) in the ICMP subgroup (41 patients) and 10% (2 patients) in the NCMP subgroup (20 patients). Causes of death did not differ (decompensation of CHF). Patients in the ICMP subgroup showed a significant improvement in Simpson's LVEF from 31.9% to 36.7% (p=0.038), a decrease in LV CSF from 148 to 139 ml (p=0.042), a decrease in NYHA chronic heart failure class > 1 in 17 (47.2%) patients (p=0.024), and an increase in 6-minute walk test from 259 to 323m (p=0.039). The subgroup of patients with NCMP showed improvement in Simpson's LVEF from 33.2% to 42.5% (p=0.015), decrease in LV ESV from 165 to 135 ml (p=0.027), LV EDV from 242 to 205 ml (p=0.034), decrease in CHF class according to NYHA by > 1 in 15 (83.3%) patients (p=0.002), increase in 6-minute walk test from 282 to 382 m (p=0.012) and improvement in quality of life according to the MHFLQ from 42.7 to 30.3 points (p=0.029). In 53.7% of patients in the total group, in 47.2% in the ICMP subgroup and in 83.3% in the NCMP subgroup, CHF decreased by > 1 grade (Fig. 2). In two subgroups, NCMP was associated with a significant improvement in quality of life, and there was a significant increase in the prevalence of a decrease in CHF > 1 class compared to ischemic patients (83.3% and 47.2%, p=0.012). After 25 months CCM of therapy, there was a trend toward an increase in LVEF and volume measures in patients with NCMP, although the results were not statistically significant. The long-term results are shown in Table 3.

The percentage of therapeutic pacing exceeded 90% in all subgroups. Two patients with Optimizer IVs developed AF over time, reducing the percentage of effective therapy. In addition to atrial tachycardia, frequent ventricular extrasystoles, atrioventricular conduction disturbances, variations in LS signal, and electrode impedance also influenced this parameter. It should be noted that the new-generation Optimizer Smart devices required less reprogramming than the Optimizer IVs.

When assessing a patient's individual sensitivity to CCM therapy, 52.4% of patients experienced significant discomfort during therapy at the maximum settings, requiring them to be lowered. Two (3.2%) patients experienced discomfort after implantation at minimal CCM therapy (even after repositioning of the ventricular electrodes), so that one of the two stimuli had to be deactivated. It was found that patients become accustomed to the perception of CCM therapy in the postoperative period. Thus, 16 patients were able to increase the amplitude of the stimuli without experiencing discomfort as early as 3 months after implantation.

DISCUSSION

In 2014, F. Giallauria et al. performed a meta-analysis of 3 randomized trials that showed a significant increase in peak oxygen consumption (PvO2), 6-minute walk test scores, and quality of life in patients with CHF class II-

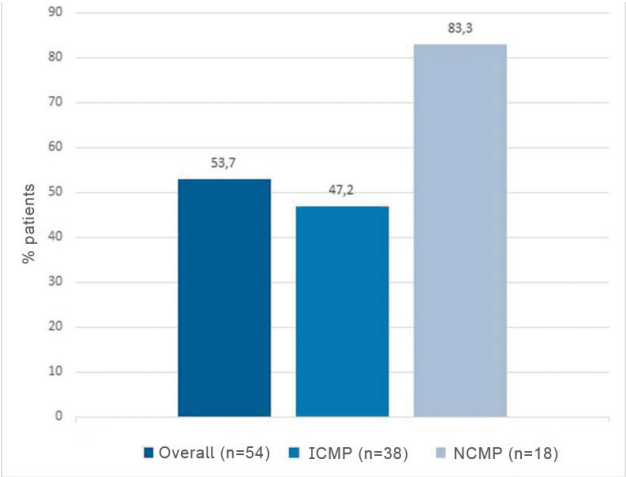

Fig. 2. Decrease in functional class of chronic heart failure according to NYHA by ≥1 in subgroups of patients over 25 months of follow-up, where ICMP - ischemic cardiomyopathy, NCMP - nonischemic cardiomyopathy.

Table 3.

Long-term (25 months) CCM results

Parameters	All patients (n=54)			ICM (n=36)			NICM (n=18)		
	baseline	25 months	P*	baseline	25 months	P*	baseline	25 months	P*
LV EF, %, M±SD	32.2±6.1	37.6±5.4	0.026	31.9±6.2	36.7±5.6	0.038	33.2±6.8	42.5±4.3	0.015
LV ESV, ml, M±SD	150.3±61.9	137+40.2	0.034	148±55.2	139±49.3	0.042	165±61.3	135±27.6	0.027
LV EDV, ml, M±SD	220±75.3	201+51.5	0.044	213±68.1	202±68.4	0.053	242±89.6	205±62.7	0.034
Decrease in HF FC >1, n (%)	-	29 (53.7)	0.015	-	17 (47.2)	0.024	-	15 (83.3)	0.002
6MWT, m, M±SD	265±103	343±102	0.029	259±99.8	323±103	0.039	282±115	382±75.4	0.012
MHFLQ score, M±SD	46.1±9.4	35.8±7.2	0.042	48.8±12.6	39.5±11.3	0.06	42.7±8.6	30.3±6.4	0.029

Note: P* - Significance of within-group differences at 25 months compared to baseline

III according to NYHA, against the background of applied CCM therapy [9]. In a 2016 prospective study, Ming Liu et al. achieved significant reductions in all-cause mortality and mortality due to cardiovascular events in a group of patients with heart failure and LVEF of 25-40% with implanted CCM devices compared with patients on optimal medical therapy by 22% and 32%, respectively, and a 30% reduction in hospitalizations related to heart failure decompensation after 75 months of follow-up [10]. It is also worth mentioning the large randomized multicenter trial FIX-HF -5, which was a milestone for long-term outcomes of CCM and formed the basis for further studies (FIX-HF -5C/C2 et al). FIX-HF -5 included 428 patients with heart failure. The study showed a significant decrease in hospitalizations and mortality (from all causes) over a 6-month follow-up period in patients with implanted CCM [11]. When analyzing efficacy in individual patient subgroups, it was found that particularly pronounced effects were seen in patients with NYHA class III with a LVEF >25%. This subgroup of patients was analyzed in more detail in the FIX-HF-5C study (160 patients with heart failure and an LVEF of 25-45%). The follow-up period was 6 months. There was a significant increase in PvO2 of 0.82 ml/kg/min, 6-minute walk test of 33.7 m, improvement in quality of life by 12 points, decrease in NYHA class by > 1 CHF class in 81% of patients. It has also been shown to significantly reduce cardiovascular mortality and the incidence of hospitalization for CHF [12].

There is currently no clear opinion on whether there is a difference in the efficacy of CCM therapy in patients with different etiologies of CHF. For example, A. Kadish et al [11] showed that the etiology of CHF has no significant effect on CHF class and 6-minute walk test. Single observations describe so-called super-responders among patients with dilated cardiomyopathy [13]. At the same time, according to the original national study [14], the dynamics of Echo parameters of LV EDV and LV ESV differed in the groups of patients with ischemic and non-coronary cardiomyopathy over 1 and 2 years of follow-up (p=0.036 and p=0.0003 for LV EDV and p=0.007 and p < 0.001 for LV ESV), which was due to the initial parameter values. When the initial value was excluded, the dynamics in the two groups were insignificant. Analysis of absolute values of LVEF showed significant differences between the two groups at 12 and 24 months. CCM therapy, (p=0.03 and p=0.01). However, there was no significant difference between the two groups (p=0.09).

It is important to note the individual physical and psycho-emotional sensitivity of patients to CCM therapy. According to our data, more than half (52.5%) required intraoperative reduction of stimulation parameters within the effective range during surgery. Most often, the stimulation amplitude (standard 7.5 V) was reduced, less frequently the pulse duration (standard 5.14 ms). Intraoperative ventricular repositioning was required in 16 (26.2%) patients because therapy was very uncomfortable at the lowest possible setting.

Study limitations

The lack of a control group is a major limitation of this study. A complete analysis of the effects of drug therapy was lacking. Inadequate sample of patients with non-ischemic cardiomyopathy.

CONCLUSION

Cardiac contractility modulators are effective in patients with CHF II-III class by NYHA, 20-40% LVEF, QRS complex width < 130 ms. There was significant improvement in LVEF, decrease in LV volume and CHF class, improvement in 6-minute walk test, and improvement in quality of life at 25 months follow-up. The presence of nonischemic cardiomyopathy was associated with a better decline in heart failure and improvement in patients' quality of life. Despite a trend toward higher LVEF and volume values in patients with NCMP, the results were not statistically significant. New long-term studies in a larger population may be able to determine the optimal indication for CCM therapy and predict efficacy in patients with different etiologies of heart failure. Implantation of cardiac modulation devices, their setting, and ambulatory monitoring require an individualized approach for each patient.

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ANTITHROMBOTIC THERAPY IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION AND HIGH RISK OF STROKE AFTER SUCCESSFUL ENDOVASCULAR LEFT ATRIAL APPENDAGE OCCLUSION

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Aim. To assess the antithrombotic therapy after left atrial appendage occlusion (LAAO) with the Watchman device (WD) and Amplarzer Cardiac Plug (ACP) for stroke prevention in patients with nonvalvular atrial fibrillation (AF) with contraindications for long anticoagulation therapy.

Methods. 200 consecutive patients with nonvalvular AF and contraindications to oral anticoagulation therapy with contraindications for long anticoagulation who undergone LAAO implantation using WD (n=108; WD group) and ACP (n=92; ACP group) were enrolled into this study. Antithrombotic therapies were prescribed after successful LAAO implantation according to indications. Patients were followed at 45 days, 3, 6 and 12 months after enrollment. At each follow-up visit the data regarding clinical events and healthcare utilization were collected. Transesophageal echo (TEE) was perfomed at 45 days and 6 months after successful LAAO implantation. The efficacy end point was the composite of transit ischemic attack (TIA)/stroke, device thrombosis and procedure-related death.

Results. During the follow-up TIA/stroke has occurred in 4.8% of patients in the WD group with no such events in ACP group (4.8% vs 0%, p=0.062). These patients had 4 or more points on the CHA_2DS_2-VASc, and they were prescribed various combinations of antithrombotic therapy, except warfarin, while patients from the WD group with 4 or more points on the CHA_2DS_2-VASc score taking warfarin had no thromboembolic events. Device thrombosis during TEE at 45 days after successful LAAO implantation was confirmed in 3 patients (2,9%) with WD with no such events in ACP group (2.9% vs 0%, p=0.251). The efficacy end point events in all groups were 4.6%: 8 events in WD group (7.6%) and 1 case in ACP group (1.1%). One patient in the ACP group died in 6 weeks after LAAO implantation. No autopsy was performed; therefore, the exact cause of death was not determined (p=0.038). Survival rate showed significantly higher rate events in WD group versus ACP group (p=0.027).

Conclusion. Any combinations of antithrombotic therapy could be prescribed to patients with contraindications for anticoagulant therapy and high risk of stroke who undergone successful (LAAO) implantation with Amplatzer Cardiac Plug. It's possible to cancel oral anticoagulants in this patient. Patients aged 70 and older with a CHA_2DS_2-VASc $\geq$4 and a history of stroke are recommended to take warfarin after successful Watchman Device implantation.

Key words: atrial fibrillation; left atrial appendage occlusion; stroke prevention; antotrombotic therapy; Watchman device; Amplatzer Cardiac Plug

Conflict of Interests: Karapet Davtyan serves as a proctor for Medtronic and Abbott. Andrey Kalemberg is a consultant for Abbott. Dmitriy Lebedev has received a speaker honorarium from Medtronic and Biosense Webster. Other authors have nothing to declare.

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Atrial fibrillation (AF) is a common heart rhythm disorder that is associated with a significantly increased risk of stroke and/or systemic embolism (SE) and death. According to recent data [1-3], 20-30% of all ischemic strokes are attributable to AF, and in the structure of all strokes in patients with AF, cardioembolic strokes account for 65%. The most common source of thromboembolism in AF (90% in nonvalvular AF, 57% in valvular AF) is the left atrial appendage (LAA) [4].

The most important way to prevent thromboembolic complications in patients with AF is long-term (virtually lifelong) anticoagulant therapy. Numerous studies have shown that treatment with anticoagulants significantly reduces the risk of stroke/SE but is often associated with side effects, the most dangerous of which are hemorrhagic complications (especially intracranial and gastrointestinal bleeding), which in some cases can be fatal [5]. In such cases, methods of non-medical stroke prevention become relevant. One of them is endovascular implantation of special devices that isolate the LAA, so-called occluders. According to international clinical guidelines, endovascular isolation of the LAA is recommended for patients with nonvalvular AF and high risk of stroke in whom long-term anticoagulant therapy is contraindicated.

Because the occluder is a foreign body, thrombi may form on its surface, so patients should receive antithrombotic therapy until the device is endothelialized.

Considering that LAA occluders were developed for patients with contraindications to anticoagulant therapy, in clinical practice patients after LAA occluder implantation are often not prescribed these drugs. It is often that the duration of dual antiplatelet agents is shortened, oral anticoagulants (OAC) are used, or treatment variants are limited to anticoagulant monotherapy, or no antithrombotic therapy is prescribed at all [6]. At the same time, after implantation of the Watchman Device (WD), it is recommended to apply the protocol of antithrombotic support used in the randomized clinical trial (RCT) PROTECTAF [7] and PREVAIL [8]. It is reasonable to prescribe warfarin with target international normalized ratio values of 2.0-3.0 in combination with acetylsalicylic acid (ASA). After implantation of the Ampltatzer Cardiac Plug (ACP), it is common to prescribe a combination of ASA and clopidogrel [9]. All these approaches have not yet been studied in RCTs and are part of the local protocols of different medical centers and are not official treatment tactics recommended by the medical community.

In our country, in 2015-2017, for the first time, a registry was established with the participation of 5 medical centers from different regions, comparing the immediate and long-term outcomes of WD and ACP occluder implantation in patients with nonvalvular AF, who cannot take OAC for a long time. These two types of devices are the most widely used in practice worldwide and are approved in the Russian Federation. We compared the safety of the implantation procedure and the effectiveness of prevention of cardioembolic complications in the postoperative period. These data are presented in another journal [10].

The aim of the research is to determine the specifics of antithrombotic therapy after implantation of the LAA occluder used in this study.

MATERIALS AND METHODS

An open-label, multicenter, prospective, nonrandomized comparative study was conducted between May 2015 and December 2017 in five centers of the Russian Federation: National Medical Research Center for Therapeutic and Preventive Medicine, Ministry of Health of the Russian Federation (Moscow); National Medical Research Center for Cardiology, Ministry of Health of the Russian Federation (Moscow); Almazov National Medical Research Center, Ministry of Health of the Russian Federation (St. Petersburg); Meshalkin Medical Research Center, Ministry of Health of the Russian Federation (Novosibirsk); Multidisciplinary Clinic No.1 of Volgograd State Medical University (Volgograd). The study was sponsored by the Ministry of Health of the Russian Federation, which selected the clinics participating in this study and divided the number of included patients by clinic.

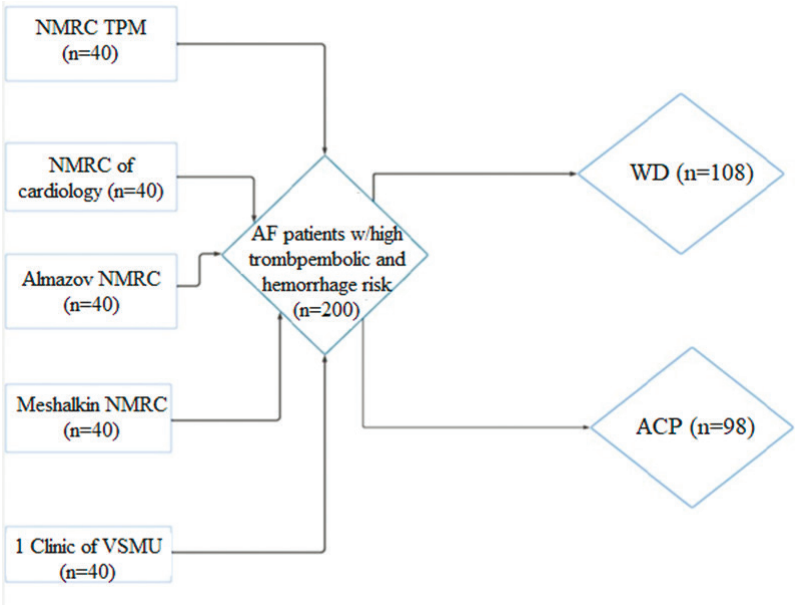

Fig. 1. Study design.

Inclusion criteria for the study were the following: age over 18 years, paroxysmal, persistent, or permanent nonvalvular AF, high risk of stroke/SE (sum of CHA_2DS_2-VASc scores > 2 in men and > 3 in women), no possibility of long-term OAC therapy, written informed consent to participate in the study.

Exclusion criteria: severe concomitant disease with a life expectancy of less than 1-year, valvular pathology requiring surgical correction, refusal to participate in the study.

After a preliminary examination, all patients were implanted with one of the occlusion systems - WD (Boston Scientific, Natwick, MA, USA) or ACP (St. Jude Medical, Plymonth, MA, USA). Accordingly, patients were divided into 2 groups:

WD (n=108) and ACP (n=92) (Fig. 1). The study was not randomized, so the choice of occluding device was at the discretion of the physician and depended on the LAA anatomy and the skills of the respective surgical team. After successful implantation of the LAA occluder, patients were prescribed antithrombotic therapy, which was not strictly regulated by the study protocol and was at the discretion of the treating physician.

The duration of the prospective study was 12 months. During the follow-up period, visits at 45, 90, and 180 days after the procedure were offered, as well as telephone contact with the patient or relatives at 12 months. At 45 and 180 days after implantation of the LAA occluder, a transesophageal echocardiographic examination was performed, and at 180 days, a transthoracic echocardiographic examination was performed. During the transesophageal echocardiographic examination the position of the device, the presence of thrombosis on its surface, and residual blood flow in the LAA were assessed.

The end points for stroke / SE prevention efficacy were 1) stroke / SE; 2) device thrombosis; and 3) procedure-related death. When stroke occurred, diagnosis was confirmed by computed tomography scan or magnetic resonance imaging of the brain. Device thrombosis was verified by the transesophageal echocardiographic examination performed at follow-up visits at 45 and 180 days.

Statistical analysis

Data were statistically analyzed using the statistical program SPSS 23.0 for Windows (SPSS Inc, USA). The nature of the distribution of quantitative characteristics was analyzed using the Kolmogorov-Smirnov one-sample test. The mean (M) and standard deviation (SD) were calculated for a parametric distribution; results are presented as M±SD. The median (Me) and interquartile range (25th percentile; 75th percentile) were calculated for qualitative ordinal and quantitative characteristics whose distribution was nonparametric; results are presented as Me (25%; 75%). When comparing the two groups, we used the Mann-Whitney test for quantitative variables and Fisher's two-sided exact test or Pearson's chi-square for qualitative and ordinal variables. The dynamics of qualitative indicators were assessed with the McNemar chi-square test. Relationships between variables were analyzed using Spearman correlation analysis. Survival analysis was performed by the Kaplan-Meier method; the log-rank criterion was used to compare survival curves.

Table 1.

Non-valvular AF patient characteristics (n=200)

Parameter	All patients (n=200)	Group WD (n=108)	Group ACP (n=92)	p
Age, years (M±SD)	66.8±7.8	67.0±7.9	66.7±7.6	0.488
Males, n (%)	112 (56)	59 (54.6)	53 (57.6)	0.672
Paroxysmal AF, n (%)	58 (29)	30 (27.8)	28 (30.4)	0.539
Persistent AF, n (%)	49 (24.5)	24 (22.2)	25 (27.2)	
Permanent AF, n (%)	93 (46.5)	54 (50)	39 (42.4)	
CHA_2DS_2-VASc*, Me (25%; 75%) M±SD	4 (3; 5) 4.01±1.58	4 (3; 5) 3.99±1.64	4 (3; 5) 4.03±1.51	0.670
HAS-BLED*, Me (25%; 75%) M±SD	3 (2; 3) 2.87±1.02	3 (2; 4) 2.98±0.93	3 (2; 3) 2.74±1.12	0.076
HAS-BLED >3, n (%)	124 (62)	74 (68.5)	50 (54.3)	0.040
Bleeding history, n (%)	79 (39.5)	36 (33.3)	43 (46.7)	0.053
Hypertension, n (%)	166 (83)	98 (90.7)	68 (73.9)	0.002
Hypertension, stage 1, n (%)	24 (14.5)	8 (8.2)	16 (23.5)	0.011
Hypertension, stage 2, n (%)	44 (26.5)	31 (31.6)	13 (19.1)	
Hypertension, stage 3, n (%)	98 (59)	59 (60.2)	39 (57.4)	
Diabetes mellitus, type 2, n (%)	60 (30)	33 (30.6)	27 (29.3)	0.853
Myocardial infarction history, n (%)	33 (16.5)	19 (17.6)	14 (15.2)	0.652
Stroke / TIA, n (%)	67 (33.5)	32 (29.6)	35 (38)	0.209
Ischemic stroke	51 (76.1)	21 (65.6)	30 (85.7)	0.054
Hemorrhagic stroke	8 (11.9)	5 (15.6)	3 (8.6)	0.464
TIA	12 (17.9)	7 (21.9)	5 (14.3)	0.418
2 strokes/TIA	4 (6)	1 (3.1)	3 (8.6)	0.615
Heart failure, n (%)	150 (75)	73 (67.6)	77 (83.7)	0.009
functional class 1 (NYHA), n (%)	9 (6.1)	7 (9.9)	2 (2.6)	0.125
functional class 2 (NYHA), n (%)	100 (68)	44 (62)	56 (73.7)	
functional class 3 (NYHA), n (%)	38 (25.9)	20 (28.2)	18 (23.7)	
Erosive gastritis, n (%)	30 (15)	4 (3.7)	26 (28.3)	<0.001

Notes: AF - atrial fibrillation; TIA - transient ischemic attack; * - scores on a scale.

Differences were considered statistically significant at a two-tailed $p < 0.05$.

RESULTS

Patient characteristics

The study included 200 patients with nonvalvular AF (56% men) aged 40 to 86 years (mean age 67±8 years), with 80% older than 60 years. The sum of CHA_2DS_2-VASc scores ranged from 2 to 8 (Me 4). The sum of HAS-BLED scores ranged from 0 to 6 (Me 3). Table 1 shows the main characteristics of the patients included in the study. As suggested by the data presented, the study included patients at high risk not only for stroke but also for bleeding. One in three patients with AF already had an episode of cerebral circulatory disorder, including four patients who had two episodes each. Of note were the high rates of arterial hypertension (83%), chronic heart failure (75%), and type 2 diabetes mellitus (30%). Although there were statistically significant differences in the incidence of arterial hypertension and chronic heart failure between the WD and ACP groups, the risk of stroke on the CHA_2DS_2-VASc score, which includes both conditions, was almost identical in both groups and averaged 4 points. The median HAS-BLED bleeding risk score was 3 in both groups, allowing us to conclude that patients in both groups were completely comparable in all important characteristics.

Before occluder implantation, the transesophageal echocardiographic examination was performed in all patients to determine the absence of thrombosis in the left atrium and LAA. After successful occluder implantation, 197 patients received antithrombotic therapy (three patients did not have the WD occluder implanted due to failure, so they were not included in further calculations) (Table 2). The following combinations of antithrombotic therapies were prescribed: ASA + clopidogrel, ASA + clopidogrel + warfarin, warfarin, OAC, aspirin + OAC. There were also patients who were not prescribed antithrombotic therapy.

Table 2 shows that antithrombotic therapy was prescribed in 90.9% of patients after successful occluder implantation, with the combination of ASA and clopidogrel used in approximately half of the cases, although the frequency was significantly higher in the ACP group, which may be since this antithrombotic treatment strategy for ACP occluder implantation has been studied and recommended in numerous registries. Similarly, warfarin monotherapy was used significantly more often in the WD group, which is likely since administration of warfarin in combination with antiplatelet therapy was recommended in WD implantation before endothelialization in a single RCT of this device, but to reduce the risk of bleeding, physicians most likely opted for warfarin monotherapy. It is important to emphasize that the prescription of antithrombotic therapy was not regulated by the study protocol and was at the discretion of the treating physician.

One-year follow-up was completed, or primary efficacy/safety end points were met in 186 (93%) of the 200 patients. Three patients were excluded from the study due to failure of WD implantation. Eleven patients discontinued the study during follow-up because they refused treatment, lost contact, or did not show up for another appointment. In these cases, the duration of prospective follow-up was 90 days in 4 patients and 180 days in 7 patients.

During the observation period, ischemic stroke occurred in 5 patients in the WD group (Table 3); there were no cases of SE. No episodes of stroke were observed in the ACP group. Table 3 shows that the incidence of ischemic stroke was 2.5% in all patients with AF. There was a trend toward a higher incidence of ischemic stroke in the WD group (p=0.062).

Of note, patients with nonvalvular AF and high risk of stroke were enrolled in the study: the mean CHA_2DS_2-VASc score was 4.01±1.58. The predicted stroke incidence based on the CHA_2DS_2-VASc scale in these patients was 4.84% per year: 4.76% in the WD group and 4.93% in the ACP group (p=0.531). In all patients, the actual stroke rate was lower than the calculated rate (2.5% vs. 4.8%), which corresponded to a 48% reduction in the risk of stroke, i.e. implantation of any occluder correlated with a reduced risk of ischemic stroke. At the same time, the reduction in stroke risk was 100% in the ACP group and 0% in the WD group, because the actual stroke rate matched the calculated one.

The characteristics of pa-

Table 2.

Frequency and structure of antithrombotic therapy after successful occluder implantation (n=197)

Drugs	All patients (n=197)	Group WD (n=105)	Group ACP (n=92)	p
As+Cl, n (%)	95 (48.2)	43 (41)	52 (56.5)	0.029
As+Cl+warfarin, n (%)	7 (3.6)	5 (4.8)	2 (2.2)	0.452
Warfarin, n (%)	22 (11.2)	18 (17.1)	4 (4.3)	0.004
NOAC, n (%)	34 (17.3)	21 (20)	13(14.1)	0.277
NOAC+As, n (%)	21 (10.7)	11 (12)	10 (9.5)	0.581
Without atithrombotics, n (%)	18 (9.1)	7 (6.7)	11 (11.9)	0.430

Notes: As - aspirine; Cl - clopidogrel; NOAC - non-vitamin-K antagonist oral anticoagulants

Table 3.

Frequency and timing of ischemic stroke in patients with AF (n=197)

Time period	All patients (n=197)	Group WD (n=105)	Group ACP (n=92)	p
First 45 days, n (%)	0	0	0	-
46-90 days, n (%)	2 (1)	2 (1.9)	0	0.500
91-180 days, n (%)	1 (0.5)	1 (1)	0	1.0
181-365 days, n (%)	2 (1.1)	2 (2.1)	0	0.498
Total, n (%)	5 (2.5)	5 (4.8)	0	0.062

tients in the WD group who experienced ischemic stroke during the follow-up period are shown in Table 4. As shown in Table 4, strokes occurred predominantly in patients aged 70 years or older who had a CHA_2DS_2-VASc score > 4 and a history of stroke. Of note, strokes occurred in patients taking various combinations of antithrombotic therapies and none of the patients in the warfarin group.

A follow-up transesophageal echocardiography 45 days after LAA occluder implantation was performed in 192 patients. In the WD group, 3 of them were found to have thrombosis of the device without systemic thromboembolic complications. These patients received subcutaneous injections of enoxaparin sodium at a therapeutic dose for 21 days. In the control group transesophageal echocardiographic examination, no thrombus was found on the surface of the device after 3 weeks. No hemorrhagic complications were noted during treatment with enoxaparin. There were no statistically significant differences in the incidence of device thrombosis between the WD and ACP groups. When a follow-up transesophageal echocardiography was performed 180 days after implantation of a LAA occluder, none of the patients' showed signs of device thrombosis.

The cumulative incidence of performance endpoint events was 4.6%: 8 events (7.6%) in the WD group and 1 event (1.1%) in the ACP group (1 patient in the ACP group died within the first 3 months after successful LAA occluder implantation; no pathological autopsy was performed, so the exact cause of death was unknown) (p=0.038). Kaplan-Meier survival analysis confirmed that the risk for adverse events of the efficacy endpoint was significantly higher in the WD group than in the ACP group (chi-square=4.87; p=0.027) (Fig. 2).

DISCUSSION

After implantation of the Watchman device, it is recommended to use the antithrombotic support protocol used in the RCTs PROTECT-AF and PREVAIL. It is reasonable to administer warfarin with a target international normalized ratio of 2.0-3.0 in combination with ASA at a dose of 75 mg q.d. for at least 45 days after the procedure. After 45 days, a transesophageal echocardiography is performed to clarify the positioning of the occluder. When the device is optimally installed (complete occlusion of the LAA orifice, residual blood flow not exceeding 5 mm) and there is no evidence of thrombosis on its surface, warfarin is discontinued and dual antiplatelet therapy (ASA combined with clopidogrel 75 mg q.d.) is prescribed for up to six months. Six months after implantation, patients should be switched to indefinite ASA monotherapy. If the device is not adequately positioned, warfarin should be continued until the residual blood flow diameter has disappeared or decreased to less than 5 mm [7, 8]. This therapeutic regimen showed greater efficacy than registry data. Therefore, we recommend adherence to this protocol for postoperative platelet aggregation inhibition.

After ACP device implantation, a combination of ASA 75 mg q.d. and clopidogrel 75 mg q.d. is usually prescribed for 3 to 6 months, followed by a transition to ASA monotherapy [9]. Thus, the main difference in the recommended antithrombotic strategy in the case of ACP occluder implantation is that warfarin does not need to be prescribed. However, it should be noted that in this study, the different antiplatelet agents did not lead to thrombotic complications.

In the PROTECT-AF RCT study [7], the reduction in stroke risk with implantation of the Watchman device was 46% in 707 patients with a median follow-up of 18 months; in the CAP study [11], 78% in 566 patients with a median follow-up of 50 months; in the CAP2 study [11], 69% in 578 patients with a median follow-up of 50 months.

The ACR/Amulet device trial registries showed a 60-65% reduction in stroke risk: a 59% reduction in 1,001 patients with a mean follow-up of 1.3 years [9]. In these studies, the efficacy of LAA occluder implantation was assessed not only by the incidence of thromboembolic events

Table 4.

Characteristics of patients from the WD group who had ischemic stroke during the follow-up

Parameter	# of patient				
	1	2	3	4	5
Age, years	79	70	62	72	70
Sex	male	male	male	female	female
AF type	persistent	permanent	paroxysmal	permanent	permanent
CHA2DS2-VASc*	7	6	4	5	4
HAS-BLED*	5	2	5	3	3
Stroke history	yes	yes	yes	yes	no
Antithrombotics**	no	As + Cl	NOAC + As	As + Cl	NOAC
LA dilatation	yes	yes	yes	yes	yes
LV EF <40%	yes	no	no	no	no
SPAP >30 mm Hg	yes	no	no	yes	yes
SEC	yes	yes	yes	yes	yes
SEC grade	2	2	2	2	4

Notes: AF - atrial fibrillation; ** - after implantation of a left atrial appendage occluder; LA - left atrium; LV EF - left ventricular ejection fraction; SPAP - systolic pulmonary artery pressure; SEC - spontaneous echocontrasting

such as stroke/ SE, device thrombosis, and cardiovascular/ unexplained death, but also by the reduction in stroke risk compared with the predicted incidence calculated using the CHA_2DS_2-VASc score.

In our study, immediately after ACP device implantation, anticoagulant drugs were discontinued in 63 patients (68.5%), whereas no antithrombotic medications were prescribed in 11 cases (11.9%). In the patient group WD, only 50 cases (49.0%) did not receive anticoagulant therapy after successful LAA occluder implantation. No thromboembolic events or device thrombosis were observed in the ACP group.

In our study, the reduction in the risk of stroke in all patients with AF was 48% (0% in the WD group, 100% in the ACP group). During the follow-up period, 5 cases of ischemic stroke were observed in the WD group, whereas there were no strokes in the ACP group. When comparing the groups in terms of stroke incidence, there was a tendency for an increase in the WD group (4.8% vs. 0%; p=0.062). A possible reason for this could be a design feature of the WD, namely the presence of a permeable polyethylene membrane on the left atrium. Thrombus may form on the surface of this membrane before endothelialization is complete. We should note right away that the same property of the occluder may be the main cause of device thrombosis, the incidence of which was also slightly higher in the WD group (2.9% vs. 0%; p=0.251); there were no cases of device thrombosis in the ACP group.

The cumulative incidence of ischemic events was evaluated in 32 of 66 studies (n=7689): it was 13.2% (37/280) in patients with device thrombosis and 3.8% (285/7399) in patients without thrombosis (OR 5.27; 95% CI 3.66-7.59; p < 0.001). In a sensitivity analysis including only RCTs and prospective multicenter registries, the device thrombosis rate was 3.7%, and thrombosis was also associated with a higher rate of ischemic events (13.5% versus 4.4% in patients without thrombosis; OR 4.15; 95% CI 2.77-6.22; p < 0.001) [12].

In our study, the thrombosis rate of the WD was similar to the meta-analysis data (2.9% versus 3.1%), whereas the thrombosis rate of the ACP device was lower (0% versus 3.6%). In all three cases identified in our work, device thrombosis was not accompanied by systemic thromboembolic complications. We should also note that all episodes of WD thrombosis were detected by transesophageal echocardiographic examination at 45 days, against a background of 3 weeks of therapy with therapeutic doses of enoxaparin, thrombus were completely resolved, and no thrombus was detected on the device surface in any patient 180 days after implantation of the LAA occluder.

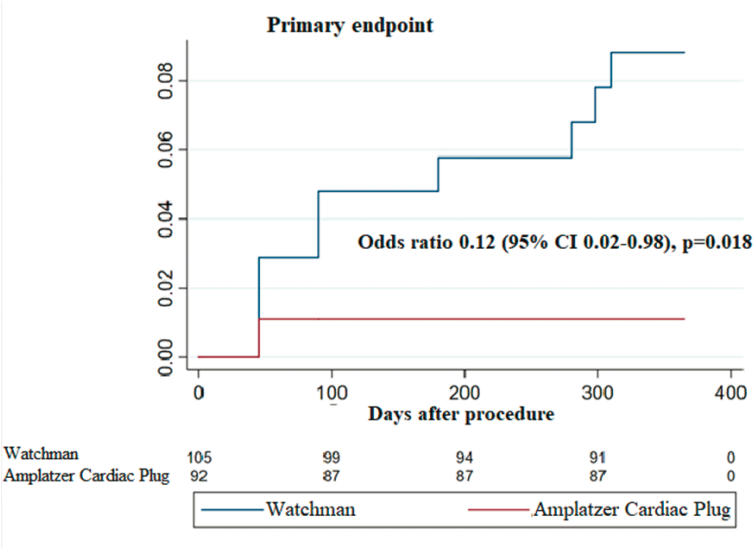

Fig. 2. The primary efficacy endpoint's adverse events depend on the occluding device (n=197).

CONCLUSION

After implantation of the ACP Occluder, it is possible to discontinue OAC and prescribe one of the combinations of antithrombotics accepted in clinical practice. This is particularly important for patients with contraindications to anticoagulant therapy and a very high risk of stroke who require effective non-drug stroke prevention. Warfarin is recommended for patients aged 70 years or older with a CHA_2DS_2-VASc score > 4 and a history of stroke after implantation of the Watchman Device closure device. It is not recommended to implant the Watchman Device in these patients if warfarin is not available.

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PERMANENT PACING IN CHILDREN: RESULTS OF FOLLOW-UP, ASSESSMENT OF COMPLICATIONS

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Aim. To present the experience and assess the complications of permanent pacing in children with bradyarrhythmias based on long-term follow-up.

Methods. Data of 145 children with structurally normal heart with implanted pacemakers at the age from 1 month to 18 years were retrospectively assessed. The follow-up was from 1999 to 2020 years. Epicardial pacemaker was implanted in 71 children, endocardial - in 74. The mean age of the primary implantation was 8.67±5.2 years.

Results. The following complications were disclosed: hemodynamic complications (heart chamber enlargement in dynamics and/or development of dyssynchrony, the appearance and increase in the regurgitation degree on the atrioventricular valves), bacterial endocarditis, hemopericardium, subclavian vein occlusion, pericarditis, infection of the pacemaker and its pocket, leads dislocation and fracture. With epicardial pacing various complications were detected in 24 (33.8%) examined patients, with endocardial - in 37 (50%). Hemodynamic complications with epicardial permanent pacing are associated with intraventricular dyssynchrony due to implantation of a ventricular lead on the lateral wall or the right ventricular outflow tract. Hemodynamic complications were not recorded in patients that performed the implantation of an epicardial lead at the left ventricular (LV) apex.

Conclusion. Children with pacemakers require careful follow-up. The most rational is the use of a primary epicardial pacemaker system with lead implantation on the apex of the LV. Such approach allows the veins to be preserved for endocardial stimulation at an older age, and to prevent hemodynamic complications. Neither epicardial nor endocardial pacemaker implantation guarantee the absence of complications. However, compliance with the above conditions will allow achieving high efficiency and safety of cardiac stimulation in children.

Key words: pacing; methods of lead implantation; complications; children

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Currently, pacemaker implantation is the only treatment option for bradyarrhythmias. Pacing in pediatric practice requires the high professionalism of specialists, especially in children, considering the prospect of lifelong pacing.

Continuous technical improvements in pacemakers have led to the emergence of modern physiological pacing systems that can be safely used in children of all ages due to their size and functionality [1]. When deciding on the optimal pacing system, the indications for permanent stimulation, the advantages and disadvantages of the different stimulation modes, and the implanting methods of pacemakers should be considered. Factors that determine the specifics of device implantation in children are: anthropometric data of the child and their correspondence to the size of the pacemaker and leads, the need for long-term (lifelong) pacemaker therapy, the high activity level of the child, intense physical development (the need for implantation of leads “with reserve” and their replacement), in some cases concomitant congenital heart defects, especially when intracardiac shunts are present, risks of possible complications that develop against permanent pacemaker [2-4].

Indications for pacemaker implantation have changed as new information about the efficacy and safety of permanent pacing has become available and because of improvements in medical technology [5, 6]. Today, many specialists use the indications for pacemaker implantation in children summarized in the 2013 review by the European Association of Arrhythmologists and Association of European Pediatric Cardiologists working group [7]. However, it should be noted that the level of evidence for these recommendations is low. Most recommendations for children requiring permanent pacemaker therapy are not supported by prospective studies and are based only on expert opinion. Generalizing the experience in the field

of pediatric pacing will allow specialists to make more informed decisions when choosing the implantation method in a particular patient, considering potential complications, planning dynamic monitoring, and clarifying indications for pacemaker implantation.

The purpose of this publication is to present the experience with the permanent pacemaker in children with bradyarrhythmia and to analyze the complications that arise from long-term follow-up.

MATERIALS AND METHODS

An analysis of pacemaker complications in children with structurally normal hearts was performed. The observation period is from 1999 to 2020, and the study included 145 patients aged 1 month to 18 years, including 103 patients with complete atrioventricular block (AVB), 25 children with sinus node disease (SND), and 17 with binodal disease. The mean age of the patients at the time of primary pacemaker implantation was 8.67±5.2 years. The age distribution was as follows: children under one year - 12 (8.3%) patients, from one to three years - 28 (19.3%) patients, from 3 to 10 years - 37 (25.5%) children. Most of the (68 (46.9%)) patients were children over 10 years of age. The division into age periods of childhood is due to the expediency of more detailed assessment of indicators in this study due to the peculiarities of the morphofunctional state of organs and systems in the process of growth and development of a child.

Inclusion criteria for patients:

- Presence of AVB, SND, or binodal pathology according to ECG and Holter monitoring (HM);
- Absence of evidence of a current inflammatory process according to blood tests;
- Absence of congenital heart disease.

On admission, all patients underwent a general clinical examination, including history, complaints, physical examination, blood cell count, urine tests, biochemical blood tests, coagulation profile, 12-lead ECG, daily ECG monitoring, echocardiography (Echo), and chest X-ray.

All patients underwent primary pacemaker implantation. In the postoperative period, repeated examinations including ECG, Echo, HM, chest X-ray in 2 projections, and control of pacemaker parameters were performed 5-7 days after the procedure. Follow-up examination, including ECG, Echo, HM, control of pacemaker parameters was performed after 6 and 12 months and then annually. Chest X-ray in two projections was performed once every 3 years after primary pacemaker implantation or more frequently, depending on the indications.

The indications for pacemaker implantation were determined considering the national recommendations developed on the basis of the recommendations of the European Association of Arrhythmologists and Pediatric Cardiologists [7]. The methods of implantation and the modes of pacing according to the age of the patients are shown in Table 1. In 5 patients with atrial pacing (AAI), a stimulator was implanted because of SND associated with symptomatic bradycardia, and 118 patients with complete AVB and binodal pathology were implanted with dual-chamber pacing systems. One patient with complete AVB and left bundle branch block was implanted with a three-chamber pacemaker system. Single-chamber ventricular pacemaker systems were implanted in 21 patients, 3 of whom were less than 1 year of age. In choosing the VVI pacing mode during primary pacemaker implantation, we were guided by the goal of minimizing the risk of complications related to excessive lead length in both endo- and epicardial approaches, avoiding sternotomy, and using a subxiphoid approach in epicardial pacing. In addition, VVI pacing at minimal frequency does not suppress AV junction function in patients with partially preserved AV conduction.

Most patients with dual-chamber epicardial pacing underwent partial sternotomy, whereas patients with single-chamber epicardial pacing used a subxiphoid approach without sternotomy.

Epicardial pacemaker implantation was performed in 71 children and endocardial implantation in 74 children. The mean age of patients with an epicardial ECS system at the time of primary implantation was 3.86±3.35 years; the mean age of patients with an endocardial ECS system at the time of primary implantation was 13.28±3.39 years. The mean duration of pacing from the time of primary implantation to the detection of complications was 2.10±2.7 years.

Statistical analysis. Statistical processing of data was performed with Statistica 10 software. Quantitative indicators are presented as M±σ, where M is the arithmetic mean and σ is the standard deviation. Differences in qualitative indicators were assessed using the $\chi 2$ criterion. Differences were considered significant at a significance level of $p<0.05$.

RESULTS

In patients with epicardial pacemaker implantation, various complications were noted in 24 (33.8%) subjects and in 37 (50%) with endocardial implantation (Table 2). The following complications were noted: hemodynamic complications (increase in ventricular dynamics and/or development of interventricular dyssynchrony, occurrence and increase in the degree of regurgitation at the atrioventricular valves), bacterial endocarditis, hemopericardium, usually associated with perforation of the right atrium, occlusion of the subclavian vein, pericarditis, infection of the pacemaker and its pocket, pacemaker dislocation, and lead failure.

In the endocardial implantation method, the ventricular lead was placed mainly in the right ventricular (RV) apex region. In epicardial pacing system, the ventricular lead was localized in the left ventricular (LV) apex and RV apex in 27 (38%) patients, and in 44 (62%) patients - in the RV free wall. It should be noted that in the “old era” (before 2013), when an epicardial pacing system was implanted, the ventricular lead was localized in the free RV wall. Most Russian clinics are still oriented to this approach. In recent years, in our clinic, during primary epicardial pacing, the ventricular lead is localized in the LV apex or RV apex.

In epicardial implantation, the most frequent complications were related to the development of hemodynamic changes in the form of signs of pacemaker-induced cardiomyopathy due to stimulation of the RV free wall. Stimulation of the above-mentioned zone leads to the development of electrical and mechanical dyssynchrony and LV dysfunction. It should be noted that the patients who under-

went primary epicardial lead implantation in the LV apex (n=27, 38%) did not have hemodynamic complications.

In the early postoperative period after epicardial pacemaker implantation, two patients were diagnosed with pericarditis and 1 patient was found to have hemopericardium. In the remote postoperative period, lead dislocation and their integrity failure were noted in 4 patients, including cardiac strangulation in one patient with congenital AVB. This complication was discovered 2 years after primary epicardial pacemaker implantation, which was performed at 1 year of age.

In the single-chamber epicardial pacing mode of VVI, only hemodynamic complications related to LV dyssynchrony were observed. In the dual-chamber pacing (DDD) mode, complications directly related to the epicardial leads were noted in addition to hemodynamic complications (Table 2).

In the transvenous (endocardial) pacing mode, complications related to hemodynamic disturbances were noted in the same number of patients as in the epicardial pacing group (Table 2). However, there were several differences in the quality of hemodynamic complications. Whereas in the epicardial pacing group, all patients with hemodynamic complications had evidence of pacemaker-induced cardiomyopathy, in the endocardial pacing group, hemodynamic complications were represented by pacemaker-induced cardiomyopathy in only 8 (47%) patients and by tricuspid regurgitation in 9 (53%) patients. The more frequent occurrence of pacemaker-induced cardiomyopathy in children with epicardial pacing compared to patients with endocardial pacing was statistically significant (p=0.047) and was observed only in patients with epicardial implantation of the ventricular lead in the region of the RV free wall.

In the group of patients with endocardial pacing, the early postoperative period was complicated by hemopericardium associated with perforation of the right atrium in 3 patients. Pericarditis was observed in one patient. In the remote postoperative period, one of the most serious complications of endocardial cardiac pacing was registered - the development of infective endocarditis. This complication occurred 10 years after primary pacemaker implantation and required open heart surgery with artificial circulation, deimplantation of the entire endocardial system, tricuspid plastic surgery followed by epicardial pacemaker implantation. In addition, remote postoperative complications of endocardial pacing were observed in two other patients: in one case - occlusion of the subclavian vein, in the other - infection of the pacemaker pocket.

DISCUSSION

One of the controversial and unresolved issues in pediatric pacing remains the choice of implantation method:

Table 1.
Pacing modes and methods of implantation of a pacemaker system in children with a structurally normal heart depending on age, n (%)

	Implantation approach							
	Endocardial, n=74 (51.03%)				Elicardial, n=71 (48.97%)			
	AAI n=5 (3.45%)	DDD n=57 (39.31%)	VVI n=12 (8.27%)	Всего n=74 (51.03%)	DDD n=61 (42.07%)	DDD-biV n=1 (0.69%)	VVI n=9 (6.21%)	Всего n=71 (48.97%)
< 1 year					9 (6.21)		3 (2.07)	12 (8.28)
1-3 years		1 (0.69)		1 (0.69)	23 (15.86)	1 (0.69)	3 (2.07)	27 (18.62)
3-7 years	1 (0.69)		1 (0.69)	2 (1.38)	16 (11.03)		3 (2.07)	19 (13.1)
7-10 years	1 (0.69)	6 (4.14)	2 (1.38)	9 (6.21)	7 (4.83)			7 (4.83)
> 10 years	3 (2.07)	50 (34.48)	9 (6.2)	62 (42.75)	6 (4.14)			6 (4.14)

Table 2.
Complications during epicardial and endocardial stimulation depending on the stimulation mode, n (%)

	Implantation approach					
	Endocardial, n=74 (51.03%)			Elicardial, n=71 (48.97%)		
	AAI n=5 (3.45%)	DDD n=57 (39.31%)	VVI n=12 (8.27%)	DDD n=61 (42.07%)	DDD-biV n=1 (0.69%)	VVI n=9 (6.21%)
Hemodanamical		12 (21.05)	5 (41.6)	14 (22.58)		3 (33.3)
Dislodgement*		11 (19.29)	2 (16.6)	4 (6.45)		
Pericarditis		1 (1.75)		2 (3.22)		
Hemopericardium		3 (5.26)		1 (1.61)		
Endocarditis			1 (8.33)			
Pacemaker infection		1 (1.75)				
Vein occlusion			1 (8.33)			
Overall		28 (49.12)	9 (75)	21 (33.87)		3 (33.3)

Notes: * - a lead disintegrates

epicardial or endocardial, depending on the age of the patient. Each method has its own advantages and disadvantages [8, 9]. Our analysis confirms this and shows that neither the epicardial nor the endocardial approach guarantees the absence of complications.

With endocardial pacing, complications include isolation failure, lead dislocation, cardiac perforation, tricuspid regurgitation, and the development of bacterial endocarditis. Endocardial pacing systems carry a high risk of venous occlusion and venous thrombosis in children, and therefore venous accesses cannot be reused in the future, leading to more complicated patient management [10, 11]. The increase in the degree of tricuspid regurgitation is related to both the excessive lead loops required due to patient growth and the number of leads passed through the patient's orifice due to transvenous reimplantation during the patient's lifetime. And because pacemaker has been required for several decades, a large number of leads passing through the transvenous valve only exacerbates intracardiac hemodynamic disturbances. Complications related to infection of the implanted devices range from 1% to 19% according to various authors [12]. At the same time, the patient can be definitively cured only if the infected leads and the pacemaker are completely removed, which concretizes the unsolved problem of endocardial lead extraction in children.

In contrast to endocardial pacemaker implantation, the most common mechanical complications associated with epicardial pacing are lead fractures, less lead "survival," and risks associated with thoracic surgery [13]. However, the problem of epicardial leads "survivability" observed in the early era of pacing is less relevant today. Steroid coating limits the inflammatory response at the contact site between the lead and cardiac tissue, resulting in lower acute and chronic pacing thresholds and longer battery life. When comparing modern steroid-coated endocardial and epicardial leads, it has been shown that there is almost no difference in the "survival rate" of the leads. Mechanical complications of epicardial pacing include rare but very serious cardiac strangulation, which is limited to the pediatric population. As the child grows, dislocation of the lead loop causes strangulation of the heart and, depending on where maximal compression occurs, can lead to coronary artery stenosis, valve insufficiency, or ventricular dysfunction, followed by myocardial infarction, which can be fatal. Particular attention should be paid to children implanted before 6 months of age because they have more intense physical development and a high likelihood of cardiac strangulation due to the excessive length of the leads in the mediastinum. Annual Echo and control chest X-ray in 2 projections every 3 years in asymptomatic patients are recommended to diagnose this complication [14-16]. To date, only 20 cases of cardiac strangulation have been described in the world literature [17, 18]. Our hospital has experience of treating such a complication in 2 patients: one of them had a pacemaker implanted at 1.5 months of age due to complete AVB after surgical correction of congenital heart disease [19]; the other patient had a pacemaker implanted at 1 year of age due to congenital AVB; 2 years after primary epicardial implantation, lead dislocation was detected. In the first clinical case, surgical correction was performed (pacemaker and leads replacement). In the second clinical case, a similar surgical procedure is planned.

It should be noted that the RV apex is the most common stimulation zone when a transvenous (endocardial) approach is used, which ensures a stable position of the lead and the absence of its displacement. However, prolonged apical endocardial pacing of the RV may lead to pacemaker-induced cardiomyopathy [20]. His bundle pacing seems promising to prevent this complication. It improves the function of the LV and alleviates the symptoms of heart failure due to ventricular dyssynchrony. This technique is currently gaining popularity in adult patients requiring cardiac resynchronization therapy, but experience with its use in children, although limited, is very promising [21].

In recent years, publications have discussed the areas of ventricular pacing for both types of lead implantation. Stimulation of the "optimal site" should aim to prevent pacemaker-induced mechanical dyssynchrony, especially in children implanted with a stimulator in early childhood with the prospect of lifelong pacing. Stimulation of LV apex and lateral wall during epicardial pacing has been shown to have the greatest potential to prevent dyssynchrony and reduce LV contractile function, whereas LV exit and lateral wall pacing is associated with a high risk of LV dysfunction [22, 23], consistent with our findings. Pacemaker-induced cardiomyopathy was noted only in patients with epicardial pacing of the LV free wall, and no hemodynamic complications were noted in patients with apical LV pacing.

The indications for pacemaker implantation in children do not provide clear recommendations for the choice of implantation method. For example, the 2013 consensus recommendations of the European Association of Arrhythmologists and the Association of European Pediatric Cardiologists recommend implantation of systems using only epicardial leads in children weighing up to 10 kg; in other patients, it is recommended to use predominantly transvenous systems [7]. However, considering the current global trends and the experience of leading foreign hospitals, epicardial lead implantation techniques are increasingly used, both because of the more serious complications of transvenous pacemaker implantation and because of the possibility of selecting the hemodynamically optimal pacing zone in the epicardial technique to prevent pacemaker-induced dyssynchrony [22, 23]. The epicardial approach is preferable for any initial pacemaker implantation in a child because it allows postponing as much as possible the installation of an endocardial pacing system, the use of which updates the previously unsolved problem of endovascular lead extraction in children. In most cases of complications, endocardial lead extraction is performed during open-heart surgery with the use of an artificial circuit, and the techniques of minimally invasive laser or mechanical lead removal in children have not yet achieved positive results not only in Russia but also worldwide [25-28].

Study limitations. In our study, direct statistical comparison of patients with epi- and endocardial pacing was difficult because these patients were not initially comparable in terms of age and type of complications. This factor contributed to the fact that no differences were found in the

number of complications of epi- and endocardial pacing in different age groups in our study.

CONCLUSION

The presence of a permanent pacemaker in children, in contrast to adult patients, requires more thorough dynamic monitoring, including HM, detailed Echo, chest X-ray in 2 projections, evaluation of pacemaker parameters. Currently, there are still unresolved issues in pediatric pacemaker therapy. The most important of these are the choice of implantation method and the prevention of complications occurring during continuous pacing.

According to recent studies and our experience, the use of a primary epicardial pacing system with lead implantation at the LV apex makes the most sense. It allows saving veins for endocardial pacing in older age and preventing the development of hemodynamic complications. It should be considered that neither epicardial nor endocardial methods of cardiac pacing guarantee the absence of complications, but compliance with the above conditions allows high efficiency and safety of cardiac pacing in children. The resolution of these issues is of great importance for the development of pediatric pacing.

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PECULIARITIES OF DABIGATRAN PHARMACOGENETICS: LITERATURE REVIEW

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Dabigatran is highly effective oral anticoagulant used in patients with atrial fibrillation, venous thrombosis, pulmonary embolism, orthopedic surgery. The most important role in activation and transport of dabigatran play hepatic carboxylesterase-1 (CES-1) and P-glycoprotein. To date were studied different polymorphisms that affect the pharmacokinetics of dabigatran such as rs2244613 (C > A), rs8192935 (T > C) u rs71647871 (G > A), rs1128503 (1236 C > T), rs2032582 (2677 G > T), rs1045642 (3435 C > T) u rs4148738 (G > A) and others. At the same time, there is no need of dabigatran pharmacogenetics testing in routine care. On the other side, existing literature data is often controversial, that's why future studies are needed to answer the above-mentioned question.

Key words: dabigatran; pharmacodynamics; pharmacokinetics; pharmacogenetics; atrial fibrillation

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Dabigatran is known to be a direct oral anticoagulant whose mechanism of action is limited to direct inhibition of the coagulation factor thrombin-IIa [1]. This drug was developed primarily as an alternative to the indirect anticoagulant warfarin because numerous shortcomings of the latter made it difficult to use it in clinical practice. Dabigatran was first approved in Europe, then in 2010 in the United States and subsequently in Russia for the prevention of stroke in patients with atrial fibrillation (AF) [2]. Since then, it has been used in patients with deep vein thrombosis, pulmonary embolism, and in orthopedics [3, 4]. The advantages of dabigatran include good tolerability, ease of use, effective anticoagulant activity, predictable pharmacokinetics, and no need for routine coagulation monitoring during administration [1, 3, 5]. However, there is now evidence of the pharmacokinetics and pharmacodynamics of this drug in various patients who may present with thrombosis or hemorrhage in clinical practice [6-8].

The aim of this review was to evaluate the impact of different genetic polymorphisms on the pharmacodynamics and pharmacokinetics of dabigatran.

DABIGATRAN PHARMACODYNAMICS AND PHARMACOKINETICS

Dabigatran is known to be administered as a prodrug, dabigatran etexilate, with a bioavailability of about 7% [9]. Dabigatran etexilate is a substrate for the transport molecule P-glycoprotein and can therefore be combined with inducers (e.g., rifampicin, antiretroviral drugs, carbamazepine, etc.) as well as inhibitors (e.g., cyclosporine, clarithromycin, dronedarone, amiodarone, verapamil, ticagrelor, etc.) of this molecule, thereby contributing to a decrease or increase in the plasma concentration of this drug, respectively [10]. In the latter case, the risk of bleeding may increase with dabigatran [11]. For example, in a study by M.Bernier et al. (2019), bleeding occurred in 30.4% of patients taking dabigatran together with P-glycoprotein inhibitors, compared with 8.6% of patients not taking the aforementioned drugs [12]. Therefore, caution should be exercised when combining dabigatran with the above-mentioned drugs, and in some cases, it is even contraindicated, e.g., in patients receiving cyclosporine, dronedarone, intraconazole, ketoconazole for systemic use, and tacrolimus [11, 13]. Dabigatran etexilate is activated by intestinal (*CES2*) and hepatic (*CES1*) carboxylesterase to form short-lived metabolites, BIBR 951 and BIBR 1087 [8, 10]. The aforementioned metabolites are hydrolyzed by hepatic carboxylesterase *CES1* in hepatocytes to form dabigatran, the active drug [4, 10, 14, 15]. The formation of dabigatran from the prodrug is more dependent on *CES1* [8]. At the same time, it should be noted that activation of *CES2* can compensate for *CES1* deficiency in patients. Dabigatran has a low plasma protein binding capacity of 35% [10, 16], regardless of its concentration, so it can be excreted by hemodialysis. Dabigatran is partially conjugated with active glucuronic acid to form four isomers of pharmacologically active glucuronides [15, 17]. Therefore, the total plasma concentration of this drug includes free and glucuronide-containing dabigatran and peaks after approximately 1.5 hours [17]. The half-life of dabigatran is relatively long, ranging from 12-17 hours [9]. This drug is not metabo-

lized by cytochrome P450 and therefore has no effect on it except at concentrations above the therapeutic range [9, 16]. In addition, dabigatran does not interact with drugs metabolized by the above system [17]. The drug is excreted mainly through the kidneys by 80-90% [10].

DABIGATRAN PHARMACOGENETICS

Genetic polymorphisms of *CES1* and P-glycoprotein that play an important role in dabigatran activation and transport have been studied to date.

Genetic polymorphisms of CES1

The *CES1* genes are located on chromosome 16 and contain 14 exons [10]. More than 2000 different polymorphisms are currently known for *CES1* [8], but only three of them have been shown to be related to the pharmacokinetics of dabigatran: rs2244613 (C > A), rs8192935 (T > C), and rs71647871 (G > A) [6-7, 18]. According to G. Pare et al. (2013), the rs2244613 minor allele was associated with a 15% reduction in minimal dabigatran concentration and a 27% reduction in relative bleeding risk, with this polymorphism present in 32.8% of patients with AF from the RE-LY study [6]. The authors also found that the minor allele of the rs8192935 polymorphism was associated with a 12% reduction in peak dabigatran concentration [6]. In a study by C. Dimatteo et al. (2016) conducted in 92 patients with AF, it was found that the T allele rs8192935 was associated with a reduction in dabigatran concentration compared with carriers of the CC-genotype, with heterozygotes showing a 3% reduction in the residual equilibrium concentration of this drug and homozygotes showing an 11% reduction [7]. However, in heterozygotes and homozygotes for the rs2244613 polymorphism, the residual equilibrium concentration of dabigatran was reduced by only 2% and 3%, respectively [7]. According to D.A.Sychev et al. (2018), no significant effect of the rs2244613 genetic polymorphism on the minimal dabigatran concentration was found in 60 patients undergoing knee replacement, with the minor allele occurring in 27.5% of cases [18]. Another study by this author in patients with AF and stage 3 chronic kidney disease found that the CC-genotype of the rs2244613 polymorphism was associated with a 70% reduction in the dabigatran concentration/dose ratio compared with patients with the AA-genotype [19]. The authors emphasized that in the above patient cohort, investigation of the rs2244613 polymorphism could help improve the safety of dabigatran [19].

In a landmark study by J. Shi et al. (2016), dabigatran etexilate activation was found to be dependent on the rs71647871 polymorphism, which leads to disruption of *CES1* function, associated with a reduction in the conversion of this prodrug and its metabolites to active dabigatran [8], but to our knowledge, no studies have been conducted to evaluate the impact of this polymorphism on dabigatran concentration in clinical practice. In a prospective study by Qiuyi Ji et al. (2021) involving 198 patients with AF taking dabigatran, the minor C allele of the *CES1* rs8192935 polymorphism was associated with an increase in the minimal plasma concentration of this drug [20]. The association described above was also found in patients with the minor A allele of the *CES1* rs2244613 polymorphism (increased minimal plasma concentrations of dabigatran). At the same time, these patients had an increased risk of minor bleeding [20]. A study by Y. Liu et al. (2021) performed in 106 patients showed that the *CES1* rs2244613 polymorphism had no effect on the peak concentration of dabigatran. In contrast, the *CES1* rs8192935 polymorphism was associated with an increase in the peak concentration of this drug [21].

Genetic polymorphisms of P-glycoprotein

The P-glycoprotein is encoded by the gene *ABCB1* (another name for MDR1), which is located on chromosome 7 and contains 29 exons [10]. Currently, more than 1200 polymorphisms of this gene are known, of which the most studied are rs1128503 (1236 C > T), rs2032582 (2677 G > T), rs1045642 (3435 C > T), and rs4148738 (G > A). Different haplotypes are formed from different combinations of the rs1128503, rs2032582, and rs1045642 polymorphisms: *ABCB1*1*, *ABCB1*2*, *ABCB1*13* [22, 23]. The above polymorphisms affect the pharmacokinetics of many drugs that are substrates for P-glycoprotein [10]. At the same time, only the rs1045642 and rs4148738 polymorphisms have been studied for their association with an increase in peak dabigatran concentration [6, 18]. In a study by G.Pare et al. (2013), the presence of the rs4148738 polymorphism was associated with a 12% increase in peak dabigatran concentration, but not with bleeding or ischemic events [6]. At the same time, this position was not confirmed in the work of C.Dimatteo (2016), D.A.Sychev et al. (2018), in which the rs4148738 polymorphism was not associated with significant changes in peak and minimum concentrations of dabigatran [7, 18]. In a study by Q.Xie et al. (2018), the rs4148738 polymorphism also had no significant effect on the pharmacokinetics of dabigatran [24].

The results regarding the rs1045642 polymorphism were generally more encouraging. For example, in Q.Xie et al. (2018) CC carriers of the rs1045642 genotype had lower plasma concentrations of direct oral anticoagulants compared with patients with the TT-genotype [24]. These findings are supported by a study by Sychev et al. which showed that patients with the TT-genotype rs1045642 had higher peak dabigatran concentrations and thus a higher risk of bleeding after knee replacement [18]. A 2021 study by J.Lähteenmäki et al. examined the *ABCB1* rs1045642, rs2032582, rs4148738, and rs1128503 polymorphisms in 1806 patients taking dabigatran, rivaroxaban, and apixaban. In the 340 patients taking dabigatran, in contrast to rivaroxaban and apixaban, no significant effect of the above polymorphisms on the development of thromboembolism and bleeding was detected [25]. These results were also confirmed by Qiuyi Ji et al. (2021), who showed no significant influence of the *ABCB1* polymorphisms rs4148738 and rs1045642 on the pharmacokinetics and pharmacodynamics of dabigatran in patients with AF [20], and by Y.Liu et al (2021), who found no association between the *ABCB1* polymorphisms rs2032582, rs4148738, rs1045642 and the pharmacokinetics of dabigatran in healthy volunteers [21]. At the same time, when the *ABCB1* haplotypes rs2032582 and rs1045642 were combined, the peak concentration of dabigatran was found to increase by 13% and 33% in patients with heterozygous and homozygous mutations,

respectively [26]. Concomitant administration of clarithromycin resulted in a significant increase in dabigatran concentration [26].

An interesting clinical case of left atrial appendage thrombosis was described in the literature, in which dabigatran was taken twice daily at a dose of 110 mg. The patient was heterozygous for the *ABCB1* polymorphisms rs4148738, rs2235046, rs1128503, rs10276036, rs1202169, rs1202168, rs1202167 and homozygous for the *CES1* polymorphisms rs2244613, rs4122238 and heterozygous for the *CES1* polymorphisms rs8192935 and rs4580160. The authors suggested that the above polymorphisms, together with interactions with atorvastatin, which was also taken in this patient, age (70 years), and impaired renal function (creatinine clearance 55 ml/min), may have caused the inefficacy of dabigatran in this case [27]. At the same time, according to the literature, concomitant administration of dabigatran and atorvastatin does not lead to clinically significant interactions and is not associated with changes in the pharmacokinetics and pharmacodynamics of these drugs [28, 29]. In 2020, another case of left atrial ear thrombosis while taking 110 mg of dabigatran for 6 months was published [30]. The patient was found to have three heterozygous *ABCB1* polymorphisms rs4148738, rs1045642, rs2032582 and 2 heterozygous *CES1* polymorphisms rs2244613, rs4580160. The authors suggested that the presence of the above polymorphisms in combination with the administration of amiodarone, which is known to increase plasma concentrations of dabigatran by 12-60% [31], may have influenced the formation of thrombi in the left atrial appendage [30]. In this patient, dabigatran was discontinued, and warfarin was administered, causing the thrombus in the left atrial appendage to resolve after 50 days on this drug [30].

Genetic polymorphisms of uridine-5-diphosphate (UDP) glucuronyltransferase

As mentioned above, metabolism of dabigatran involves conjugation with glucuronic acid to form glucuronides, a process catalyzed by UDF-glucuronyltransferases, among others. It is therefore likely that various genetic polymorphisms of this enzyme may influence the effect of dabigatran. At least three UDF-glucuronyltransferases are involved in the conjugation of dabigatran: *UGT1A9*, *UGT2B7* и *UGT2B15* [10]. According to the in vitro literature, *UGT2B15* contributes the most to the binding of dabigatran to glucuronic acid compared to the other two enzymes [32]. Consequently, it can be assumed that drugs metabolized by the above enzyme (lorazepam, oxazepam, morphine, loratadine, and others) can slow the metabolism of dabigatran when administered concomitantly [33, 34]. At the same time, studies on the effect of the genetic polymorphisms *UGT1A9*, *UGT2B7*, and *UGT2B15* on the pharmacokinetics of dabigatran have not been performed to our knowledge [33]. However, it can be assumed that in patients with the rs1902023 (*UGT2B15*2*) polymorphism of the *UGT2B15* gene, glucuronidation of xenobiotics, including dabigatran, is delayed, which is associated with an increase in the plasma concentration of dabigatran and increases the risk of side effects [35]. This assumption is based on the results obtained for the above polymorphism for other drugs that are substrates of UGT2B15, such as oxazepam, acetaminophen, cypoglitazar, etc. [35-38].

Finally, we present information from the PharmGKB pharmacogenomics database [39], according to which the determination of rs2244613 and rs8192935 *CES1* polymorphisms and rs1045642, rs2032582 and rs4148738 *ABCB1* polymorphisms in patients, taking dabigatran has a level of evidence of 3 (low), which does not allow us to recommend the determination of the *CES1* and *ABCB1* data genetic polymorphisms in routine clinical practice because of insufficient or conflicting data. For the other *CES1* and *ABCB1* polymorphisms discussed in this article, no information is available in the PharmGKB database for patients taking dabigatran.

Recently, data from P. Zubiaur et al. (2020) in a study of 107 patients reported that CYP2D6 and CYP3A5 polymorphisms affect the pharmacokinetics and safety of dabigatran [40], which is also reflected in the PharmGKB database with an evidence level 3 [39]. It is also interesting to note that for the most studied *CES1* and *ABCB1* polymorphisms, the authors were unable to demonstrate any association with the pharmacokinetics of dabigatran [40]. However, interpretation of the results should consider that the patients in this study were taking pantoprazole, which is known to be metabolized by the cytochrome P450 system and is thought to affect the pharmacokinetics of dabigatran. Dabigatran, on the other hand, is not metabolized through the cytochrome P450 system, as mentioned above, so the impact of genetic polymorphisms of this system on the pharmacokinetics of dabigatran is questionable and needs to be clarified in further studies.

It should be noted that a literature review by A.V.Savinova et al. was published in 2021 in the journal Rational Pharmacotherapy in Cardiology, also addressing the pharmacogenetics of dabigatran [33]. Although the article is similar in some important respects, our review contains the following differences: it includes an analysis of 2021 literature sources, an analysis of the PharmGKB pharmacogenomics database; our review includes a discussion of a study on the effect of CYP2D6 and CYP3A5 polymorphisms on the pharmacogenetics and safety of dabigatran therapy. If further studies are conducted in this direction, this could be a new aspect of the pharmacogenetics of this drug.

Of course, pharmacogenetics is a relatively new and under-researched field that plays an important role in the development of personalized medicine. The rapid pace of development, accompanied by increasing publication activity, necessitates regular updating of existing knowledge in this field and has been the impetus for the preparation and writing of this review.

CONCLUSION

Currently, there is no conclusive evidence supporting the need for routine determination of the pharmacogenetics of dabigatran in patients with indications for its use in clinical practice. On the other hand, the literature is sparse and often contradictory, so future research in this area is likely to answer the question more precisely.

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PERCUTANEOUS EPICARDIAL MAPPING AND ABLATION OF THE VENTRICULAR TACHYCARDIA SUBSTRATE IN A PATIENT AFTER PERICARDIOTOMY: CASE REPORT

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We present a case of successful percutaneous epicardial access in patients with non-ischemic cardiomyopathy with limited mapping and ablation of the ventricular tachycardia substrate on the epicardial surface.

Key words: ventricular tachycardia; epicardial mapping; epicardial ablation; pericardiotomy; pericardial adhesions

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Epicardial access is used for mapping and ablation of ventricular tachycardia (VT) after an ineffective endocardial procedure or initially when there is evidence of a subepicardial VT substrate (which may be indicated by the etiology of the heart disease, ECG criteria for clinical VT, subepicardial contrast latency on magnetic resonance imaging, endocardial bipolar and unipolar mapping results). In patients with a history of pericardiotomy, epicardial access is extremely difficult and mapping and ablation options are limited due to adhesions in the pericardium.

The aim of our work is to present a case of successful percutaneous epicardial access in a patient with nonischemic cardiomyopathy with limited mapping and ablation of the VT substrate on the epicardial surface.

A 54-year-old patient with no history of structural heart disease was admitted for repeat catheter ablation of the substrate of paroxysmal VT (Fig. 1 a,b), which was refractory to medical therapy and accompanied by unstable hemodynamics.

Examination revealed no coronary artery changes, diagnosed dilatation of both atria, normal left (LV) and right ventricular (RV) systolic function. ECG showed prolongation of PQ interval, atrial fibrillation (CHA_2DS_2-VASc - 1 point, HAS-BLED - 0 point) for more than a year ambulatory, for which the patient received anticoagulant therapy with apixaban at a dose of 5 mg b.i.d. A clinical VT with a ventricular contraction rate of 200 bpm recorded on ECG did not fully meet the criteria for epicardial localization: 2 of 4 possible criteria in the stepwise algorithm (QS in leads II, III, avF, maximum deflection index, internal deviation time index - 0.81, pseudo-delta wavelength 90 ms, no q in lead I) were met [1]. Delayed contrast magnetic resonance im-

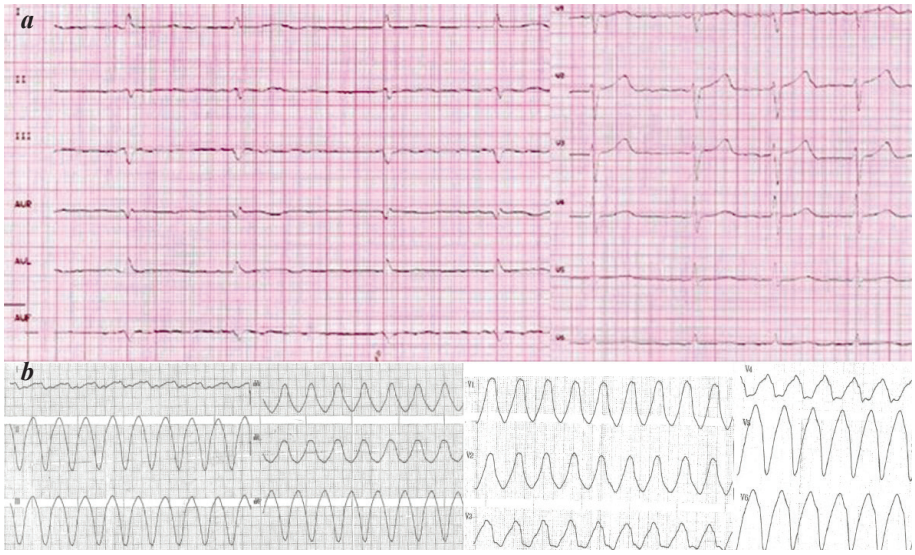

Fig. 1. ECG of the patient: a - atrial fibrillation, b - ventricular tachycardia.

aging confirmed atrial dilatation in both atria and showed increased trabecularity in the apex and medial-apical regions of the lateral and posterior LV walls. There was no evidence of subepicardial localization of the arrhythmia substrate.

The first attempt at substrate ablation from VT was performed 2 months ago. Endocardial mapping of the LV and RV myocardium showed no zones of low amplitude or fragmented activity on analysis of bipolar and unipolar voltage maps (CARTO 3 navigation system, Biosense Webster: SmartTouch ThermoCool Ablation and Cartridge Catheter, Biosense Webster, USA). For LV access, atrial transseptal puncture was performed, and mapping was anterograde. Programmed ventricular stimulation induced a clinical VT with a cycle of 375 ms accompanied by a drop in blood pressure that prevented detailed activation mapping. Stimulation mapping of the LV revealed the greatest overlap of the stimulated QRS complex with the clinical VT at the border between the apex and the lateral wall of the LV (95% overlap, PASO module used, Biosense Webster), which did not correspond to the 'ideal' tachycardia exit point mapping. With evidence of a likely subepicardial VT output, radiofrequency applications were performed in this area on the endocardial surface (40W; up to 90s). Further mapping attempts resulted in mechanical perforation of the LV wall with the ablation catheter. Because of the nature of the perforation, a decision was made to correct it surgically and perform a median sternotomy, pericardiotomy, removal of the ablation catheter that had penetrated the myocardium, and suturing of the LV defect. Surgical ablation was not possible during the emergency sternotomy because no electrophysiological equipment was available for open-heart radiofrequency (RF) or cryoablation. The patient was discharged on amiodarone saturation therapy without spontaneous episodes VT.

Two months later, on treatment with amiodarone in combination with a beta-blocker, VT recurred and the patient was referred for repeat catheter ablation of the arrhythmia substrate.

After cardiologists, electrophysiologists, and cardiovascular surgeons discussed intervention tactics with the patient, it was decided to attempt epicardial ablation under general anesthesia via a punctured subxiphoid approach in the presence of a cardiovascular surgeon and to be prepared for open surgery should complications arise. Despite a history of pericardiotomy, a minimally invasive approach to epicardial mapping seemed warranted.

Percutaneous access to the pericardial space was achieved by subxiphoid puncture. The method of access was described in detail in a previous publication [2].

Attempted pericardial punctures showed adhesions between the parietal and visceral pericardial leaflets, and inadvertent puncture of the RV was observed (without consequences in follow-up). On repeated puncture attempts on the diaphragmatic surface of the heart, limited guidance with a diameter of 0.035 inch (Emerald, Cordis, USA) between the pericardial leaflets was observed against a background of bolus injection of a small amount of contrast medium (Omnipack-300, GE Healthcare, Ireland). Partial separation of the pericardial leaflets was achieved by careful movements of the guidewire under fluoroscopic control and then by alternating 5-10 ml boluses of contrast medium and saline through the soft dilator of a 6F vascular introducer (Avanti+, Cordis, USA) (Figs. 2, 3). An unguided 8F multipurpose introducer (Cordis, USA) was then inserted into the nonadherent area, and a 3.5 mm NaviStar

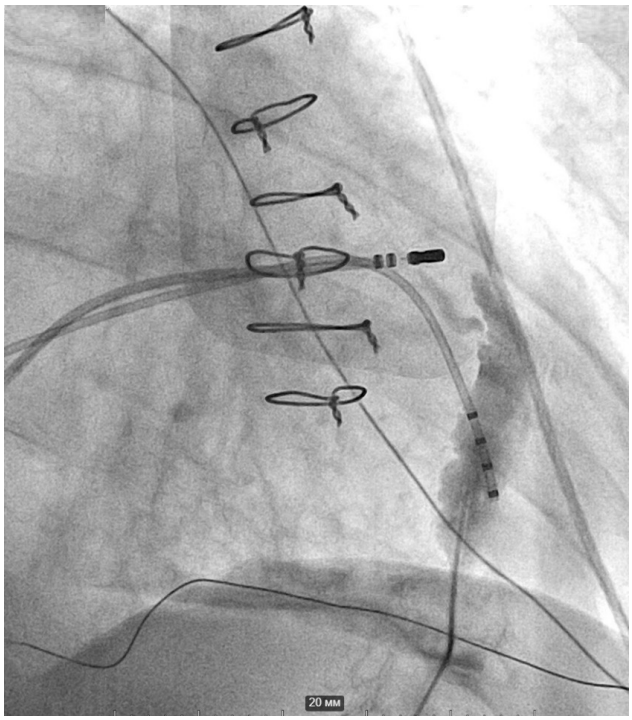

Fig. 2. Subxiphoid approach to the pericardial 'space'. Direct projection, 0°. A 6F intraductal dilator is inserted and a small bolus of contrast through the dilator separates the pericardial leaflets.

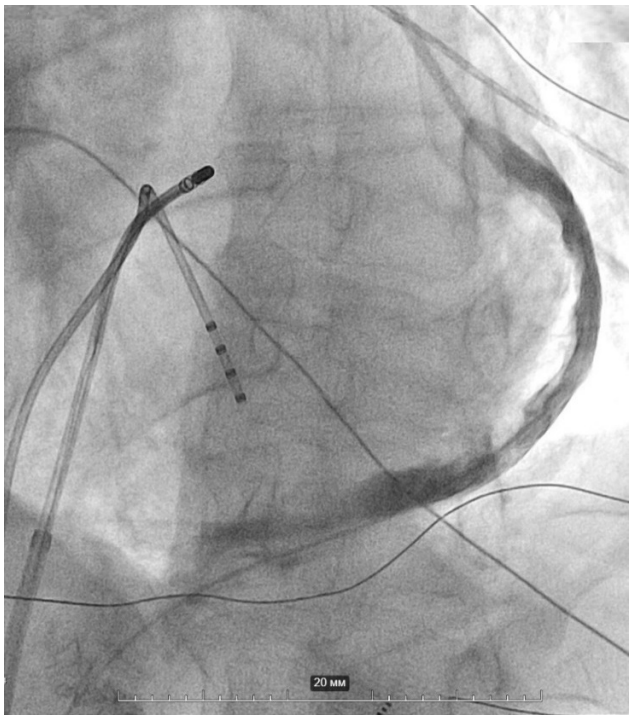

Fig. 3. Contrasting a limited area between the pericardial leaflets after partial separation of the adhesions. Left oblique projection, 30°.

Termocool irrigated tip ablation catheter (Biosense Webster, USA) was inserted through it with the irrigation turned off. The ablation catheter is used in a flexion-extension method and movements in the released space to further separate the pericardial sheets on the lateral wall of the LV, partially on the inferior wall and in the cardiac apex. During separation of the adhesions, limited bleeding into the pericardial cavity (approximately 10 ml) occurred, and spontaneous hemostasis was achieved within 5 minutes.

The epicardial mapping area was limited to the area of adhesion separation and was opposite the area of greatest correspondence between the morphology of the stimulated QRS and the spontaneous clinical VT at the previous procedure.

Endocardial mapping was performed retrograde via transarterial access. Electroanatomic mapping was performed using the CARTO 3 nonfluoroscopic 3D navigation system with the Confidense module (Biosense Webster) with the following settings: LAT Stability - 10 ms, Position Stability - 6 ms, Density - 1 mm, Color Threshold - 10 mm. Endo- and epicardial voltages were mapped with preset limits of 0.5-1.5 mV (bipolar) and 5.0-9.0 mV (unipolar). For endocardial cardiac surface mapping, 1198 and 638 points were recorded for LV and RV, respectively. Epicardial mapping yielded 682 points.

Endocardially, both bipolar and unipolar voltage mapping showed no areas of low amplitude signals (scarring/fibrotic changes) or altered electrical activity (fragmented, late potentials). Epicardially, areas of myocardium with low signal amplitude were identified, located at the cardiac apex (Fig. 4).

Endocardial stimulation and activation mapping identified the most satisfactory criteria for localization of the VT substrate in the apex of the RV in the septal wall (the morphological agreement of the stimulated QRS with the clinical VT when assessed by PASO was 0.978). When stimulation was mapped from LV to this point - PASO correlation was 0.89. Programmed stimulation induced clinical VT with a cycle length of 470 ms mapped in the background of VT - the earliest activation was detected in the apex of the RV endocardially. A series of 40-50 W RF applications (lasting up to 60 seconds at an electrode irrigation rate of 30 ml/min) was applied in this area, resulting in a transient exacerbation of VT. Based on the above, it was decided that RF applications to the epicardial surface of the cardiac apex were necessary.

A series of epicardial RF applications (40-50 W, flush 17 ml/min, ablation time 40-60 seconds) was applied apically at the cardiac apex, at the border between the RV and LV. Subsequent programmed pacing from the RV and LV (up to 5 extrastimuli) and increasing pacing from different parts of the RV and LV did not elicit tachycardia.

Catheher was removed from the femoral vessels, and a drain was left in the pericardial cavity for 6 hours and then removed without sequelae. The patient was discharged on continued antiarrhythmic therapy.

Given the lack of evidence of structural myocardial damage and the absence of a history of circulatory arrest, the decision to implant a cardioverter-defibrillator is made only after an evaluation of the efficacy of the surgical procedure. The patient had no recurrence of VT within one year of epicardial ablation, even after discontinuation of amiodarone.

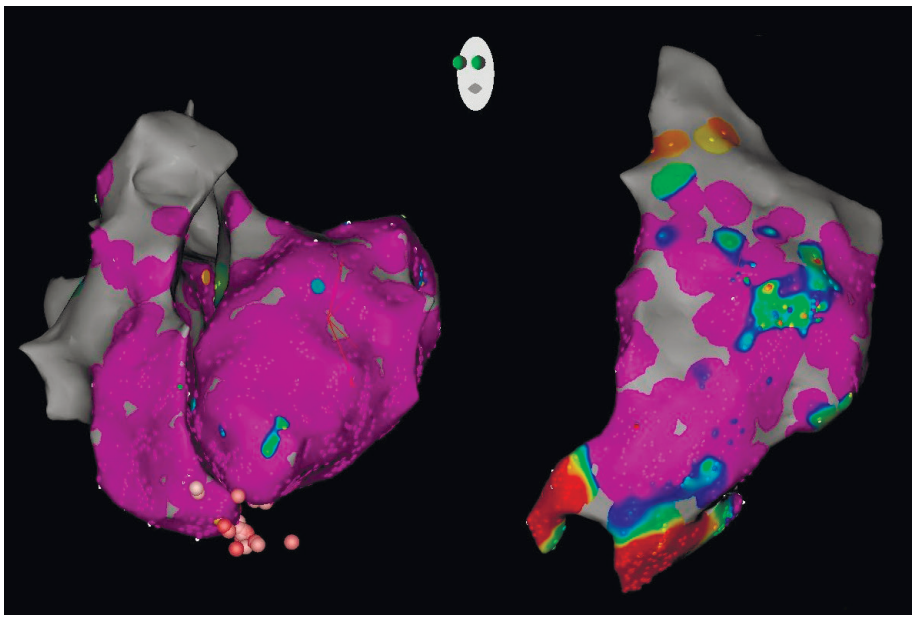

Fig. 4. Electroanatomical mapping, left oblique projection 30º. Left is a bipolar voltage map of the endocardial surface of the left and right ventricles; right is a bipolar voltage map of the epicardial surface of the lateral wall of the left ventricle and the apex of the heart. The detection limit of the scar zones is 0.5-1.5 mV. Purple indicates unchanged myocardium with normal signal amplitude and red indicates myocardium with low signal amplitude. The pink dots are projections of the applied RF applications on the epicardial surface, located on the endocardial map opposite the cardiac apex, where no reduction in signal amplitude or recording of altered potentials was detected.

DISCUSSION

This clinical case demonstrates successful epicardial mapping and ablation of the VT substrate in a patient with postoperative pericardial adhesions.

The issue of safe epicardial access in patients with previous cardiothoracic surgery is very important. Often, patients requiring epicardial mapping/ablation have a history of myopericarditis or cardiac surgery associated with adhesions that complicate access and manipulation between the pericardial leaflets. Dissection of adhesions may be associated with hemorrhage because they may contain new blood vessels or fuse closely with the myocardium or small epicardial vessels. Dissection of adhesions may also be associated with coronary artery damage, as described in the literature [3, 4].

Previously, a history of cardiothoracic surgery was considered an absolute contraindication

for percutaneous epicardial access. However, in 2004, E. Sosa et al. published the first experience with epicardial ablation in patients with a history of cardiothoracic surgery [4].

More recently, in 2013, observations on epicardial ablation in patients with a history of pericarditis and cardiac surgery (without coronary artery bypass grafting) were published: 10 patients were found to have dense adhesions requiring blunt separation [5].

There are now several ways to release pericardial leaflets in patients with adhesions in the pericardial cavity. These include administration of fluids (saline, radiopaque contrast agent), administration of carbon dioxide, and positioning of a balloon catheter in the area of concern may be an additional tool to separate the leaflets [6-8].

In our clinical case, access to the pericardial space was performed after a recent pericardiotomy (2 months later). On the one hand, the short postoperative time may be associated with the active formation of a large number of fresh adhesions; on the other hand, unformed "soft" adhesions allow separation of pericardial prostheses without risk.

Therefore, in patients who have recently undergone cardiothoracic surgery that does not involve coronary artery disease bypass grafting and pericardiotomy, percutaneous epicardial access may be feasible but should be performed in the hospital with the possibility of emergency cardiac surgery after weighing the benefits and risks of potential complications.

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MYXOFIBROSARCOMA OF THE HEART: CASE SERIES

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Intraluminal formations of the heart are a heterogeneous group: from blood clots to malignant neoplasms. The nosology of these formations can only be determined by morphological research. Myxofibrosarcoma of the heart is a rare malignant tumor. According to modern concepts, myxofibrosarcoma belongs to the group of intimal sarcomas, subgroup of undifferentiated pleomorphic sarcomas. We describe two cases of myxofibrosarcoma of the heart: in one subject against the background of inflammatory myofibroblastic heart tumor; in another subject - with a history of breast cancer and diffuse large B-cell lymphoma. An attempt was made to identify similar mutations in patients with these tumors according to the literature.

Key words: myxofibrosarcoma of the heart; inflammatory myofibroblastic tumor of the heart; immunohistochemical study; tumor of the heart

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Primary cardiac tumors are rare and present a major difficulty in diagnosis. According to a systematic review, the incidence of primary cardiac tumors is 0.002-0.3%. Myxomas account for 90% of cardiac tumors, and the most common malignant cardiac tumor is sarcoma. The prevalence of myxofibrosarcoma (MFS) is less than 1% of cardiac malignancies [1].

Inflammatory myofibroblastic tumor (IMT, plasma granuloma, inflammatory pseudotumor, xanthomatous granuloma, inflammatory fibromyxoid tumor, pseudosarcomatous inflammatory proliferation) was first described by H. Brunn et al. in 1939. The tumor has been described in all organs and in all age groups but occurs most frequently in childhood. The most frequent localization of the tumor is in the lung [2]. The literature contains data on the possibility of metastases and angioinvasion of extracardiac IMT [3]. According to some authors, tumor recurrence occurs in 8% of patients and is attributed to inadequate tumor resection or adjuvant treatment [4]. The World Health Organization classifies IMT as a tumor of uncertain biological potential.

The World Health Organization defines MFS as a malignant tumor composed of fibroblasts with varying amounts of intercellular collagen and abundant myxoid stroma. According to modern concepts, MFS belongs to the intimal sarcoma group, a subgroup of undifferentiated pleomorphic sarcomas [5]. The molecular pathogenesis of MFS remains incompletely elucidated.

The aim of our paper is to present and discuss 2 rare cases of myxofibrosarcoma of the heart.

Clinical Case No.1.

A 40-year-old male patient complained of increasing dyspnea on exertion with an increase in NYHA functional class from II to IV within 1-month, lower extremity edema, dry cough, chest pain at night in the supine and left lateral positions, and the ability to sleep only in the sitting position. Differential diagnostic search included tuberculosis, hypothyroidism, lower respiratory tract infection, and chronic heart failure. Echocardiography (Echo) revealed a mass in the left atrial cavity (LA) obstructing outflow from the LA; myxomatous changes in the mitral and tricuspid valve leaflets, LA dilatation. The mass floated, rushed into the left ventricle, and obstructed the mitral valve orifice with the formation of critical mitral stenosis. Blood flow at the valve was accelerated, and the mean gradient increased. There was early systolic mitral regurgitation with two eccentric narrow jets along 2/3 of the LA lateral wall and interatrial septum, signs of high pulmonary hypertension.

Based on the vital signs, the decision was made to perform surgery to remove the LA mass. The mass was a round-oval lobular tissue of white-yellow color, soft-elastic consistency, and a size of 4.0 x 4.5 x 3.5 cm. At one of the poles was a 2.0 x 1.5 cm "pedicle" attached to the posterior wall of the LA. In section, the tissue was heterogeneous: the periphery was white-yellow, whereas the central part was red-pink (Fig. 1). The mass was removed with adjacent atrial sections; it was not possible to reliably assess the resection margin.

Histologically, the mass was a low cellular tumor lined with endothelium with a distribution of cells predom-

Fig. 1. Macroscopic view of inflammatory myofibroblastic cardiac tumor.

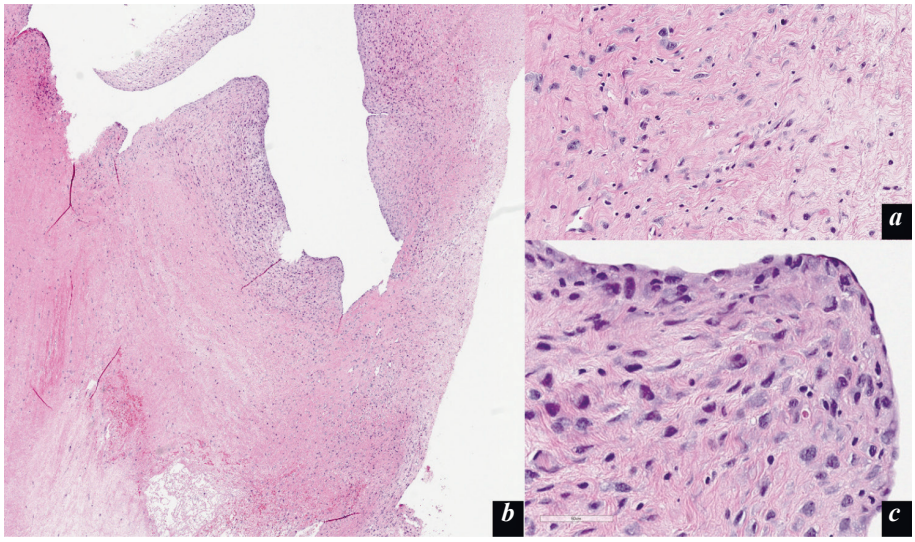

Fig. 2. Inflammatory myofibroblastic tumor of the heart: a - low cellular tumor lined with endothelium, with cell distribution mainly along the tumor periphery; b, c - round, oval and spindle-shaped tumor cells in dense stroma (magnification 20, 200 and 400, respectively, staining with hematoxylin and eosin, further HE).

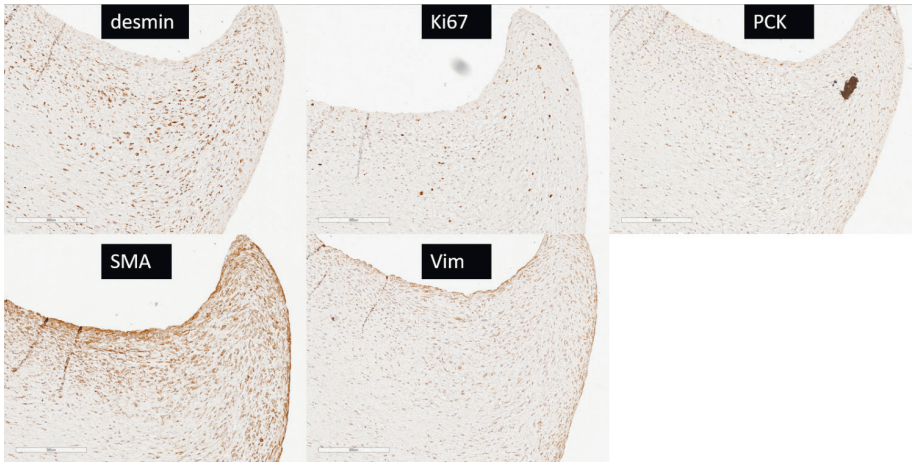

Fig. 3. Immunohistochemical examination of an inflammatory myofibroblastic cardiac tumor with different antibodies (brown stain), magnification 100.

inantly at the periphery of the tumor and few in the central parts, which were during an abundant eosinophilic, dense, loose, and myxoid stroma. Spindle-shaped cells without clear boundaries, round, and elongated nuclei, with finely distributed chromatin, with single small nuclei in individual cells, visible under 200× magnification. Nuclear atypia was not pronounced. Cells with mitotic figures are scattered. The stroma is vascularized due to some thin-walled vessels. Faint diffuse and small focal infiltration by small lymphocytes with mature nuclear morphology was noted (Fig. 2).

The main differential diagnoses were myxoma, fibroelastoma, IMT, myxofibrosarcoma, and myxoid leiomyosarcoma. Immunohistochemical examination revealed cytoplasmic expression of vimentin, smooth muscle actin, desmin, and pancytokeratin on tumor cells. Expression of S100 protein (a family of multigenic group of non-biquitous cytoplasmic intracellular Ca^{2+}-binding proteins), anaplastic lymphoma kinase, and myogenin was not detected on the tumor cells. The Ki67 index of proliferative activity of tumor cells was 5-15% (Fig. 3). The patient was diagnosed with an inflammatory myofibroblastic cardiac tumor, which was surgically removed.

In the early postoperative period, complications occurred due to postpericardiotomy syndrome, which was successfully treated. No intracavitary LA masses were detected on the control Echo. The patient received extensive therapy with nonsteroidal anti-inflammatory drugs in the postoperative period and was discharged to a sanatorium.

Two years later, the patient again developed dyspnea on light exertion and on the left side. She was examined as an outpatient and a LA mass was discovered. ECG findings: atrial flutter with irregular conduction of excitation to the ventricles and a heart rate of 130 bpm, incomplete right bundle branch block, repolarization disturbance in the form of negative and biphasic T waves in most leads. Echo: marked mitral valve obstruction with high pulmonary hypertension, mass of LA.

Given the possibility of embolic complications, emergency surgery was performed to remove a mass in the left atrium through the right atrium and interatrial septum. It was impossible to radically remove the mass because it had visibly invaded the orifice of the pulmonary veins and the area of the mitral

valve fibrous ring. The mass was resected as much as possible, preserving the unmodified atrial tissue.

The removed mass was lobular, 5.0 x 4.0 x 2.5 cm in size, partially covered by smooth endocardium, yellowish-white in section, with necrosis and hemorrhage (Fig. 4). On histologic examination, the tumor was a lobular tumor composed of polymorphic atypical spindle-shaped and round cells in a myxomatous and fibrous stroma. Necrosis and hemorrhages were present (Fig. 5).

On immunohistochemical examination, tumor cells expressed p53 protein, vimentin, smooth muscle actin, membrane-binding mucin type 4, mouse microchromosome subtype 2 protein, and focal expression of CD56 (CD, differentiation cluster) was observed (Fig. 6). There was no expression of desmin, myogenin, anaplastic lymphoma kinase, pancytokeratin, epithelial membrane antigen, CD99, CD34. The patient was diagnosed with myxofibrosarcoma. The proliferative Ki67 activity was 20%. Thus, this patient developed myxofibrosarcoma on a background of inflammatory myofibroblastic tumor.

In the postoperative period, atrial flutter was recorded on the ECG (Fig. 7). No complications occurred in the postoperative period and the patient was discharged for outpatient treatment. The condition and dynamics of the patient's disease in the next phases of treatment are unknown.

Clinical case No.2

A 50-year-old patient with infiltrating ductal carcinoma of the left breast, intermediate malignancy grade T4N1M1, diffuse B-cell lymphoma, with radiotherapy and chemotherapy in 2010, complained of marked weakness, shortness of breath that occurred with minimal physical activity, in the prone position, insomnia, and dry cough 11 years later.

The ECG showed incomplete left bundle block, incomplete right bundle block, repolarization changes in the form of decreased T amplitude of diffuse nature.

According to the Echo data, the right ventricle (RV) shows a volumetric mass of in-

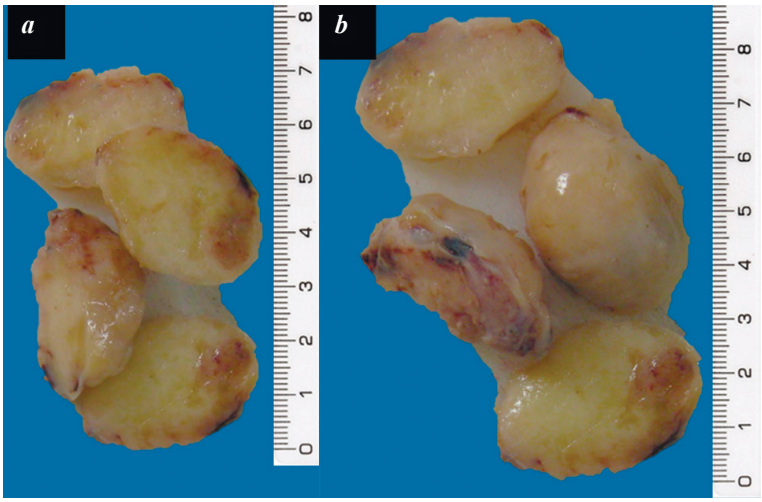

Fig. 4. Macroscopic view of a myxofibrosarcoma of the heart from two surfaces a and b, respectively.

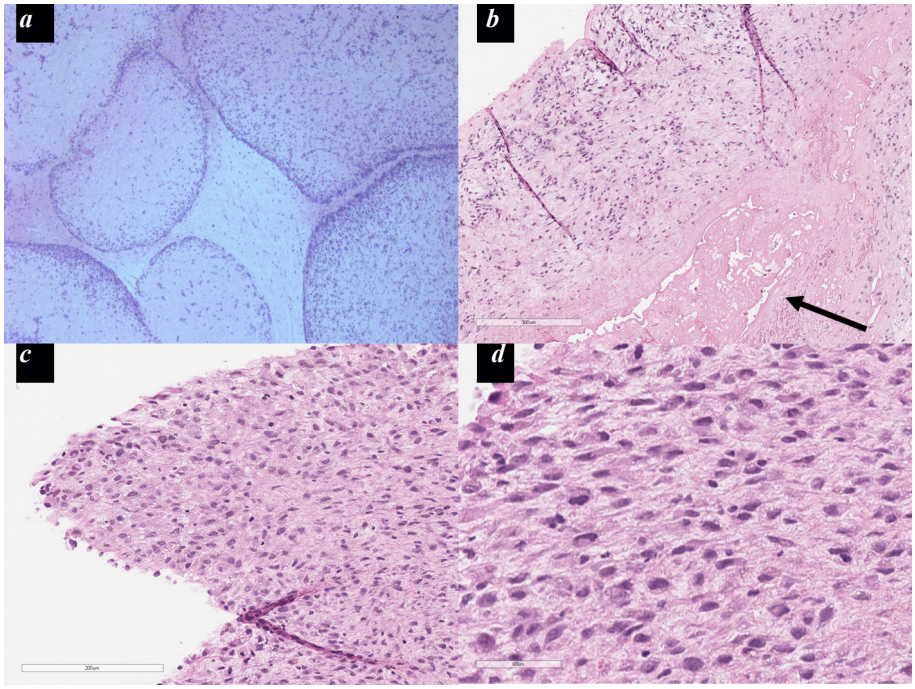

Fig. 5. Myxofibrosarcoma of the heart (HE stain): a - lobular tumor structure, magnification 50, b - tumor necrosis (indicated by arrow), magnification 40, c, d - atypical spindle-shaped and oval tumor cells with polymorphic nuclei, magnification 200 and 400, respectively.

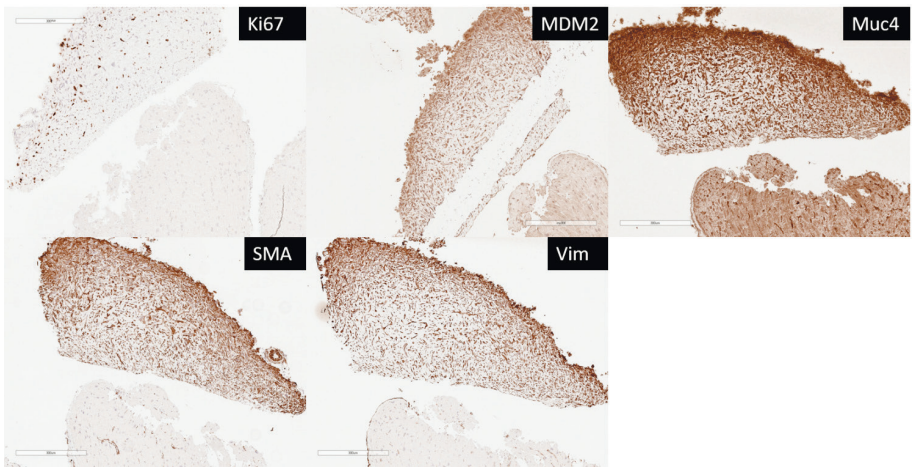

Fig. 6. Immunohistochemical examination of myxofibrosarcoma of the heart with different antibodies (brown stain), magnification 100.

homogeneous, heterogeneous structure with a size of 3.5 x 3.8 cm, originating from the basal portions of the anterolateral wall of the RV and obstructing blood flow. The RV exit tract pressure gradient was 48 mm Hg, and the effusion in the pericardial cavity was approximately 250 ml (Fig. 8).

After multispiral computed tomography of the chest organs: an image of the RV mass with infiltration into the pericardium. Pericardial effusion. Drainage into the left pleural cavity. Formation of the left mammary gland. Left S4 atelectasis.

Whole-body positron emission tomography showed a focus with pathologic accumulation of radiopharmaceuticals in the RV with irregular contours; heterogeneous, with scintigraphy dimensions of 78 x 73 x 56.5 mm. Primary multiple neoplasia was suspected: primary cardiac and left breast tumors with secondary involvement of axillary lymph nodes (Fig. 9).

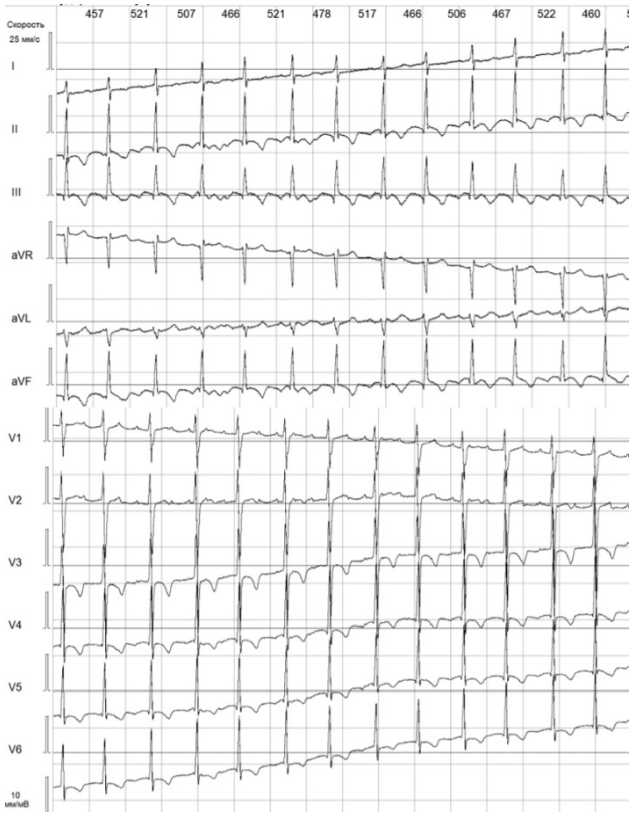

Fig. 7. ECG: atrial flutter.

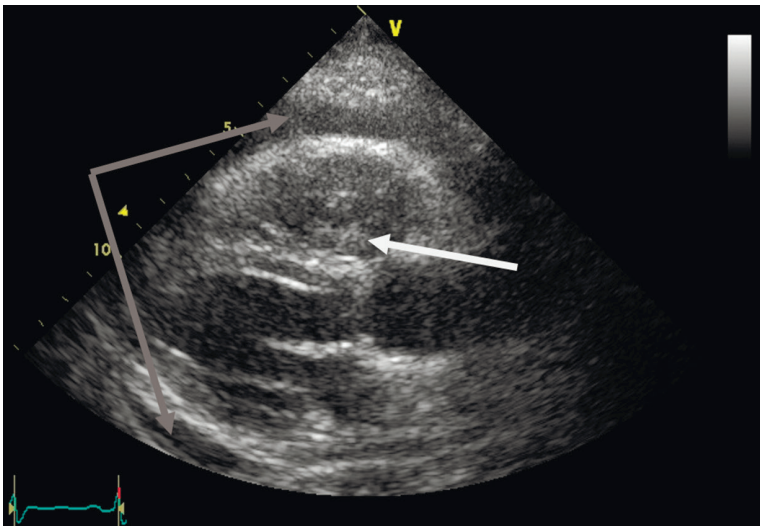

Fig. 8. Echo: effusion in the pericardial cavity (gray arrows), tumor in the lumen of the RV (white arrow).

Cytologic analysis of pericardial fluid revealed no evidence of the presence of lymphoproliferative disease. The main differential diagnostic search included: cardiac lymphoma, metastasis of breast carcinoma, and primary cardiac mass. It was decided to perform an endomyocardial biopsy to decide on further treatment tactics.

Histologic examination revealed the tumor as spindle-shaped cells in a myxoid matrix (Fig. 10). On immunohistochemical examination, the tumor cells did not express CD20, prolactin-induced protein (PIP), mammoglobin, or pancytokeratin; proliferative activity Ki-67 was 22%. Immunophenotyping of the sarcomas expressed murine microchromosome subtype 2 protein, vimentin and smooth muscle actin, and membrane-binding mucin type 4; there was no expression of myogenin, desmin, S100 protein, myoblast determination protein 1, or CD34 (Figure 11). The immunophenotype of the tumor was consistent with that of cardiac myxofibrosarcoma.

The patient had tumor infiltration of the anterior and lateral walls of the RV. As a result, complete surgical excision of the tumor was not possible. The patient was treated with palliative chemotherapy. The patient's condition and dynamics as well as further treatment in the next stages are not known.

DISCUSSION

The pathogenesis of IMT is not fully understood. Despite numerous studies, only hypotheses about the origin of this tumor have been presented. More than 21 partner genes involved in the pathogenesis of IMT have been discovered, and the spectrum of these genes is updated every year [6]. It is known that 50 to 70% of tumors have a rearrangement of the ALK gene resulting in a chimeric protein with tyrosine kinase activity, which can be detected by immunohistochemical examination or FISH. Genetically, more than half of IMTs belong to the so-called "ALKom" family (ALK - anaplastic lymphoma kinase; ALK is activated in some types of solid tumors). Thus, oncogenic activation of ALK plays an important role in the pathogenesis of the following tumors: anaplastic large cell lymphoma, non-small cell lung carcinoma, medullary renal carcinoma, neuroblastoma, and anaplastic thyroid carcinoma [7]. In 2011, the Food and Drug Administration (FDA) approved the first targeted drug, crizotinib, for the treatment of patients with ALK-positive tumors [8]. There are also data on the possibility of listeriosis infection as a cause of cardiac WMD [9].

In the heart, IMT usually grows as a cavitary mass on a pedicle connected to the endocardium, but there are also data about the growth of this tumor around the coronary arteries, which can lead to acute coronary syndrome and sudden cardiac death of the patient [10].

The clinical manifestations of IMT vary widely, ranging from an asymptomatic course to manifestations of heart failure, angina, and

transient ischemic attacks [11]. The leading diagnostic method is Echo examination, which can detect an intracavitary mass in the ventricle and establish the primary differential diagnosis with thrombotic masses. If a ventricular cavity mass is found, the primary differential diagnosis includes thrombi, myxomas, and non-myxomatous masses.

IMT exhibit high morphologic variability, ranging from predominantly hyalinized stroma with a small number of spindle-shaped cells with a background inflammatory infiltrate to highly cellular myofibroblastic proliferates.

The gold standard of treatment is complete surgical excision of the tumor. Radiation therapy is successfully used for inoperable neoplasms and recurrences. If the lesion has invaded the heart, complete surgical removal may not be possible because the tumor spreads directly to vital structures such as coronary arteries or pulmonary veins, so additional treatments should be considered. There are numerous data on successful regression of the tumor with oral corticosteroid therapy, in which most patients experienced a significant reduction in the size of the residual lesion and did not require additional surgery [12].

In our case, it remains unclear whether this was a recurrence of IMT with conversion to MFS or whether MFS developed de novo after removal of IMT or whether MFS developed from residual IMT tissue. There are no reports in the literature of conversion of IMT to MFS, but rapid recurrence of IMT in a five-month-old child [13] and rapid growth of MFS in a 57-year-old woman [14] have been described.

MFS have a very heterogeneous karyotype with different clones observed not only in each individual patient but also in different sections of the same tumor. There is evidence in the literature that activation of the AKT/mTORC2 pathway correlates with the histological grade of malignancy and progression of MFS [15]. It is also described that two-thirds of MFS exhibit overexpression of MET (tyrosine kinase receptor; upon binding to its ligand, hepatocyte growth

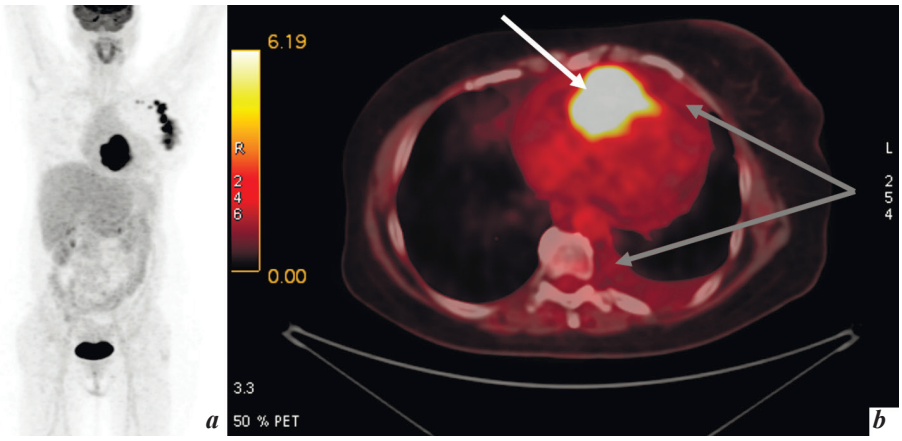

Fig. 9. Positron emission tomography - whole body imaging (a). Foci of pathologic accumulation of 18F-fluorodeoxyglucose radiopharmaceutical (RPC) in the left mammary gland, left axillary region, giant focus of pathologic RPC accumulation in the right ventricle. RPC accumulates in the urinary bladder as it is physiologically excreted through the urinary tract. In the right ventricle (b), a volumetric mass occupying ¾ of the cavity can be seen and is characterized by pathologic accumulation of RPC (indicated by a white arrow). Fluid is detectable in the pericardial cavity and left pleural cavity (indicated by gray arrows).

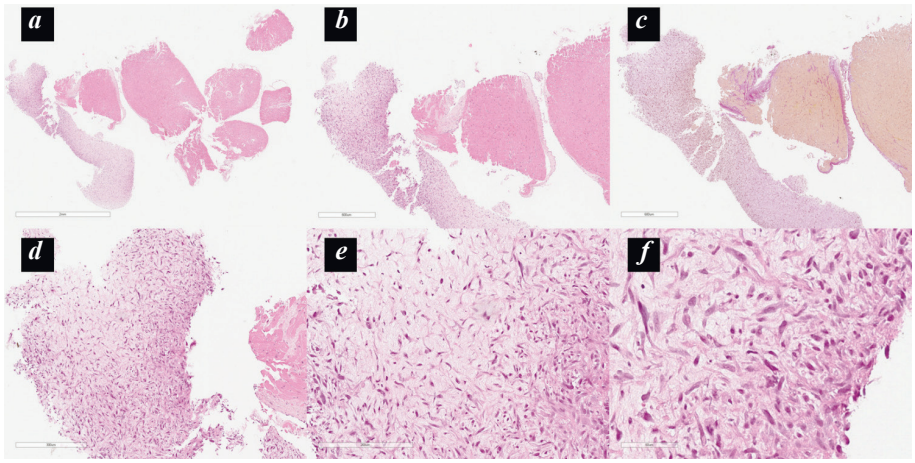

Fig. 10. Endomyocardial biopsy, cardiac myxofibrosarcoma in 2 biopsy fragments: a - magnification 20 (HE stain), b - magnification 40 (HE stain), c - magnification 40, van Gieson stain, d, e, f - magnification 100, 200 and 400, respectively (HE stain).

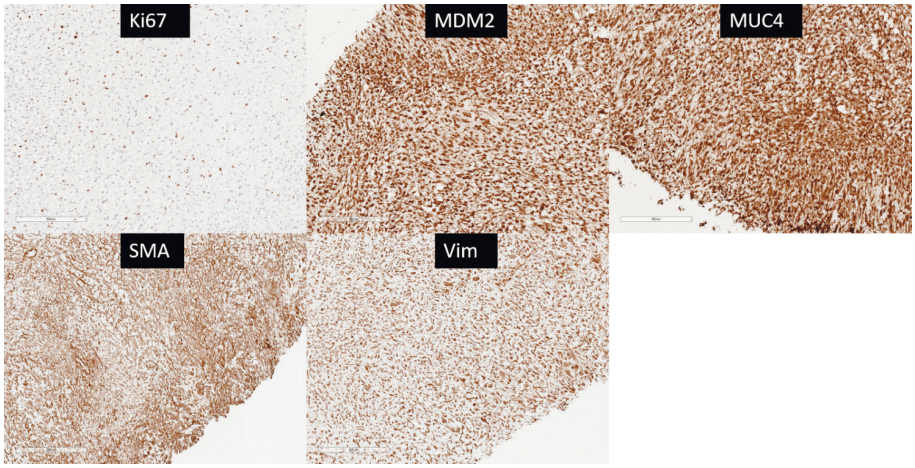

Fig. 11. Immunohistochemical examination of myxofibrosarcoma of the heart with different antibodies (brown stain), magnification 100.

factor, it activates a variety of cellular signaling pathways, including involvement in proliferation, motility, migration, and invasion), which correlates with unfavorable clinicopathologic factors and independently predicts shorter survival [16].

The most common complaints in patients with MFS are dyspnea and syncope. Syndromally, patients most commonly show signs of cardiac and valvular failure. On physical examination, heart murmurs, paradoxical pulse, hypotension, and tachycardia are most noted in these patients [17]. ECG changes have been described, some of which were also observed in our cases: bundle branch block and decreased amplitude of the T wave. Bundle branch block may be associated with invasive growth. Decreased amplitude of T wave may be caused by myocardial and endocardial damage. MFS cardiac metastases may present as epileptic seizures, acute impairment of cerebral blood flow, and intracerebral hematoma [18].

Surgical treatment is the main treatment for sarcomas of the heart. Depending on tumor stage and degree of differentiation, the results of surgical treatment vary widely. However, there is evidence in the literature that patients who have tumor resection have a significantly higher survival rate than patients without surgery [19].

In the second patient, we have a history of primary multiple cancers and the occurrence of primary cardiac MFS, which can be explained by common mutations in the genome. As described above, progression of MFS correlates with activation of the AKT pathway. We found evidence in the literature that this pathway may also be involved in the oncogenesis of breast ductal carcinoma. HER2 activates the cytoplasmic domain of HER3, which in turn triggers the AKT pathway and thus the prooncogenic cascade [20]. There is evidence of MET overexpression in breast tumors, which is associated with higher mortality. However, in Asian patients as well as in HER -2-positive breast carcinomas, overexpression of MET does not affect prognosis [21]. There are reports of PIK3CA-mutated B-cell lymphomas such as that of our patient. Mutations in PIK3CA lead to activation of the same AKT pathway, which triggers another prooncogenic cascade [22]. Thus, in our patient, activation of the ACT pathway may have triggered the oncogenesis of multiple tumors. Unfortunately, we can neither confirm nor deny this assumption at this stage. Therefore, genome sequencing will be performed in this patient to identify mutated genes and to find a possible targeted therapy.

Currently, several targeted drugs are known to block the ACT pathway: Ipatasertib (GDC-0068), Capivasertib (AZD5363), Afuresertib (GSK2110183) Uprosertib (GSK2141795), Triciribine (PTX-200), Cenisertib (R763/AS703569). However, only the drug alpelizib is approved for clinical use, whose indication is a combination of the following conditions: HR +, HER2- advanced or metastatic breast cancer; PIK3CA gene mutation (PIK3CA+); disease progression during or after hormone therapies. Theoretically, if mutations in the AKT pathway are detected, it could be reasonable to treat this patient with alpelizib off-label if no other drugs are available for treatment in clinical trials.

The trend toward personalized medicine has been actively discussed in the world recently. For patients with primary multiple cancers as well as rare tumors, this principle should be applied first. Since surgical resection of MFS is not a radical treatment of the tumor, patients require additional chemotherapy. It is reasonable to consider the biological characteristics of the tumor when choosing this therapy. Unfortunately, we currently do not know enough about all genetic rearrangements of MFS. For this reason, NGS genome screening is recommended for these patients. Further treatment of patients should ideally be done with targeted therapy or CAR -T-cell therapy to achieve the best possible long-term results.

CONCLUSION

Myxofibrosarcoma may develop on a background of inflammatory myofibroblastic tumor. Immunohistochemical examination and FISH for ALK mutations in an inflammatory myofibroblastic tumor is recommended. If ALK mutations are detected, clinical follow-up is required to rule out other tumors in the ALK family. Myxofibrosarcoma may share genetic disorders with other tumors involving the AKT pathway and characterized by overexpression of MET, which should be further investigated for targeted therapy.

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TEMPORARY BALLOON OCCLUSION OF SUBCLAVIAN VEIN IN ITS INJURY DURING TRANSVENOUS LEADS EXTRACTION IN PATIENT WITH A SUPERIOR VENA CAVA SYNDROME: CASE REPORT

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In this article we have described clinical case of successful balloon catheter for peripheral angioplasty usage for occlusion of subclavian vein which was damaged during transvenous lead extraction of old leads. It helped to prevent life-threatening bleeding.

Key words: transvenous lead extraction; superior vena cava syndrome; permanent pacemaker; bleeding

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Patients with implanted electronic cardiac devices frequently experience infectious complications, which can be life-threatening if sepsis and infective endocarditis develop [1, 2]. Complete removal of the pacing system with transvenous lead extraction (TLE) appears to be the treatment of choice in most cases of device infection [3].

Myocardial damage and hemopericardium with cardiac tamponade constitute the most common complications of TLE [4]. Vein injury is a rare complication of TLE. It occurs in 0.16-0.41% of extractions [5]. Superior vena cava (SVC) injury poses the highest risk. The mortality rate for this dangerous complication can exceed 50% [6]. A Bridge balloon (Philips, Netherlands) has been proposed for temporary hemostasis of SVC (not registered in the Russian Federation) [7]. However, subclavian and axillary veins injury often related with major bleeding. Manual compression for hemostasis may be ineffective, whereas surgical reconstruction of the subclavian vein is technically challenging and may be associated with major bleeding blood loss.

We are aware of only one clinical case in which a balloon was used to stop bleeding from a subclavian vein injury during TLE [8]. In this particular clinical case in a patient with SVC syndrome, we also performed temporary hemostasis from an injured subclavian/axillary vein with a balloon.

The patient is a 35-year-old woman with a body mass index of 18.6 kg/m2. Due to congenital complete atrioventricular block, she was implanted with a Relay dual-chamber pacemaker with passively fixed leads (Intermedics, USA) in 1998, when she was 11 years old. The pacemaker pocket was formed in the left subclavian region. The ventricular lead was fixed at the apex of the right ventricle, and the atrial lead was fixed at the appendage of the right atrium. The pacemaker was subsequently replaced twice (2010, 2017) preserving initial leads. In 2018, the patient experienced an unmedicated vaginal delivery and breastfed her child for three years. The woman noted that there was traumatization of the pacemaker pocket area when feeding the child and decanting milk. In 2021, the patient noticed skin darkening in the pacemaker pocket area and subsequently devel-

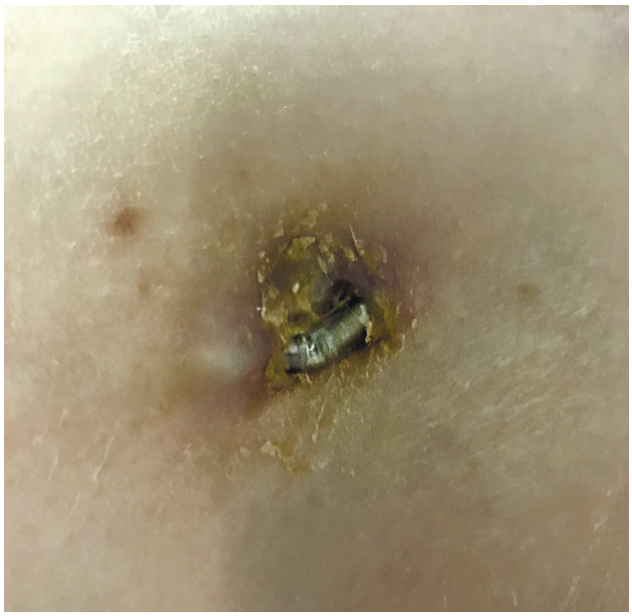

Fig. 1. Lead-associated skin erosion in the area of the pacemaker pocket.

oped a skin defect with cloudy discharge through which a foreign body was visually identified. No fever was observed in the patient.

Face and eyelids swelling was revealed during the first examination. When a more detailed history was taken, the patient reported that the face and upper extremities swelling had developed about two years ago. Enlarged veins are observed on the anterior and lateral surfaces of the chest. A 2x1 cm skin defect with a small amount of mucopurulent discharge is observed in the area of the pacemaker pocket. A section of the lead can be seen through the skin defect (Figure 1). No abnormal pacing is noted on analysis of the ECG data and during device interrogation. Lead-associated endocarditis ruled out by transoesophageal echocardiography (Echo):the heart valves are not altered, no vegetations are present. Haemoglobin on admission was 120 g/l. No inflammatory markers are detected in the blood. It was decided to completely remove the pacing system with TLE and implant a new system on the right side. The EROS and SAFeTY TLE scales define the risk of extraction as high [9, 10].

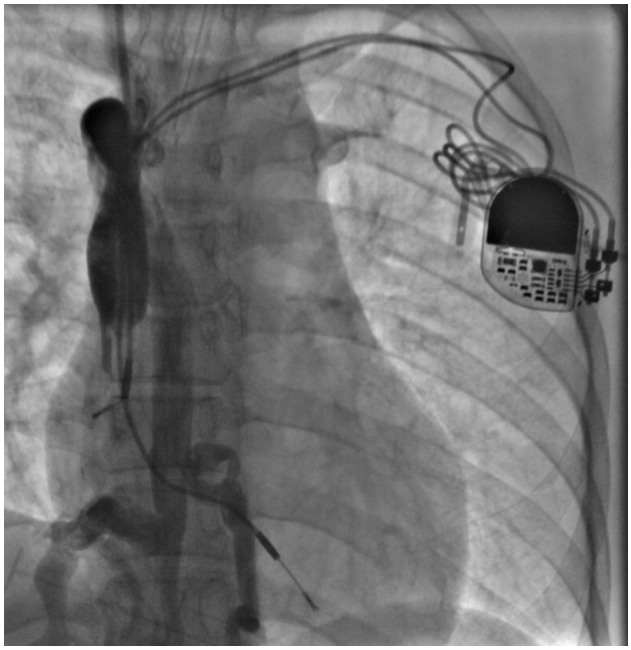

Fig. 2. Phlebography: narrowing of the superior vena cava at its junction with the right atrium (extensive collateral network).

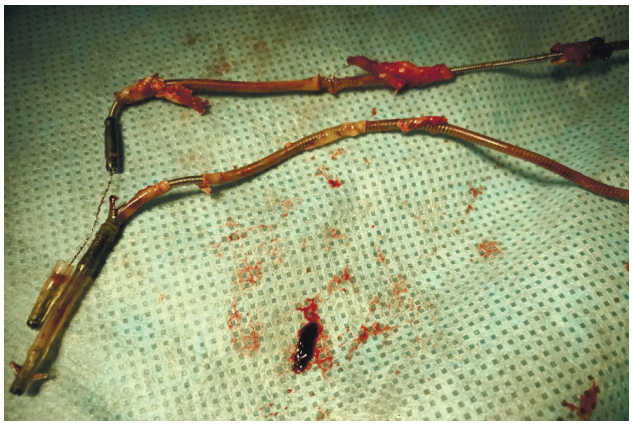

Fig. 3. Removed leads showing areas of calcified fibrous capsule.

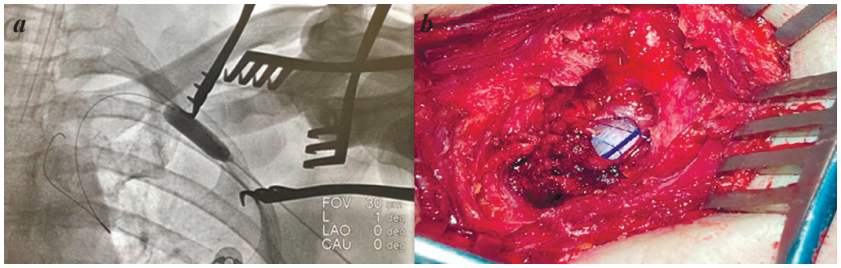

Fig. 4. Balloon catheter inflated in the left subclavian vein: a) chest radiograph, b) photograph of the surgical phase.

Operation description

The operation was performed in a hybrid operating room by a cardiovascular surgeon together with a specialist in endovascular diagnosis and treatment under complete intravenous anaesthesia with mechanical ventilation. Invasive blood pressure monitoring via the radial artery was performed. A Prelude 6Fr haemostatic introducer (Merit Medical Systems, USA) was inserted into the right internal jugular vein. Phlebography was performed through the introducer. SVC stenosis greater than 20 mm in length and over 90-95% in diameter was noted at the junction of the vein with the right atrium with the formation of collaterals and overflow into the inferior vena cava via the non-compartmental vein (Figure 2). For diagnostic purposes, a 145 cm Roadrunner PC.035 hydrophilic guidewire (Cook, USA) was inserted into the SVC through the introducer set. The lead was placed behind the stenosis in the right atrium. The possibility of implanting new leads on the right side was thereby determined. The right femoral vein was catheterized with a double lumen infusion catheter, and a Prelude 6Fr introducer (Merit Medical Systems, USA) was inserted into the right femoral vein through which a temporary pacing lead was inserted into the right ventricle. A Radifocus 10Fr introducer (Terumo, Japan) was inserted into the left femoral vein through which an AcuNav 8Fr transducer (Siemens, Germany) was passed for intracardiac echocardiography.

The surgical field was treated for the subsequent sternotomy. The skin defect was dissected, and the pacemaker and leads were isolated from the scar tissue using a monopolar coagulator. The mucous secretion from the pocket was collected for culturing and determining the sensitivity of the flora to antibiotics. The fibrous capsule of the pocket was removed with a coagulator. The leads were exposed through a separate incision in the left subclavian region. It was not possible to locate the fixation sleeves. In the search for fixation sleeves, the atrial lead was isolated at the entrance to the subclavian vein, and the ventricular lead was isolated at the entrance to the axillary vein. After cutting off the connector part of the leads, the LLD EZ stilettos (Spectranetics, USA) were inserted. The atrial lead was removed using a TightRail 11Fr device (Spectranetics, USA). The section of the SVC around the stenosis was calcified (Figure 3), which caused difficulty in

extraction. The ventricular lead was then also removed using a rotary dilator, with technical difficulties. When the device was inserted into the axillary vein, there was severe venous bleeding from the axillary/subclavian vein. Manual compression for 10 minutes showed no effect. TLE was continued using a TightRail 11Fr device (Spectranetics, USA) with single stage manual venous compression by an assistant. The lead was removed.

Intracardiac Echo showed no fluid in the pericardial cavity after lead extraction. Prolonged manual compression of the axillary/subclavian vein (about 30 minutes) showed no effect. The attempt to suture the venous defect was complicated by massive venous hemorrhage. It was decided to perform temporary hemostasis with a balloon catheter and suture the venous defect. The left cubital vein was punctured, a hemostatic introducer (5Fr) was inserted into the vein and a hydrophilic guide V18 (Boston Scientific, USA) with a diagnostic catheter Radiofocus OPTITORQUE JR 3.5 cm 5Fr (Terumo Europe N.V., Belgium) was inserted into the subclavian vein. A Sterling 10x60 mm balloon catheter (Boston Scientific, USA) was guided to the defect site; the balloon was inflated to 4 atmospheres (Figure 4a). Manual compression was then discontinued. The bleeding was stopped.

An axillary vein with a junction with the subclavian vein was visualized in the wound. There was a 30x6 mm defect on the anterior wall of the vein and an inflated balloon was observed through the defect in the vein (Figure 4b). The vein was isolated medial and lateral to the defect and placed on turnstiles. The venous defect was sutured with 5/0 Prolene. Blood flow was released. The vein filled and the lumen of the vein appeared to be 50% narrowed. It was decided not to perform vein reconstruction. There was no disturbance of haemodynamics during the procedure. The wounds on the left side were sutured after control of hemostasis. Given the mild clinical features of SVC syndrome and the calcification of the vein, it was decided not to stent the vein.

A new Estella DR -T dual chamber pacemaker (Biotronik, Germany) was implanted on the right side against the background of temporary pacing. A new pacemaker pocket was formed under the right pectoralis major muscle. The right axillary vein was punctured twice and 145 cm long Roadrunner PC.035 hydrophilic guidewires (Cook, USA) were passed behind the subtotal SVC stenosis and into the right atrium and further into the inferior vena cava. A 25 cm Radifocus 7 Fr (Terumo, Japan) introducer was placed along the leads, through which ventricular and atrial leads were positioned with active fixation were positioned with satisfactory pacing parameters (Figure 5). In the postoperative period, hemodynamics remained stable. Blood tests showed a decrease in haemoglobin to 88 g/l and no haemotransfusions were performed. The wounds healed with primary tension.

DISCUSSION

Subclavian or axillary veins injury with major bleeding is a rare complication of TLE. In this case, we mistakenly inserted a rotary dilator (11Fr), which is essentially a mechanically driven cutting tool, without proper visual inspection after visualizing the exposed axillary/clavicular vein (usually no vein is visualized in scar tissue in TLE), and thereby significantly damaged the anterior wall of the vein. The injury may also have been induced by the fact that the entry point of the ventricular lead into the vein was calcified (see Figure 3). Calcification of the fibrous capsule of the leads presents a typical situation in patients whose leads are more than 15 years old and who were implanted in childhood or at a young age. It is recognized that the time the leads remain in the body is a significant risk factor for extraction on the EROS and SAFeTY scores. In our opinion, to prevent this complication, the vein entry should be performed with close preliminary visual inspection using a SightRail Telescope propylene dilator (Spectranetics, USA) and preceded by a double cicatricial suture around the lead. A stenosis of the superior vena cava of more than 90% and the resulting venous hypertension also contributed to severe bleeding.

New device implantation after infected system removal is a significant problem, especially in patients with venous access issues. The methods to solve this problem are the following: epicardial implantation of the system, implantation through the iliac/femoral vein, recanalization and endovascular plastic surgery of the occluded/stenotic vein. Leadless pacemaker (not registered in the Russian Federation) may be considered in the future in a small group of patients with infectious complications of pacemaker and SVC occlusion [11,12]. According to current guidelines, implantation of a leadless pacemaker is recommended in the absence of venous access to the SVC or the presence of the high risk of device infection (history of infectious complications, haemodialysis patient) [13].

In this clinical situation, we believe that a leadless pacemaker is not recommended for several reasons: 1) the patient is indicated for implantation in the DDD mode; 2) the patient has a low risk of reinfection of the

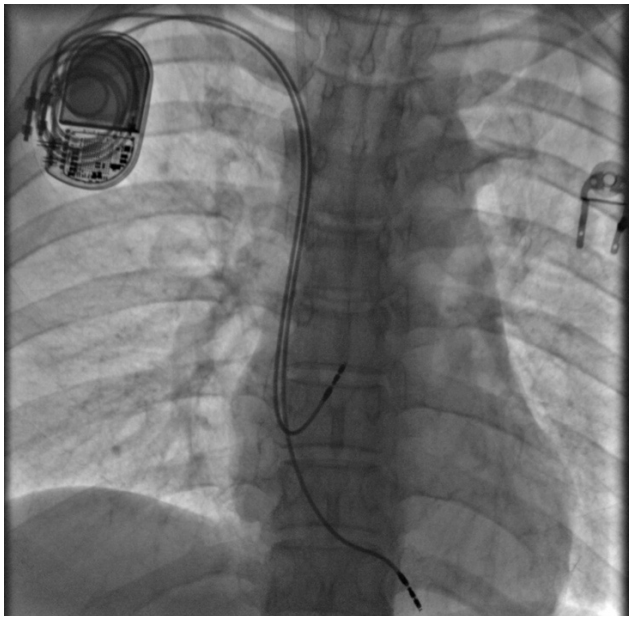

Fig. 5. X-ray after new pacing system implantation.

pacing system; 3) implantation of this device is not recommended in young patients with a life expectancy of more than 20 years [13].

We opted for endocardial lead implantation via long introducer through the stenosis of the superior vena cava as the most feasible, easiest, and least traumatic option. Modern surgical rooms in which cardiac electronic devices implanted and TLE performed are should include hydrophilic leads 140-200 cm long, introducers 23-25 cm long and balloon catheters. In some cases, a multidisciplinary approach needs to be considered in the management of patients with complications following electronic cardiac device implantation. In our case, temporary occlusion of the vein with a balloon catheter prevented life-threatening bleeding and we were able to suture the vein defect.

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TAKOTSUBO CARDIOMYOPATHY AFTER CRYOBALLOON PULMONARY VEIN ABLATION IN A PATIENT WITH PERSISTENT ATRIAL FIBRILLATION: CLINICAL CASE

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We present a case of takotsubo cardiomyopathy characterized as acute transient left ventricular systolic dysfunction in a patient with persistent atrial fibrillation, that occurred after cryoballoon pulmonary vein ablation procedure.

Keywords: takotsubo cardiomyopathy; left ventricular systolic dysfunction; echocardiography; cryoballoon pulmonary vein ablation; atrial fibrillation

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Takotsubo cardiomyopathy (TTC) or stress-induced cardiomyopathy represents a clinical syndrome characterized by acute transient systolic dysfunction of the left ventricular (LV) apex of the heart against a background of relatively intact contractility or hyperkinesis of the basal segments. The syndrome was first described by H.T.Sato in Japan in 1990 in predominantly postmenopausal women [1]. The syndrome was named 'tako-tsubo' by Japanese researchers due to the similarity of the configuration of the LV in systole to the shape of the traditional Japanese squid fishing jar (tako-tsubo). Typical of the disease is the balloon shape of the LV, which results from akinesia of the apex and narrowing of the basal area due to hyperkinesis. In the 30 years since the first case was described, the number of publications on TTC patients has steadily increased, but the mechanisms of development remain poorly understood.

It is generally believed that severe emotional stress or depression, physical pain, severe somatic illness and surgical procedures of all kinds are the most common triggers for TTC [2]. The presence of this association is reflected in synonyms for the condition, such as «broken heart syndrome» and stress-induced cardiomyopathy.

The transient nature of LV dysfunction and the absence of irreversible myocardial damage initially suggested a favourable prognosis. However, current long-term follow-up and registry data show comparable mortality and complication rates in the acute phase of TTC and acute coronary syndrome (ACS). Factors that worsen the prognosis of TTC include age, male sex, physical exertion, type 2 diabetes mellitus, cardiogenic shock and reduced ejection fraction (EF) [2]. According to the TTC consensus paper, cardiac arrhythmias are one of the most important factors determining the clinical outcome of this syndrome [3]. According to recent publications, the presence of atrial fibrillation (AF) in patients with TTC may be an independent predictor of in-hospital mortality and worse long-term prognosis [4, 5]. The present paper presents the clinical case of a patient with TTC after elective cryablation of the pulmonary veins for persistent AF.

Patient P., 66 years old, was admitted to hospital with complaints of palpitations with rapid, irregular heartbeat, accompanied by severe dyspnoea and weakness. The occurrence of cardiac arrhythmia has been known since 2016 and has led to repeated pharmacological cardioversions with amiodarone. Allapinin, propafenone and bisoprolol were administered as prophylactic antiarrhythmic therapy without significant clinical effect. Since 2019, the patient has been receiving amiodarone at a dose of 200 mg/day with a positive effect. However, after 1.5 years, autoimmune thyroiditis with nodularity, amiodarone-induced thyrotoxicosis, was diagnosed and the drug was discontinued. Prednisolone and thiamazole were administered, whereupon thyrotropic hormone and free thyroxine levels normalized over the course of 6 months of antithyroid therapy. Given the symptomatic AF (EHRA score III), failure of antiarrhythmic drug therapy and development of side effects with antiarrhythmic drugs, the patient was indicated for interventional treatment - pulmonary vein (PV) cryablation.

Preoperative examination revealed dyslipidemia (total cholesterol 6.93 mmol/l, LDL 4.87 mmol/l, HDL 1.45 mmol/l) and subclinical drug-induced hypothyroidism (thyrotropic hormone 7.6 μIU/ml, free thyroxine normal) with thiamazole administration. The electrocardio-

gram (ECG) on admission recorded sinus rhythm with a heart rate of 60 beats per minute, deviation of the electrical axis of the heart to the left, left bundle anterior branch block, no abnormal ST -T segment changes (Figure 1).

Transthoracic echocardiography (Echo) showed that the left atrium was undilated (antero-posterior dimension 4.0 cm, volume 58 ml), volume index of the left atrium 30.9 ml/m², LV contractility preserved, no signs of LV local contractility disturbances, no signs of pulmonary hypertension and increased central venous pressure. On admission, the patient was taking apixaban 5 mg b.i.d., atorvastatin 20 mg q.d. and thiamazole 10 mg q.d. The preliminary diagnosis was: «Cardiac arrhythmias: persistent AF, tachysystole. Autoimmune thyroiditis with nodularity, drug-induced subclinical hypothyroidism».

Cryoablation (isolation) of the pulmonary veins

Based on the indication, the patient underwent PV cryoablation [6]. The procedure was performed after pre-sedation with Sibazone 5 mg and Promedol 20 mg once under combined anesthesia with bolus injection IV of propofol and endotracheal anesthesia. The right femoral vein was punctured twice. A diagnostic multipolar lead was inserted into the coronary sinus under fluoroscopic control, and the left atrium was accessed by puncture of the atrial septum under transoesophageal Echo monitoring. When mapping the PV with a circular multipole electrode, all potentials of the PV were recorded. Cryoballoon ablation was performed once in the antral part of each PV with an exposure duration of 240 seconds and temperatures between -40 and -55 °C. To avoid cold damage of diaphragm innervation, exposure to the right LV was controlled by stimulation of the phrenic nerve. After cryoablation, repeated mapping confirmed evidence of isolation of all PV (pulse input and output). Hypocoagulation was maintained throughout the procedure with IV heparin and monitored with an activated clotting time of at least 350 seconds.

After surgery, the patient was transferred to the intensive care unit (ICU) in a hemodynamically stable condition, where she was observed for 24 hours. Immediately after transfer to the ICU, the patient had moderate chest pain that increased on the left side. However, the ECG recorded 10 minutes after the onset of pain showed no coronary dynamics in the form of ST -T increase/decrease. With two-dimensional bedside Echo, no reduction in local and global LV contractility was detected in the ICU. The pain syndrome is partially controlled with non-steroidal anti-inflammatory drugs.

On the morning of the second day after the operation, the patient still had the above-mentioned complaints. The ECG showed an inversion of the T waves in leads I, II, aVL, aVF, V1-V6, a prolongation of the QTc interval up to 540 ms. (Figure 1). According to two-dimensional Echo on the morning of the second day after surgery, there was a zone of dyskinesia with deformation in the apical LV segments with concomitant hyperkinesia of the basal and middle LV segments; LV EF decreased to 42-43%. (Figure 2). Blood tests showed a moderate increase in troponin T to 821 pg/ml, C-reactive protein to 97 mg/l, LDH to 422 U/L.

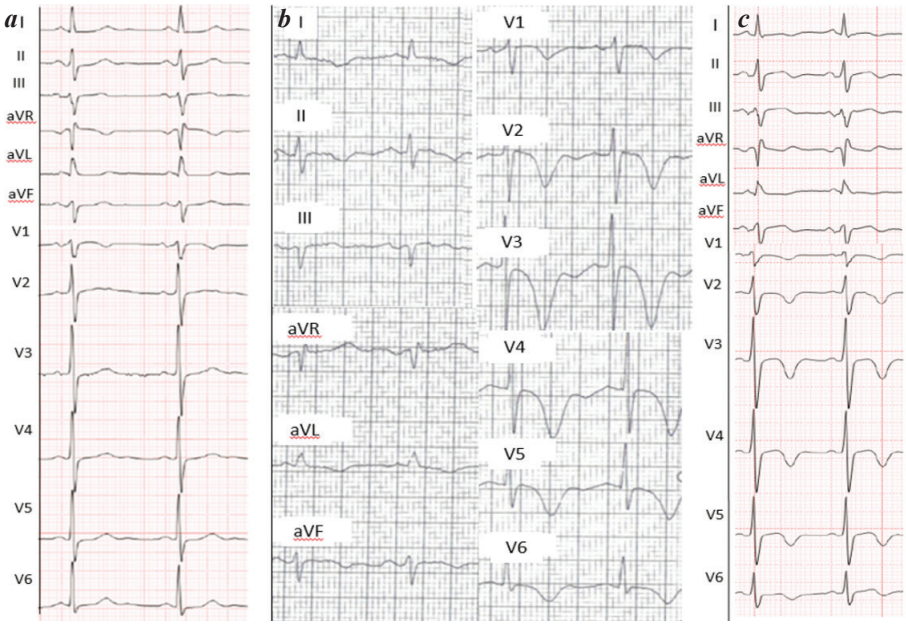

Fig. 1. ECG of patient P.: a - on admission to hospital; b - on the second day after PV cryoablation (against a background of sinus rhythm with a heart rate of 78 beats per minute, an inversion of the T waves in leads I, II, aVL, aVF, V1-V6 and a prolongation of the QTc interval to 540 ms were noted); c - on the seventh day after PV cryoablation (inversion of T waves in leads I, II, V1-V6 with lower amplitude than on the second day, shortening of the QTc interval to 470 ms persisted). Note: PV - pulmonary vein.

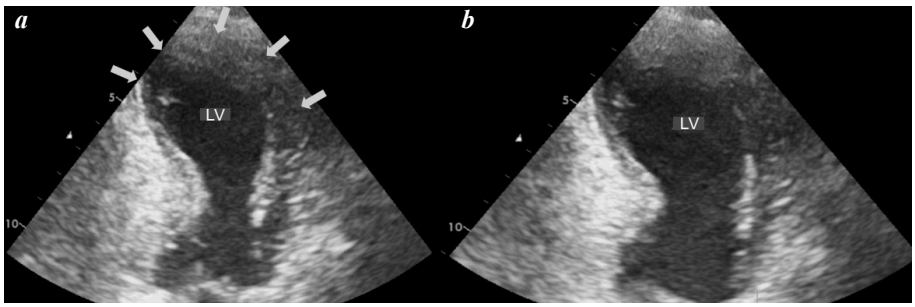

Fig. 2. Two-dimensional Echo of patient P. after PV cryoablation (the revealed zone of dyskinesia (marked by arrows) corresponds to the apex segments of LV of all its walls with marked LV cavity deformation, hyperkinesis of the basal segments): A - two-chamber position in the apex approach, LV systole; B - two-chamber position in the apex approach, LV diastole. Note: LV - left ventricle, PV - pulmonary vein.

In view of the pain syndrome, presence of potential risk factors for coronary heart disease, differential diagnosis and exclusion of acute myocardial damage in ACS and visualization of the coronary artery, coronary angiography (CAG) was performed. CAG showed 'borderline' coronary artery stenoses: 70% stenosis of the anterior descending artery, 70% stenosis of the right coronary artery, 60% stenosis of the circumflex artery (Figure 3).

Considering the ECG changes (inversion of T waves in all thoracic leads), the characteristic LV deformation in systole (apical «ballooning» of LV in combination with basal hyperkinesis) according to Echo, the discrepancy between angiographic and Echo image (no obstructive lesion and coronary thrombosis), a diagnosis of takotsubo cardiomyopathy of apical type was established.

During further dynamic follow-up, the patient's condition remained hemodynamically stable. A sinus rhythm with a heart rate of 65-80 bpm was maintained, BP remained within 100-110/60-70 mmHg and there were no signs of circulatory failure. Brain natriuretic peptide level was 118.6 pg/ml. Holter monitoring showed sinus rhythm with a mean / maximum / minimum heart rate of 78 / 99 / 68 bpm, no rhythm or conduction abnormalities. By the third day, the patient's chest pain had completely resolved. Further ECG recordings showed a decrease in the amplitude of the inverted T waves, the QTc interval was 470 ms (Figure 1).

Due to the circular nature of the local contractility abnormalities, myocardial dyssynchrony and deformation were investigated with speckle tracking imaging [7]. The method showed a decrease in Global Longitudinal Strain Average-GLPS Avg to -10.9% (standard -21.6±2.3%) (Figure 4). On the fourth day of acute TTC, a repeat Echo was performed, which showed positive dynamics in the form of a decrease in LV asynergy, an increase in LV ejection fraction from 42 to 51%.

Anticoagulant therapy with apixaban 5 mg b.i.d and adjusted hypolipidaemic therapy with atorvastatin to 40 mg q.d. were continued in the unit. Angiotensin-converting enzyme inhibitors were prescribed as pathogenetic therapy for TTC. The patient was discharged on the 7th day after LV cryoablation in satisfactory condition and was advised to take the above medications.

After 1 month, a repeat Echo study was performed which showed LV EF normalized to 60% and no areas of local LV contractility abnormalities. The study also showed no dilatation of the heart cavities and no signs of pulmonary hypertension. Speckle tracking Echo showed improvement in LV myocardial deformation characteristics with a GLPS Avg of -16.4% (Figure 4). Given the coronary artery stenoses detected with CAG, a negative stress Echo was performed to rule out myocardial ischaemia. Palpitations did not recur during the following 6 months of follow-up. No rhythm or conduction abnormalities were detected during repeated daily checks at 3 and 6 months.

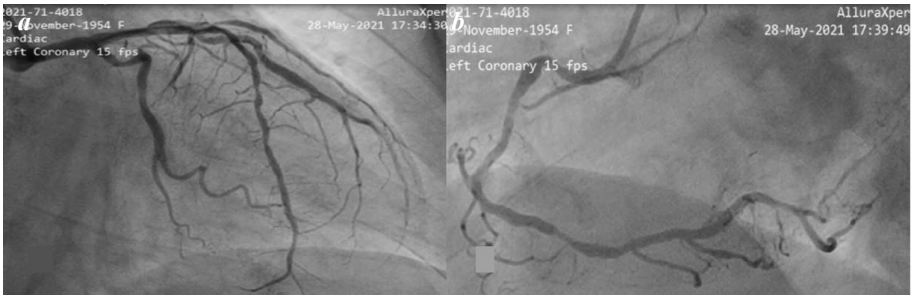

Fig. 3. Coronary angiography of patient P. after PV cryoablation, a diffuse atherosclerotic coronary artery disease was found: a - the anterior descending artery is 50% narrowed at the orifice, 60% narrowed in the proximal segment and 70% narrowed in the middle segment, the circumflex artery is 60% narrowed in the proximal third (right caudal projection); b - in the proximal segment of the right coronary artery multiple stenoses with a narrowing of up to 70%, in the middle segment a narrowing of 40%, in the distal segment a narrowing of 65-70% (left caudal projection). Note: PV - pulmonary vein.

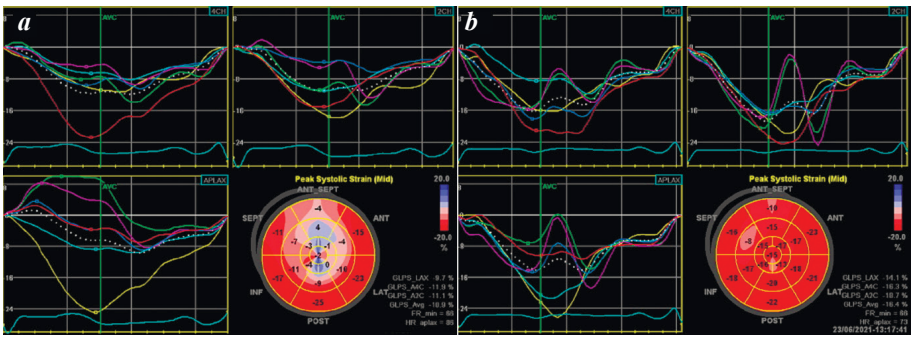

Fig. 4. Speckle tracking echocardiography with evaluation of curves and indices of longitudinal myocardial deformation in 17 segments, maximum systolic deformation for each of the 17 LV segments in the form of a «bull's eye»: a - evaluation of indices on the fourth day after PV cryoablation (significant decrease in segmental longitudinal deformation in the LV apex of all its walls, typical for apical TTC, GLPS avg -10.9%); b - in dynamics 1 month after PV cryoablation (a significant decrease in the area of segmental longitudinal deformation in the LV apex is noted, GLPS avg -16.4%). Note: GLPS - Global Longitudinal Strain, LV - left ventricle, PV - pulmonary vein, TTC - takatsubo cardiomyopathy.

DISCUSSION

Data on TTC collected over the past decades allow timely detection of the disease and its potential complications. According to a follow-up registry of 3.265 patients, 1% of patients admitted to hospital urgently with a diagnosis of ACS were found to have TTC. Based on the US Nationwide Inpatient Sample database, most TTC patients are women (5.2 per 100,000 women versus 0.6 per 100,000 men) [8].

The primary diagnostic criteria for TTC scanning, formulated by the Mayo Clinic in 2008, have subsequently been repeatedly updated and revised [9]. A 2018 European Society of Cardiology consensus paper established the following diagnostic criteria for the diagnosis [3]: 1) transient LV dysfunction (hypokinesia, akinesia or dyskinesia) in apical or middle segments not corresponding to the blood supply zone of a single coronary artery, often leading to circular changes in LV segments; 2) previous physical or emotional stress (optional condition); 3) significant coronary artery lesion not refuted by the presence of CT; 4) ECG changes in the form of ST-segment elevation/reduction, inversion of T waves, prolongation of the QTc interval in the acute phase of the disease; 5) moderate troponin elevation, increased plasma natriuretic peptide level; 6) no evidence of infective endocarditis; 7) predominance of post-menopausal women; 8) recovery of systolic function from LV in dynamic cardiac imaging.

It is still unclear whether TTC is exclusively a cardiovascular disease. A significant proportion of patients with TTC have extracardiac pathology, particularly pheochromocytoma and acute cerebral disorders. Previous surgical procedures or administration of sympathomimetics, which act as triggers of TTC, also suggest a polypathogenetic nature of the disease [3, 10].

The understanding of the pathogenetic mechanisms of TTC is based on several hypotheses, and the available approaches to the treatment of the syndrome are not supported by randomized trials. The presence of emotional or physical stress as a trigger of TTC has been the basis for the hypothesis of a central role of catecholamines in the development of the syndrome [10]. Activation of the sympathetic nervous system can lead to spasms of the coronary arteries and disruption of the microcirculation. The characteristic shape of the LV on the TTC may be due to the different density of beta-adrenoceptors in the apex and basal regions. Stimulation of beta-adrenoceptors by catecholamines leads to a negative inotropic effect, local hibernation and myocardial dysfunction, which recovers completely within a few weeks or months [11].

Despite transient LV dysfunction in TTC, there is a risk of serious, even life-threatening, complications. It is important to note that the initial perception of a favourable course of TTC has not been confirmed in several registries and studies. The mortality rate in the acute phase of TTC is similar to that of acute myocardial infarction, at 5.6% at one year follow-up [2]. Potentially dangerous complications of TTC include cardiogenic shock (up to 10% of cases), LV thrombosis, LV outflow tract obstruction and LV wall rupture [12,13]. Life-threatening arrhythmias, including Torsade de Pointes ventricular tachycardia (TdP) and ventricular fibrillation, were observed in 3.4-9% of patients in the acute phase of TTC. Prolongation of the QTc interval of more than 500 ms over several days (as in our patient) is to be expected and significantly increases the risk for these arrhythmias [14].

Patients with TTC are not only prone to ventricular tachyarrhythmias but also to supraventricular arrhythmias. The prevalence of AF in patients with TTC is between 5 and 25%. According to a retrospective analysis by I. El-Battrawy et al. (2017) of patients with TTC, AF was associated with an increased risk of in-hospital mortality and was the worst long-term predictor of adverse disease outcomes [4]. In addition, AF increases the risk of acute heart failure and thromboembolic events, which is more pronounced in patients with LV wall hypo- and akinesia in TTC. Similar prognostic results reported by L. Jesel et al. (2019) showed that markers of myocardial damage and systemic inflammatory response (C-reactive protein, troponin I, BNP) were significantly more frequent independent predictors of cardiovascular mortality in patients with TTC at AF. Thus, the results may suggest a significant role of inflammation in the development of AF in the cohort of patients with TTC [15]. Coronary artery disease is found in 10-29% of patients with TTC [16]. Therefore, the presence of a stenotic coronary artery lesion does not exclude a diagnosis of TTC in the patient.

Circular systolic LV dysfunction, detected by Echo in the form of apical «ballooning» of the LV apex, which does not correspond to the coronary blood supply of the LV, combined with basal segment hyperkinesis, is the most characteristic feature for distinguishing TTC from ACS and other diseases. In acute TTC, this circular pattern of LV local contractility abnormalities is usually accompanied by a significant decrease in regional longitudinal deformation from the base towards the LV apex, where the most marked changes are seen [17]. These abnormalities of LV local contractility are not only detectable by two-dimensional Echo, but can be particularly clearly visualized by assessing LV deformation using speckle tracking technology and determining LV «bull's-eye» diagrams [7, 17].

CAG and contrast-enhanced magnetic resonance imaging are also important diagnostic techniques. CAG can exclude the presence of thrombosis or «complicated» coronary artery plaque. Magnetic resonance imaging with contrast agent makes it possible to distinguish TTC in the acute phase from the development of myocarditis.

Many patients cannot be completely excluded from ACS by Echo and CAG, especially in clinically stable patients with TTC and no ST -T-segment elevation. The InterTAK diagnostic score, proposed by the European Society of Cardiology in 2018, provides a specific way to confirm a TTC diagnosis and determine the method of coronary imaging [3]. Our patient had an intermediate risk of TTC (56 points), which also warranted CAG.

The most important approaches to the management of TTC in the acute phase are timely diagnosis and prevention of potentially dangerous complications. The question of long-term drug therapy for TTC, which influences the course and prognosis of the disease, remains unresolved. There is evidence of a beneficial effect of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on the prognosis of cardiovascular events for 1 year before the function of LV is restored [2].

The initial description of TTC as a «stress-induced» cardiomyopathy suggested a possible involve-

ment of the beta-adrenergic system in the development of the syndrome. Experimental *ex vivo* heart models of TTC patients demonstrated increased beta-adrenergic activity of cardiomyocytes in response to catecholamine exposure [10]. Based on this work, the potential benefit of prescribing beta-blockers for patients with TTC has been suggested. However, according to the InterTAK registry, 60% of patients with recurrent TTC have received beta-blockers, and these are predominantly β1-specific. There are also no data on the effect of beta-blockers on mortality in patients with TTC. Routine prescription of these drugs to prevent TTC recurrence is therefore not advisable [2, 18].

The clinical case we studied demonstrates the importance of early diagnosis of TTC developing in the postoperative period after LV cryoablation and the importance of ruling out irreversible myocardial damage in ACS. There are only 2 cases of TTC after LV cryoablation in the literature [19, 20]. The clinical case we describe shows the development of TTC after intervention for persistent AF combined with widespread atherosclerotic coronary artery disease. The correlation with the surgical intervention, the pathological changes in the ECG and the apical LV dyskinesia in the Echo are classic signs of the disease. Due to the prolongation of the QTc interval to a maximum of 540 ms in our patient, continuous cardiac rhythm monitoring was performed in ICU during the acute phase of TTC. This allowed possible causes of QTc prolongation (bradycardia, hypokalemia and hypomagnesaemia) to be corrected if necessary to prevent life-threatening arrhythmias. Although our patient did not experience any serious complications in the manifestation of TTC, the cryoballoon isolation of the pulmonary veins performed at follow-up enabled the patient to avoid symptomatic recurrences of AF and improve her quality of life.

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ATRIAL ECTOPIA ASSOCIATED WITH PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

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Fragments of Holter monitoring of a 64-year-old patient with paroxysms of supraventricular tachycardia are presented, atrial ectopic activity during tachycardia is recorded, which does not interrupt the tachycardia, but changes the sequence of RR intervals. The possibility of remote analysis of the data of 3-day monitoring of the patient's electrocardiogram in 12-channel is provided.

Keywords: Holter monitoring; supraventricular tachycardia; atrial ectopic beats; atrioventricular conduction; electrophysiology study; radiogrequency catheter ablation

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The differential diagnosis of supraventricular tachycardia (SVT) on Holter monitoring (HM) presents a significant challenge in the absence of clearly distinguishable atrial waves, evidence of accessory pathways or atrioventricular (AV) node dissociation into fast and slow conduction zones. However, the presence of P waves does not always permit an unequivocal determination of the type of SVT. While positive P waves in the inferior leads indicate atrial tachycardia, the presence of negative P waves with a downward-upward vector can lead to different mechanisms of SVT, depending on the ratio of PR to RP intervals and the absolute values of these intervals.

If negative P waves are detected in the leads II, III and aVF closer to the preceding QRS complex than to the following one, we are inclined to consider SVT as paroxysmal orthodromic AV reentry tachycardia due to the presence of Wolf-Parkinson-White (WPW) syndrome. However, it should not be overlooked that atrial tachycardia with delayed AV conduction can look exactly the same. In our opinion, it is impossible to differentiate these tachycardias based on an ECG recorded at the "peak" of the paroxysm without having records of the onset and termination of the paroxysm.

A similar situation occurs when negative P waves are closer to the following QRS complex than to the preceding one. In most cases, this pattern masks atrial tachycardia. However, paroxysmal orthodromic AV reentry tachycardia may appear this way if the RP interval is prolonged due to retrograde conduction via "slow" additional conduction.

The shape of the P waves must also be considered. For example, the presence of narrow (already sinus P waves) negative P waves in the inferior leads may indicate that the atria are covered by the excitation of the AV node and facilitate a correct diagnosis. Such P waves are characteristic of paroxysmal AV nodal reentry tachycardia and paroxysmal antidromic AV reentry tachycardia, in which the excitation propagates anterogradely along an additional conduction pathway and retrogradely along AV node. The identical P waves can be recorded in AV nodal tachycardia and atrial tachycardia, with the source of excitation located in close proximity to AV node.

A correct diagnosis is greatly facilitated if ECG or an ECG with sinus rhythm indicates WPW syndrome or signs of AV nodal dissociation into fast and slow conduction zones. The criteria for the diagnosis of WPW syndrome are well established, whereas signs of dissociation of the atrioventricular node from sinus rhythm are less common and are usually interpreted as first-degree AV block. AV node dissociation is indicated by signs similar to those found on a programmed stimulation in the form of a discontinuity in the AV conduction curve. In a sinus rhythm ECG, if we observe a rapid increase in the PQ interval of 80 ms or more from one P-QRS-T complex to the next, followed by an equally rapid decrease, we suspect that the fast channel of AV node is blocked and conduction has occurred via the slow channel, which has then returned to its original position. This can be validated using a PQ interval diagram or a histogram of the distribution of this interval. Unfortunately, these options are not available in all HM systems. However, it should be emphasized that the presence of evidence of WPW or AV nodal dissociation is not a guarantee that a patient's SVT paroxysms are related to this arrhythmic substrate.

Nevertheless, it can be stated that ECG and HM allow determination of the type of SVT without electrophysiological study in most cases. In some cases, it helps to form an idea of the "details and peculiarities"

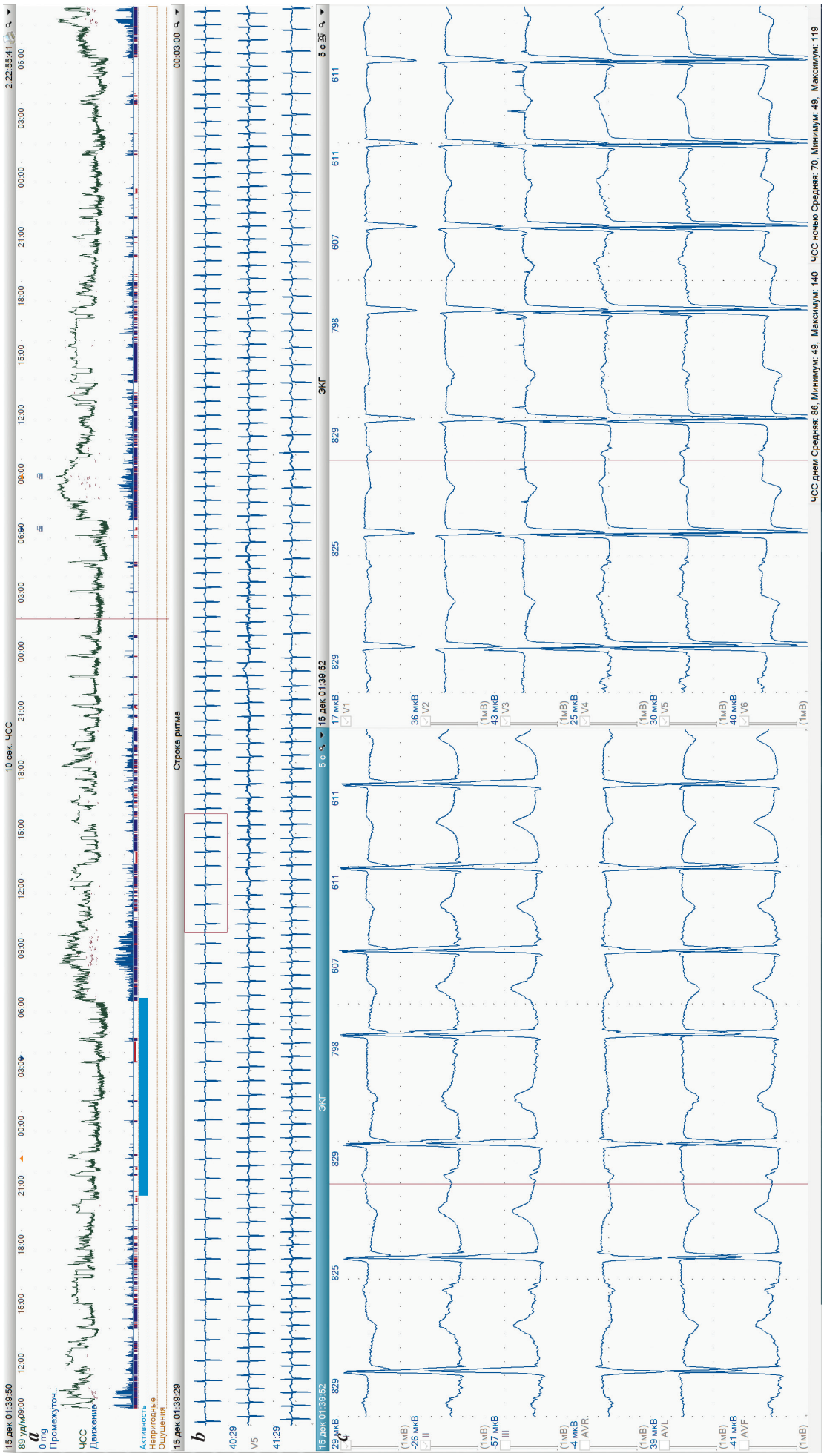

Fig. 1. Fragment of three-day electrocardiogram monitoring in twelve standard leads from patient B. 64 years old: a - HR graph (the cursor position indicates one of the tachycardia paroxysms), b - rhythm line of three minutes duration (the rectangular cursor marks the onset of the paroxysm), c - ECG fragment corresponding to the rectangular cursor on the rhythm line (after three sinus complexes P-QRS-T, a paroxysmal tachycardia with a rate not exceeding 100-110 bpm begins).

(as E.A. Berezniy said) of the electrophysiological mechanisms of arrhythmia. We therefore invite you to analyze what we consider to be very interesting HM data or fragments thereof, presented in this publication. We will present our interpretation of the electrophysiological features of SVT recorded during this monitoring in the next issue of the journal.

We obtained the recording of three-day ECG monitoring in twelve standard leads from patient B. 64 years old. At the time we analyzed the recording, we had no information about the patient. The first "encounter" with the monitor was nothing unusual. However, it should be noted immediately that the combination of persistent first-degree block AV with SVT paroxysms occurring at a comparatively low frequency was thought-provoking. One of the SVT paroxysms was characterized by ectopic atrial activity that did not interrupt the tachycardia but caused some changes in the interval dynamics (Figure 1-3). This elicited quite natural questions from the doctor recording the monitor and this was the reason for the consultation.

Determining the nature of SVT would not present any major difficulties. Nevertheless, it is the "details and

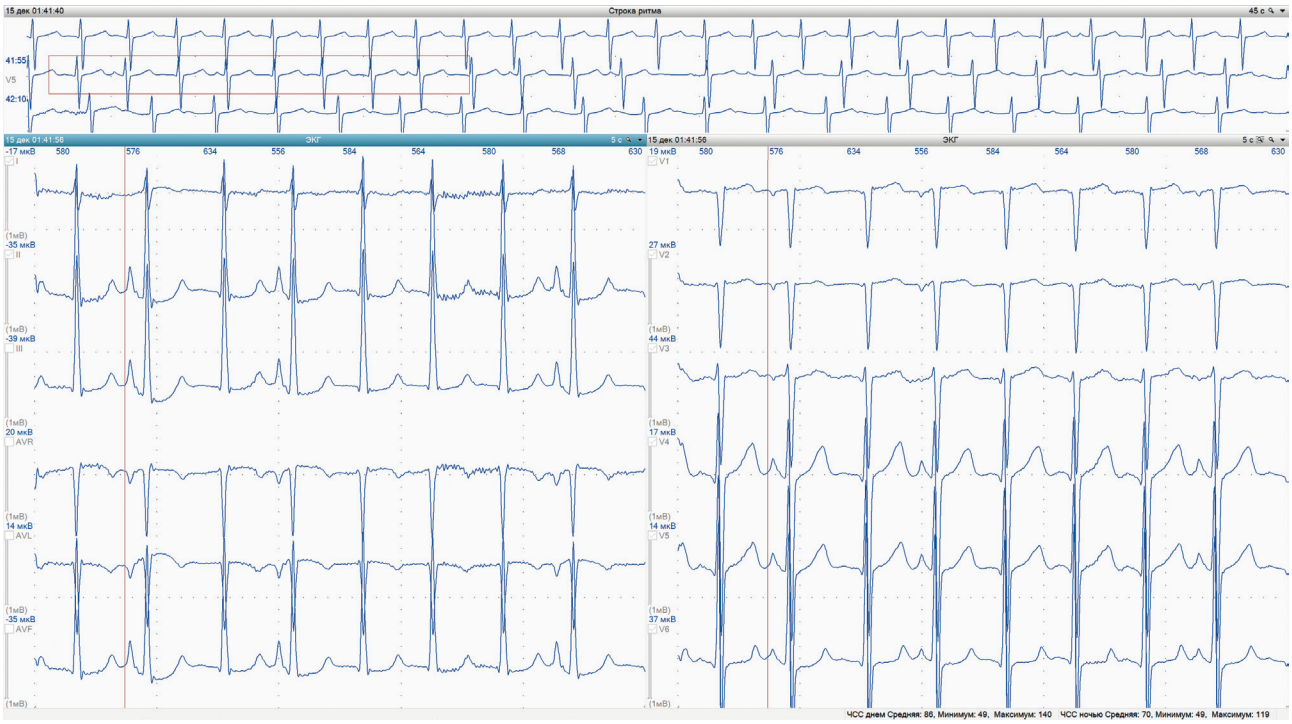

Fig. 2. Fragment of electrocardiogram for monitoring patient B. 64 years old: the ectopic activity of the atria does not interrupt the paroxysmal tachycardia but does influence RR intervals.

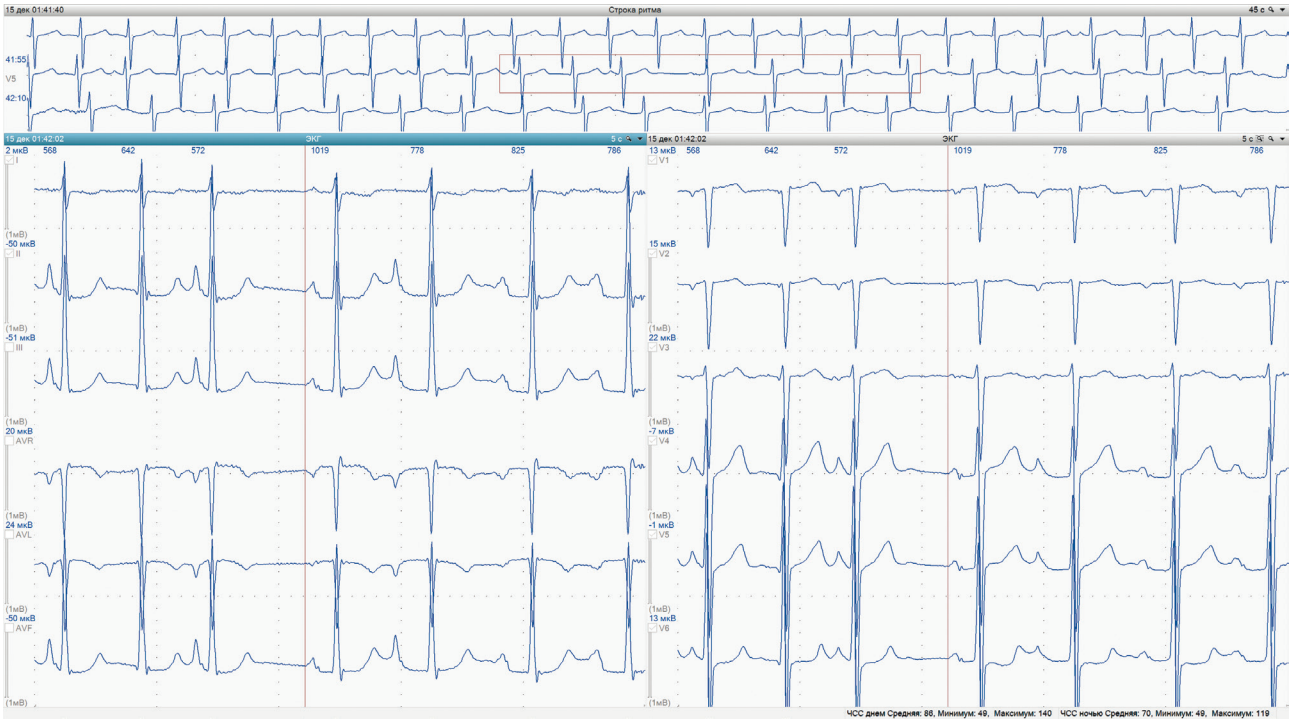

Fig. 3. Fragment of electrocardiogram monitoring of patient B. 64 years old: end of paroxysmal tachycardia with restoration of sinus rhythm.

peculiarities“ of this recording that we believe are of undeniable interest. We have noted ventricular extrasystoles on several occasions without interruption of the course of SVT. We observe for the first-time recordings of atrial ectopy that do not interrupt SVT but alter the sequence of RR intervals. No such descriptions could be found in the literature either. However, it must be emphasized again that the salient features of this SVT are unlikely to have a significant impact on further treatment strategy.